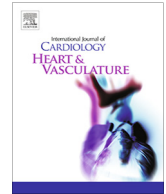




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## Isolated left atrial cryoablation of atrial fibrillation in conventional mitral valve surgery

Giuseppe Gatti<sup>a,\*</sup>, Ilaria Fiorica<sup>a,1</sup>, Luca Dell'Angela<sup>b,1</sup>, Marco Morosin<sup>a,1</sup>, Giorgio Faganello<sup>a,1</sup>, Chiara Cappelletto<sup>c,1</sup>, Linda Pagura<sup>a,1</sup>, Alessandro Ceschia<sup>a,1</sup>, Rita Piazza<sup>c,1</sup>, Aniello Pappalardo<sup>a,1</sup>

<sup>a</sup> Cardio-Thoracic & Vascular Department, Trieste University Hospital, Trieste, Italy

<sup>b</sup> Division of Cardiology, Gorizia & Monfalcone Hospital, Gorizia, Italy

<sup>c</sup> Department of Cardiology, Santa Maria degli Angeli Hospital, Pordenone, Italy

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### ABSTRACT

**Background:** Recent trends of surgery for atrial fibrillation (AF) are towards more safe and effective energy sources, as well as to simplified sets of atrial lesions.

**Methods:** One hundred eighteen (mean age,  $67.4 \pm 9.2$  years) selected patients with paroxysmal/persistent AF and mitral valve (MV) disease underwent cryoablation of AF combined with conventional (not via mini-thoracotomy) MV surgery; the lesion set was limited to only the left atrium. Multivariable analyses identified predictors of cardiac rhythm at hospital discharge and follow-up.

**Results:** There were 7 (5.9%) hospital deaths; 33 (28%) patients were discharged on AF. Higher values of preoperative left atrial volume index (odds ratio [OR] = 1.07, 95% confidence interval [95%CI]: 1.01–1.13) and mixed etiology of MV disease (OR = 4.19, 95%CI: 1.23–14.2) were predictors of hospital discharge on AF. Seventy-four (66.7%) patients were on stable sinus rhythm at follow-up (median period, 6.6 years); the 1, 5, and 10-year nonparametric estimates of adjusted freedom from AF were 98.1%, 89.2% and 45.6%, respectively. Higher values of preoperative systolic pulmonary artery pressure (hazard ratio [HR] = HR = 1.04, 95%CI: 1.01–1.08) and AF at hospital discharge (HR = 4.14, 95%CI: 1.50–11.4) were predictors of AF at follow-up.

**Conclusions:** During conventional MV surgery, a cryo-lesion set limited to only the left atrium may give good, immediate and long-term results. Left atrial dilation and mixed etiology of MV disease were predictors of hospital discharge on AF. Preoperative pulmonary hypertension and AF at discharge combined with an increased risk of AF at follow-up.

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## 1. Introduction

Atrial fibrillation (AF) affects nearly 4.5 million people in Europe and 2.2 million people in the United States, and accounts for almost one-third of all hospital admissions due to cardiac arrhythmias. The most severe complication is thromboembolism and resultant stroke. However, significant morbidity and mortality also derive from hemodynamic instability secondary to loss of atrial contraction, exacerbations of congestive heart failure (CHF) from atrioventricular asynchrony, and tachycardia-induced cardiomyopathy [1–4].

\* Corresponding author at: Division of Cardiac Surgery, Ospedale di Cattinara, via Pietro Valdoni, 7, 34148 Trieste, Italy.

E-mail address: [giuseppe.gatti@asugi.sanita.fvg.it](mailto:giuseppe.gatti@asugi.sanita.fvg.it) (G. Gatti).

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The available medical treatments for AF have many shortcomings. Anti-arrhythmic drug therapy has limited efficacy, can lead to significant side effects, and may necessitate oral anticoagulation. Rate control strategies, conversely, leave the patient in AF and therefore do not address impairment of hemodynamics [1,4]. On the other hand, the Cox-Maze III [5], namely the last total surgical version of the first effective surgical treatment for AF (the Cox-Maze procedure [6]), involves a complex pattern of surgical incisions across both the right and left atria that allow for most of the atrial myocardium to be activated. This technique results in preservation of atrial transport function in many patients, but prolong significantly cardiopulmonary bypass time. The development of ablation technology over the last decade has transformed this time-consuming and challenging operation into procedures such as the Cox-Maze IV that are technically easier, shorter, and less invasive [7]. However, the incorporation of new technologies has led to lack of reliable information as to the best energy source or

atrial lesion set [8,9]. The most recent trends of surgery for AF are towards more safe and effective energy sources, as well as to simplified patterns of atrial lesions.

This retrospective study aimed to explore the immediate and long-term outcomes of a selected series of patients undergoing ablation of AF in addition to mitral valve (MV) surgery. The selection of patients was performed according to the MV approach, energy source, and set of atrial lesions for treating AF.

## 2. Methods

### 2.1. Study patients, methods of data collection and follow-up

From 2005 throughout 2017, 270 consecutive patients with AF and MV disease underwent ablation of AF concomitant with MV repair or replacement at the Cardio-Thoracic & Vascular Department of the University Hospital of Trieste, Italy. The patients who underwent surgery via mini-thoracotomy, and/or received lesions across both the right and left atria (i.e. not limited to only the left atrium [LA]), and/or had any concomitant cardiac operation (in addition to MV surgery plus cryoablation of AF) other than coronary artery bypass grafting (CABG) and tricuspid valve (TV) annuloplasty for functional tricuspid regurgitation (secondary to MV disease) were excluded from the study. Consequently, the study population consisted of all 118 (43.7%; mean age,  $67.4 \pm 9.2$  years; females, 49.2%) patients with paroxysmal (28.8%) or persistent AF (71.2%) and MV disease who underwent isolated LA cryoablation of AF combined with conventional MV surgery.

Baseline characteristics of patients, etiology of MV disease, concomitant (mild) aortic valve disease, used surgical techniques and operative data, as well as relevant details of perioperative drug use, hospital course of patients, and follow-up were retrospectively collected from patient files of institutional and national databases. Perioperative pulmonary artery pressure (PAP) was measured using the pulmonary artery (Swan-Ganz) catheter, which was removed in postoperative day two in case of uneventful hospital course. Thereafter, PAP was measured with echocardiography (when at least a trivial tricuspid regurgitation was present). In-hospital deaths, deaths during the follow-up period, need of repeated cardiac operation and a permanent pacemaker (PPM) implantation, as well as, among the adverse events after hospital discharge, hospital readmission due to CHF, stroke, and major hemorrhagic events were recorded. A seven-day continuous rhythm monitoring was performed after surgery for all asymptomatic patients and restarted whenever palpitations or other symptoms of CHF occurred. For every patient, both electrocardiographic and echocardiographic evaluation was performed immediately before hospital discharge. Cardiac rhythm at discharge and at follow-up, as well as the corresponding date of suspension of any anti-arrhythmic drug and of oral anticoagulation, when occurred, were recorded for each (discharged) patient. For every study patient, postoperative monitoring of the cardiac rhythm was carried out with 24 or 48-hour Holter recording at six months after surgery, and yearly afterwards. The Holter monitoring was anticipated in the presence of symptoms of CHF. Clinical follow-up was completed by the following sequential procedure: telephone contact with the patient, or the patient's family; if they could not be contacted, telephone contact with the general practitioner, referring cardiologist or other specialists listed in the patient's medical file; finally, consultation of the national death registry or the town halls of the place of birth to obtain data regarding the vital status (dead or alive at the cut-off date).

The last patient enrolled in the study was operated in October 2017. The cut-off date for collecting data was on December 31,

2018. These dates were chosen to dispose of a gap between surgery and follow-up of at least one year for every patient.

The outcomes were compared with those of more relevant studies on the topic of Literature. The studies that included concomitant aortic valve operations were retained when the results of MV surgery alone had been explicitly reported (Suppl. Table S1) [10–32].

### 2.2. Definitions

The most commonly used classification system for AF, namely that published jointly by the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society in 2006, was adopted [1]. In this system, AF is defined as either paroxysmal or persistent, and it is considered recurrent if a patient has had two or more episodes. If recurrent AF terminates spontaneously, it is designated paroxysmal, whereas if it lasts beyond seven days, it is termed persistent. Patients with AF that has lasted longer than one year were labelled as having long-standing AF.

Unless otherwise stated, the definitions and cut-off values of preoperative variables were those used for the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) [33]. The risk of stroke per year of each patient was established preoperatively according to the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (Congestive heart failure-Hypertension-Age  $\geq 75$  years [doubled]-type 2 Diabetes-previous Stroke, transient ischemic attack, or thromboembolism [doubled]-Vascular disease-Age 65–75 years-Sex category) [34]. The risk profile of each patient was established preoperatively according to EuroSCORE II [33]. Internationally agreed definitions of complications after heart valve surgery were adopted, as validated and published in the literature [35].

### 2.3. Surgical techniques

Almost all the operations were performed via a median sternotomy, with cardiopulmonary bypass and cross-clamping of the aorta; right thoracotomy was used occasionally. While ascending aorta and bicaval cannulation was used for the sternotomy approach, the common femoral artery was adopted as the arterial cannulation site for the right thoracotomy approach. Myocardial protection was achieved either with multidose, cold blood cardioplegia, generally before May 2009, or a single-dose Custodiol-histidine-tryptophan-ketoglutarate solution (Custodiol®-HTK; Essential Pharmaceuticals, Durham, North Carolina), usually from May 2009. Cardioplegia was delivered in both antegrade and retrograde mode.

After aortic cross-clamping and cold cardioplegic arrest, MV exposure was obtained either by a LA incision, through the interatrial groove, or by a right atrial incision via the interatrial septum, especially when TV annuloplasty was scheduled. After having repaired or removed the MV, LA cryoablation was started on, and a set of lesions including (1) two separate box lines for the right and the left pulmonary veins, (2) a connecting line between the two boxes, and (3) a lesion connecting the left box line to the mitral annulus. In order to pursue a quick surgery, the line surrounding the right pulmonary veins was performed simultaneously to the line connecting the two boxes, and the line encircling the left pulmonary veins was performed simultaneously to the line to the mitral annulus. In the case of left atriotomy, the surgical incision was part of the right pulmonary box line (Suppl. Fig. S1). The technology employing Argon (Medtronic, Minneapolis, Minnesota) was used and each lesion was made using a manually shapeable probe that was applied to the LA endocardial layer for two minutes, down to  $-200$  °C of temperature. No electrophysiological assessment of the lines to confirm block was performed intraoperatively. The cryoablation procedure did not change

during the study period. Each surgical report was carefully examined by the first author and there were no significant differences between surgeons about the performed lesions for all 118 study patients. In the absence of LA clots or thrombi, the LA appendage obliteration was achieved using an endocardial purse-string suture. Finally, a prosthetic valve or annuloplasty ring was fixed to the mitral annulus.

TV annuloplasty was performed during aortic cross-clamp time or after clamp removing, according to the surgeon's preference. All coronary anastomoses on the inferolateral cardiac wall were performed before MV surgery and cryoablation.

#### 2.4. Perioperative echocardiographic assessment

Two-dimensional echocardiographic assessment and Doppler color-flow imaging were performed on for every patient. Preoperative echocardiographic evaluation (both transthoracic and transesophageal) was completed within two months before the operation. Postoperative transthoracic echocardiographic evaluation was performed at three months and every year afterwards. Measurements of a limited number of relevant cardiac parameters early before surgery and at four steps (3 months, 1, 5 and 10 years) after surgery were reported. Doppler flow mapping was used for semi-quantitative evaluation of mitral regurgitation. MV orifice area was estimated by using the pressure half-time method. LA size was measured based on its anteroposterior diameter on the parasternal long-axis view at end-systole.

#### 2.5. Postoperative management

Postoperative supraventricular tachyarrhythmias were treated with intravenous Amiodarone (1500 mg in 470 ml of dextrose 5%; rate of infusion, 20 ml/h), which was commenced immediately after surgery with prophylactic purposes for every patient having no atrioventricular block; after 12 or 24 h, it was tapered according to the patients' cardiac rate and replaced with Amiodarone per os (400 mg/day) till to discharge; after discharge, Amiodarone per os (200 or 400 mg/day according to the patient's cardiac rate) was maintained till to documented stable SR recovery (in the presence of contraindications for its long-term use, Amiodarone was replaced with other antiarrhythmic drugs). During hospital course, rapid ventricular rate despite Amiodarone treatment was controlled either with  $\beta$ -blockers or  $Ca^{2+}$ -channel blockers. Because of concomitant mitral valve surgery, every patient was anticoagulated with Acenocumarol for 3 to 6 months postoperatively (with a target international normalized ratio of 2.0–3.0) at the attending surgeon's discretion. The maintenance of oral anticoagulation therapy was determined according to cardiac rhythm status and the individual patient's risk factors for thromboembolism. The use of mechanical valves, absence of effective atrial contraction despite P-wave at electrocardiographic examination, and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or more resulted in anticoagulation therapy that was continued.

#### 2.6. Ethical considerations

The study was performed in accordance with the 1975 Declaration of Helsinki. Approval to conduct the study, as well as to contact the patients and their families, was obtained from the institutional ethics committee (October 23, 2018 – odg 5.18), based on retrospective data retrieval. Each patient had given specific written consent both to operation and the study.

#### 2.7. Statistical methods

Discrete variables were reported in accordance with internationally agreed categories; values are the number of patients with the corresponding percentage. Continuous variables with Gaussian distribution were reported as mean  $\pm$  standard deviation, while those having non-Gaussian distribution were reported as median, with a range between the first and the third quartile in brackets. Categorical variables were compared using the  $\chi^2$ -test. Continuous variables were compared using the paired or unpaired Student's *t*-test or the Mann-Whitney *U* test, as appropriated. Backward stepwise logistic regression was used to identify independent predictors of hospital discharge on AF. All variables with a P-value < 0.1 by the univariable analysis were included in the multivariable model. For each variable, the odds ratio (OR) and the corresponding 95% confidence interval (95%CI) was calculated. Cox proportional hazards regression (method: backward stepwise) was used to identify independent predictors of residual or recurrent AF at follow-up. For each variable, the hazard ratio (HR) and the corresponding 95%CI was calculated; the proportional hazards assumption was verified with the Schoenfeld residuals test. Non-parametric estimates and curves for survival (including in-hospital deaths) and freedom from hospital readmission due to CHF, stroke, major hemorrhagic events, PPM, AF, and recurrent AF at follow-up, as well as for freedom from any anti-arrhythmic drug(s) and oral anticoagulation were prepared using the Kaplan-Meier method. Both EuroSCORE II and covariates-adjusted estimates (Cox regression) for survival (including in-hospital deaths) were also calculated. Finally, nonparametric curves for freedom from AF at follow-up according to each variable with a P-value < 0.05 at the Cox regression were prepared using the Kaplan-Meier method and compared with the log-rank test. A P-value < 0.05 was considered significant. Data analysis was performed using the SPSS software for Windows, version 13.0 (SPSS, Inc., Chicago, IL, USA).

### 3. Results

In 25% of patients there was an expected operative risk (by EuroSCORE II) of 7.7% or more. At least one cerebral embolic event was documented, preoperatively, in 5.1% of subjects, and the mean expected risk of stroke per year (by CHA<sub>2</sub>DS<sub>2</sub>-VASc score) was of almost 4%. There was a median delay of three years (mean, 2.9  $\pm$  4 years) between the AF-onset and cryoablation of AF. MV repair or replacement was performed in 60.2% and 39.8% of patients, respectively. Concomitant LA appendage obliteration, TV annuloplasty, and CABG were carried out in 36.4%, 70.3% and 25.4% of cases, respectively (Tables 1–5).

#### 3.1. In-hospital outcomes

There were 7 (5.9%) hospital deaths: One patient died immediately after MV replacement because of left ventricular rupture; Six patients died within 30 days from operation due to low cardiac output syndrome (in 5 patients there was a LVEF < 50%). Prolonged invasive ventilation, multiple blood transfusion, and mediastinal re-entry were the most frequent (>10%) major complications after surgery. Permanent neurological dysfunctions, persistent arrhythmias requiring PPM, acute kidney injury requiring renal replacement treatment, and sepsis occurred in 1.7%, 5.9%, 1.7% and 2.5% of cases, respectively (Table 6).

#### 3.2. Predictors of AF at hospital discharge

Of 111 hospital discharged patients, cardiac rhythm at discharge was stable SR in 78 (70.3%) cases and AF in 33 (29.7%).

**Table 1**  
Baseline characteristics of patients, MV disease (etiology and lesion) and cardiac rhythm at hospital discharge.<sup>†</sup>

Variable	n = 118 <sup>‡</sup>	AF n = 33	SR n = 78	P
Period of surgery				0.02
[2005–2008]	50 (42.4)	8 (24.2)	37 (47.4)	
[2009–2012]	39 (33.1)	11 (33.3)	26 (33.3)	
[2013–2017]	29 (24.6)	14 (42.4)	15 (19.2)	
Age (yr)	66.5 ± 9	66.4 ± 8.3	65.9 ± 9.4	0.781
Female	58 (49.2)	19 (57.6)	34 (43.6)	0.254
Hypertension on drug treatment	50 (42.4)	14 (42.4)	31 (39.7)	0.959
Body mass index (kg/m <sup>2</sup> )	25.4 ± 4	25.9 ± 4.9	25.3 ± 3.5	0.477
Diabetes mellitus	16 (13.5)	5 (15.2)	10 (12.8)	0.865
Anemia <sup>§</sup>	24 (20.3)	7 (21.2)	14 (17.9)	0.892
Chronic obstructive pulmonary disease	12 (10.2)	4 (12.1)	7 (9)	0.873
Extracardiac arteriopathy	11 (9.3)	2 (6.1)	7 (9)	0.894
eGFR (ml/min) <sup>#</sup>	65.2 ± 25.6	70.7 ± 27.3	65.3 ± 24.2	0.305
MV disease: Etiology				0.140
Rheumatic	26 (22)	10 (30.3)	15 (19.2)	
Degenerative	51 (43.2)	13 (39.4)	35 (44.9)	
Ischemic (pure)	13 (11)	1 (3)	10 (12.8)	
Myxomatous	9 (7.6)	2 (6.1)	7 (9)	
Congenital	3 (2.5)	0	3 (3.8)	
Dilated cardiomyopathy	3 (2.5)	0	2 (2.6)	
Mixed <sup>  </sup>	13 (11)	7 (21.2)	6 (7.7)	
MV disease: Lesion				0.341
Stenosis	22 (18.6)	6 (18.2)	15 (19.2)	
Regurgitation	71 (60.2)	17 (51.5)	49 (62.8)	
Mixed	25 (21.2)	10 (30.3)	14 (17.9)	
Tricuspid regurgitation (functional)	74 (62.7)	19 (57.6)	51 (65.4)	0.573
Aortic valve disease (mild)	8 (6.8)	3 (9.1)	5 (6.4)	0.922
AF				0.704
Paroxysmal <sup>**</sup>	42 (35.6)	13 (39.4)	25 (32.1)	
Persistent <sup>**</sup>	55 (46.6)	15 (45.5)	42 (53.8)	
Long-standing <sup>**</sup>	21 (17.8)	5 (15.1)	11 (14.1)	
AF: delay between onset and cryoablation (yr)	1.1 [0.3–4]	1 [0.3–6]	1.1 [0.3–3.3]	0.998
NYHA class				0.938
I	15 (12.7)	4 (12.1)	10 (12.8)	
II	35 (29.7)	10 (30.3)	24 (30.8)	
III	54 (45.8)	16 (48.5)	34 (43.6)	
IV	14 (11.9)	3 (9.1)	10 (12.8)	
CCS class 4	10 (8.5)	2 (6.1)	7 (9)	0.894
LVEF (%)	55.9 ± 11.2	53.1 ± 10.7	57.8 ± 11.1	0.045
Recent myocardial infarction	5 (4.2)	2 (6.1)	2 (2.6)	0.729
PAP systolic (mmHg)	66.9 ± 13.8	67 ± 10.5	65.9 ± 15.2	0.910
Cardiac reoperation	7 (5.9)	0	6 (7.7)	0.238
Cerebral embolism (documented)	5 (4.2)	3 (9.1)	2 (2.6)	0.310
Risk of stroke per year (by CHA <sub>2</sub> DS <sub>2</sub> -VASc score) <sup>††</sup>	2.6 ± 1.3	2.7 ± 1.4	2.4 ± 1.3	0.328
Critical preoperative state	1 (0.8)	1 (3)	0	0.656
Surgical priority				0.512
Elective	92 (78)	24 (72.7)	62 (79.5)	
Urgent	25 (21.2)	9 (27.3)	16 (20.5)	
Emergency	1 (0.8)	0	0	
Expected operative risk (by EuroSCORE II) (%) <sup>†††</sup>	3.5 [1.7–6.8]	3.5 [1.7–4.7]	2.8 [1.7–6.8]	0.772

AF = atrial fibrillation; CCS = Canadian Cardiovascular Society; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive heart failure-Hypertension-Age ≥ 75 years [doubled]-type 2 Diabetes-previous Stroke, transient ischemic attack, or thromboembolism [doubled]-Vascular disease-Age 65–75 years-Sex category; eGFR = estimated glomerular filtration rate; EuroSCORE II = European System for Cardiac Operative Risk Evaluation II; IQR = interquartile range; LVEF = left ventricular ejection fraction; MV = mitral valve; NYHA = New York Heart Association; PAP = pulmonary artery pressure; SD = standard deviation; SR = stable sinus rhythm.

<sup>\*</sup> Values are number of patients with corresponding percentage, mean ± SD, or median with IQR in brackets.

<sup>†</sup> Definitions and cutoff values are those used for EuroSCORE II.

<sup>‡</sup> Seven patients died in hospital following operation.

<sup>§</sup> Defined as haemoglobin <12 g/dl for women, and <13 g/dl for men.

<sup>#</sup> The creatinine clearance rate, calculated according to the Cockcroft-Gault formula, was used for approximating GFR.

<sup>||</sup> Ischemic plus rheumatic, degenerative or myxomatous.

<sup>\*\*</sup> Ref. [1].

<sup>††</sup> Ref. [34].

<sup>†††</sup> Ref. [33].

According to the univariable analysis (Tables 1–6), operation carried out between 2013 and 2017, higher LA volume index (LAVI), lower preoperative left ventricular ejection fraction (LVEF), mixed etiology of MV disease, and use of Custodiol-HTK solution were associated ( $P < 0.05$ ), or tended to be associated ( $P = 0.05–0.1$ ), with an increased risk of hospital discharge on AF. Higher preoperative

LAVI (OR = 1.07, 95%CI: 1.01–1.13,  $P = 0.017$ ) and mixed etiology of MV disease (OR = 4.19, 95%CI: 1.23–14.2,  $P = 0.038$ ) were predictors of hospital discharge on AF according to the multivariable analysis. Following the receiver-operating characteristic curve analysis, the LAVI value corresponding with the Youden index J was 85 ml/m<sup>2</sup> (Suppl. Table S2).

**Table 2**  
Other preoperative echocardiographic parameters.\*

Parameter	n = 118 <sup>†</sup>	AF n = 37	SR n = 74	P
LA diameter (mm)	51.3 ± 9.3	51.5 ± 8.6	51.0 ± 8.7	0.896
LAV (ml)	137.8 ± 63	161.4 ± 65.4	126.9 ± 59.7	0.061
LAVI (ml/m <sup>2</sup> )	76.3 ± 35.7	89.7 ± 40	70.2 ± 32.3	0.061
RAV (ml)	56.8 ± 24	62.9 ± 28	54 ± 21.7	0.206
RAVI (ml/m <sup>2</sup> )	31.2 ± 13.4	34.5 ± 16	29.6 ± 11.9	0.218
LVEDVI (ml/m <sup>2</sup> )	60.3 ± 26.1	56.9 ± 30.6	61.2 ± 24.1	0.506
LVESVI (ml/m <sup>2</sup> )	28.4 ± 21.1	27.7 ± 27.6	28.3 ± 17.7	0.863

AF = atrial fibrillation; LA = left atrial; LAVI = left atrial volume index; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; RA = right atrial; RAVI = right atrial volume index; SD = standard deviation; SR = stable sinus rhythm.

\* Values are mean ± SD.

<sup>†</sup> Seven patients died in hospital following operation.

**Table 3**  
Surgical techniques, operative data and cardiac rhythm at hospital discharge.\*

Variable	n = 118 <sup>†</sup>	AF n = 33	SR n = 78	P
Surgical approach				0.656
Median sternotomy	116 (98.3)	33 (100)	77 (98.7)	
Right thoracotomy	2 (1.7)	0	1 (1.3)	
MV surgery				0.147
Replacement	47 (39.8)	17 (51.5)	27 (34.6)	
Repair	71 (60.2)	16 (48.5)	51 (65.4)	
Mitral prosthetic device				0.358
Biological valve	38 (32.2)	13 (39.4)	22 (28.2)	
Mechanical valve	9 (7.6)	4 (12.1)	5 (6.4)	
Annuloplasty ring	70 (59.3)	16 (48.5)	50 (64.1)	
None	1 (0.8)	0	1 (1.3)	
Mitral orifice area index (cm <sup>2</sup> /m <sup>2</sup> )				0.378
1.5–2.0	17 (21.8)	7 (21.2)	9 (11.5)	
2.0–2.5	45 (38.1)	10 (30.3)	30 (38.5)	
>2.5	56 (47.5)	16 (48.5)	39 (50)	
TV surgery				0.867
Suture annuloplasty	7 (5.9)	1 (3)	4 (5.1)	
Ring annuloplasty	76 (64.4)	24 (72.7)	54 (69.2)	
None	35 (29.7)	8 (24.2)	20 (25.6)	
LA appendage obliteration	43 (36.4)	13 (39.4)	28 (35.9)	0.894
CABG	30 (25.4)	9 (27.3)	18 (23.1)	0.819
Length of surgery (min)	298.6 ± 72.1	287.2 ± 68.2	303.1 ± 74.1	0.298
Cardiopulmonary bypass time (min)	163.8 ± 43.4	163.4 ± 44.2	161.8 ± 39.2	0.850
Aortic cross-clamp time (min)	126.6 ± 30.9	125.4 ± 28.0	128.3 ± 32.3	0.664
Cardioplegia				0.021
Multidose cold blood	59 (50)	10 (30.3)	44 (56.4)	
Custodiol <sup>®</sup> -HTK solution <sup>‡</sup>	59 (50)	23 (69.7)	34 (43.6)	

AF = atrial fibrillation; CABG = coronary artery bypass grafting; HTK = histidine-tryptophan-ketoglutarate; LA = left atrial; MV = mitral valve; SD = standard deviation; SR = stable sinus rhythm; TV = tricuspid valve.

\* Values are number of patients with corresponding percentage, or mean ± SD.

<sup>†</sup> Seven patients died in hospital following operation.

<sup>‡</sup> Essential Pharma, Newtown, PA, USA.

**Table 4**  
Cardiac rhythm after aortic cross-clamp removing, in-hospital anti-arrhythmic treatment and cardiac rhythm at hospital discharge.\*

Variable	n = 118 <sup>†</sup>	AF n = 33	SR n = 78	P
Rhythm after cross-clamp removing				0.356
SR	93 (78.8)	29 (87.9)	62 (79.5)	
AF	9 (7.6)	0	4 (5.1)	
Paced	16 (13.6)	4 (12.1)	12 (15.4)	
Anti-arrhythmic treatment				0.265
Amiodarone	87 (73.7)	25 (75.8)	59 (75.6)	
Amiodarone + β-Blocker agent or Ca <sup>2+</sup> -channel blockers	24 (20.3)	8 (24.2)	12 (15.4)	
Amiodarone + β-Blocker agent + Electrical cardioversion	3 (2.5)	0	3 (3.8)	
None	4 (3.4)	0	4 (5.1)	

AF = atrial fibrillation; SR = stable sinus rhythm.

\* Values are number of patients with corresponding percentage.

<sup>†</sup> Seven patients died in hospital following operation.

**Table 5**  
Perioperative drugs and cardiac rhythm at hospital discharge.\*

Drug	n = 118 <sup>†</sup>	AF n = 33	SR n = 78	P
<b>Preoperative</b>				
Anti-arrhythmic				0.216
Digoxin	22 (18.6)	3 (9.1)	18 (23.1)	
β-Blockers	18 (15.3)	4 (12.1)	11 (14.1)	
Ca <sup>2+</sup> -channel blockers	4 (3.4)	0	4 (5.1)	
Amiodarone	70 (89.7)	25 (75.8)	43 (55.1)	
Other <sup>‡</sup>	4 (3.4)	1 (3)	2 (2.6)	
Anti-hypertensive				
ACE-inhibitors	46 (39)	14 (42.4)	23 (29.5)	0.271
Diuretics	14 (11.9)	3 (9.1)	11 (14.1)	0.679
β-Blockers	18 (15.3)	4 (12.1)	11 (14.1)	0.980
Ca <sup>2+</sup> -channel blockers	4 (3.4)	0	4 (5.1)	0.443
Catecholamines <sup>§</sup>	3 (2.5)	1 (3)	5 (6.4)	0.794
Intravenous nitrates <sup>§</sup>	12 (10.2)	3 (9.1)	8 (10.3)	0.873
Antiplatelet	42 (35.6)	11 (33.3)	25 (32.1)	0.928
Anti-coagulant <sup>§</sup>				0.894
Oral anticoagulant	1 (0.8)	0	0	
Heparin (subcutaneous)	107 (90.7)	31 (93.9)	71 (91)	
Heparin (intravenous)	10 (8.5)	2 (6.1)	7 (9)	
<b>Intraoperative/Postoperative</b>				
Catecholamines				
Dobutamine	98 (83.1)	29 (87.9)	64 (82.1)	0.631
Epinephrine	9 (7.6)	3 (9.1)	2 (2.6)	0.310
Norepinephrine	56 (47.5)	19 (57.6)	33 (42.3)	0.206

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; SR = stable sinus rhythm.

\* Values are number of patients with corresponding percentage.

† Seven patients died in hospital following operation.

‡ Quinidine, Flecainide or Propafenone.

§ Early before surgery.

**Table 6**  
Postoperative complications, hospital course of patients and cardiac rhythm at hospital discharge.\*

Postoperative complication	n = 118 <sup>†</sup>	AF n = 33	SR n = 78	P
<b>Neurological dysfunction</b>				
Transitory	6 (5.1)	1 (3)	4 (5.1)	0.713
Permanent	2 (1.7)	0	1 (1.3)	
None	110 (93.2)	32 (97)	73 (93.6)	
Prolonged (>48 hr) invasive ventilation	16 (13.5)	5 (15.2)	8 (10.3)	0.682
<b>No. of episodes of supraventricular tachyarrhythmias</b>				
0	85 (72)	22 (66.7)	57 (73.1)	0.488
1	10 (8.5)	3 (9.1)	6 (7.7)	
2	13 (11)	3 (9.1)	10 (12.8)	
≥3	10 (8.5)	5 (15.2)	5 (6.4)	
<b>High-grade atrioventricular block<sup>‡</sup></b>				
Transitory	12 (10.2)	4 (12.1)	8 (10.3)	0.533
Permanent <sup>‡</sup>	8 (6.8)	1 (3)	7 (9)	
None	98 (83.1)	28 (84.8)	63 (80.8)	
Myocardial infarction	1 (0.8)	0	1 (1.3)	0.656
Acute kidney injury	13 (11)	3 (9.1)	9 (11.5)	0.964
48-hr Chest tube drainage/BSA (ml/m <sup>2</sup> )	417.7 (254.7–693.6)	371 (216.4–824.1)	430.4 (276.6–614.1)	0.867
<b>No. of transfused units of RBCs</b>				
0	47 (39.8)	15 (45.5)	40 (51.3)	0.650
1–2	48 (40.7)	14 (42.4)	26 (33.3)	
≥3	23 (19.5)	4 (12.1)	12 (15.4)	
Pericardial effusion	6 (5.1)	1 (3)	5 (6.4)	0.794
Mediastinal re-entry	16 (13.5)	4 (12.1)	9 (11.5)	0.814
<b>Infection</b>				
Focal	15 (12.7)	3 (9.1)	12 (15.4)	0.673
Sepsis	3 (2.5)	1 (3)	2 (2.6)	
None	100 (84.7)	29 (87.9)	64 (82.1)	
Any complication	82 (69.5)	20 (60.6)	55 (70.5)	0.425
Any major complication	35 (29.7)	10 (30.3)	18 (23.1)	0.574
Length of hospital stay (d)	12 (8–17)	13 (9–18)	12 (8–17)	0.574
Intensive care unit stay (d)	2 (1–4)	2 (1–4)	2 (1–3)	0.339

AF = atrial fibrillation; BSA = body surface area; IQR = interquartile range; PPM = permanent pacemaker; RBCs = packed red blood cells; RRT = renal replacement therapy; SR = stable sinus rhythm.

\* Values are number of patients with corresponding percentage, or median with IQR in brackets.

† Seven patients died in hospital following operation.

‡ Requiring PPM.

### 3.3. Late outcomes

Follow-up was complete for 118 (100%) patients. During the follow-up period (median, 6.6 years; mean,  $6.6 \pm 3.8$  years; range, 0.3–13.7 years; cumulative, 774.1 patient-years), there were 38 deaths (4.9 per 100 patient-years); preoperative systemic hypertension on drug treatment (HR = 4.16, 95%CI: 2.07–8.38,  $P = 0.0001$ ), lower glomerular filtration rate estimated by the Cockcroft-Gault formula (HR = 0.92, 95%CI: 0.94–0.96,  $P < 0.0001$ ) and lower LVEF (HR = 0.93, 95%CI: 0.9–0.95,  $P < 0.0001$ ) were independent predictors of death. The 1, 5, and 10-year EuroSCORE II-adjusted survival after surgery was 93.6%, 87% and 58.9%, respectively; the 1, 5, and 10-year covariates-adjusted survival after surgery was 97.8%, 94.2% and 68.5%, respectively (Suppl. Table S3; Suppl. Fig. S2A).

Twenty-four hospital discharged patients experienced at least one hospital readmission due to CHF; six patients suffered from a stroke and other six from a major hemorrhagic event. At least moderate mitral regurgitation or stenosis was demonstrated in 26 patients and two of them underwent repeated MV operation (2 other patients underwent percutaneous aortic valve implantation) (Suppl. Fig. S2B–D).

### 3.4. Cardiac rhythm at follow-up

At least one postoperative monitoring of the cardiac rhythm with Holter recording was performed for 109 subjects (2 patients died within 6 months after discharge). Of 111 hospital discharged patients, cardiac rhythm at follow-up was stable SR in 74 (66.7%) cases and AF in 37 (33.3%). According to the Cox regression analysis, higher preoperative values of systolic pulmonary artery pressure (PAP systolic; HR = 1.04, 95%CI: 1.01–1.08,  $P = 0.016$ ) and hospital discharge on AF (HR = 4.14, 95%CI: 1.50–11.4,  $P = 0.0062$ ) were associated with an increased risk of AF at follow-up; higher levels of PAP systolic were associated with an increased risk of recurrent AF (HR = 1.06, 95%CI: 1.01–1.12,  $P = 0.027$ ). Following the receiver-operating characteristic curve analysis, the PAP systolic value corresponding with the Youden index J was of 60 mmHg. The 1, 5, and 10-year covariates-adjusted freedom from AF at follow-up was 98.1%, 89.2% and 45.6%, respectively (Suppl. Tables S4,5; Fig. 1).

Of 118 patients, 24 received a PPM after surgery, 10 (8.5%) within hospital discharge (9 for atrioventricular block or sinus bradycardia/arrest, and 1 for low frequency AF) and other 14 during the follow-up period (10 for an atrioventricular block or sinus bradycardia/arrest, and 4 for AF with slow ventricular rate). For patients undergoing concomitant TV annuloplasty, there was a trend towards receiving a PPM (HR = 2.17, 95%CI: 0.94–4.98,  $P = 0.111$ ) (Suppl. Fig. 3A, B).

### 3.5. Freedom from anti-arrhythmic drug therapy and oral anticoagulation

Any anti-arrhythmic drugs were ceased in 31 cases during the follow-up period. After having documented an effective atrial contraction by echocardiographic examination, oral anticoagulation was terminated in 35 subjects (Suppl. Fig. 4A,B) (Table 7).

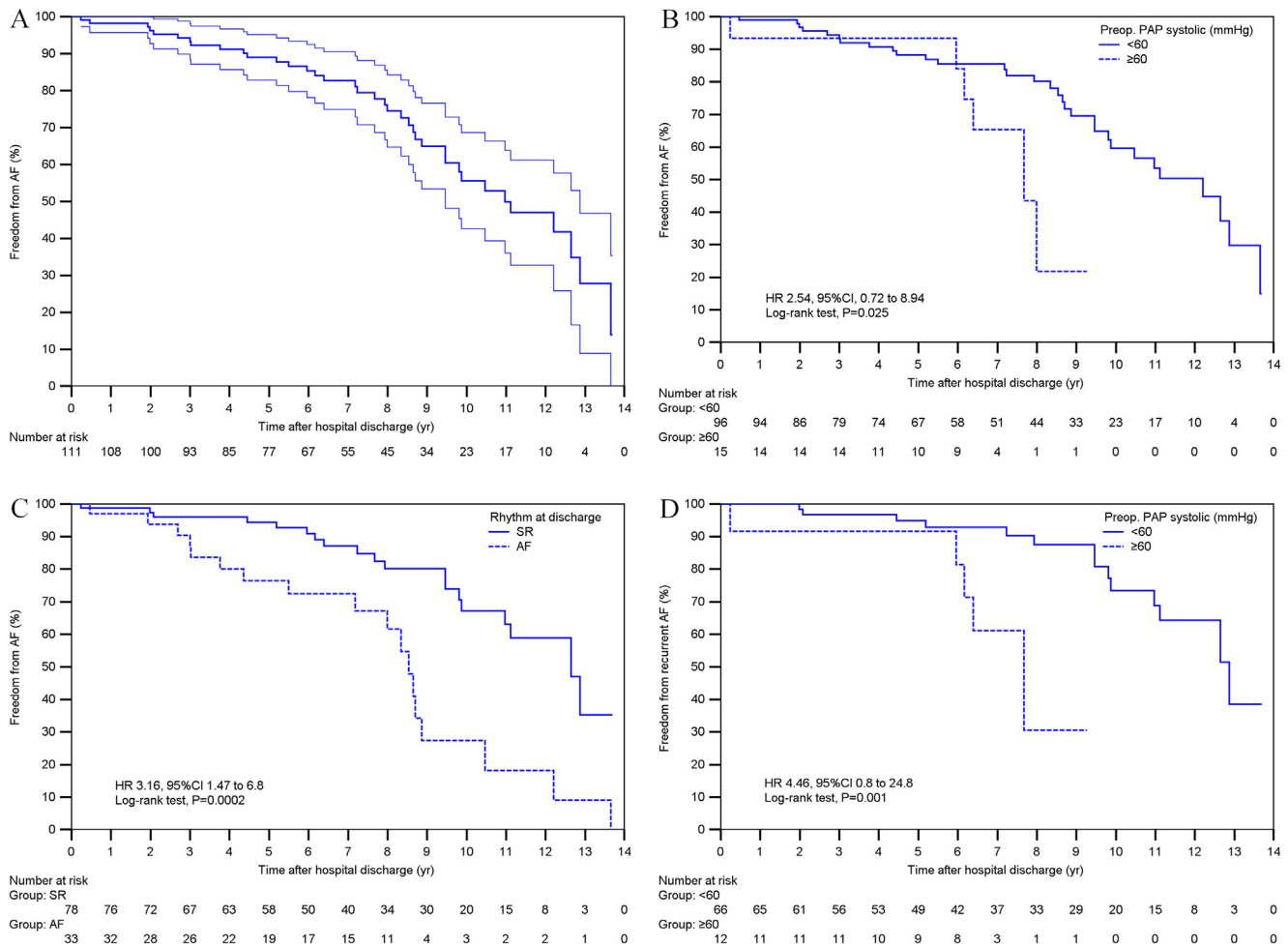
## 4. Discussion

Immediate and long-term outcomes of a selected series of patients undergoing surgical treatment of paroxysmal/persistent AF during MV surgery were reviewed retrospectively in this study. The inclusion criteria were: (1) MV approach (median sternotomy or right thoracotomy); (2) energy source for treating AF (cryother-

mal energy employing Argon); (3) set of atrial lesions (limited to only the LA); and, finally, (4) other concomitant cardiac operations (CABG and/or TV annuloplasty). Mini-thoracotomy, energy sources other than cryothermal energy, more complex sets of surgical incisions involving both atria, as well as concurrent aortic valve procedures and combined left ventricular restorative operations were adopted as exclusion criteria. This step was taken so that all post-operative changes in cardiac rhythm, volumes, and function could be attributed exclusively to isolated LA cryoablation and conventional MV surgery (and CABG and/or TV annuloplasty, when performed).

The most important findings of the study were the following: (1) a simplified set of cryo-lesions that was limited to only the LA yielded good, immediate and long-term outcomes after MV surgery, and comparable with those of more complex sets of lesions involving both atria; (2) out of the considered variables, the sole independent predictors of AF at follow-up were higher preoperative PAP systolic values and hospital discharge on AF; (3) out of the considered variables, higher preoperative LA size (based on LAVI but not on LA diameter) and mixed etiology of MV disease were independent predictors of hospital discharge on AF; (4) while the LA did not dilate significantly during the follow-up period both according to LA diameter and LAVI, the right atrium increased significantly from 5 to 10 years after surgery ( $P = 0.0016$ ); there was also a trend towards higher values of PAP systolic ( $P = 0.18$ ). As no ablation involved the right atrium in this study, this fact could be used as argument to sustain biatrial ablation to prevent right atrial dilation on a long-term basis. A significant reduction of LVEF ( $P = 0.033$ ) between preoperative and postoperative echocardiographic evaluation was observed at three months after surgery. This fact may be due to preoperative overestimate of LVEF in the presence of mitral regurgitation and to more extended use of  $\beta$ -blockers after surgical correction.

Since 2005 the present authors are using cryothermal energy employing Argon for every patient undergoing surgery of AF at their institution. Ice crystals caused by cryoablation produce acute disruption of cell membranes and the microvascular injury leads to local tissue ischemia. As this mechanism has the benefit of preserving the myocardial fibrous skeleton and collagen structure, cryoablation is safe for use around valvular tissue. There is also evidence that induction of apoptosis plays a role in late lesion expansion. Lesion size and depth depend on the probe temperature, the duration of the ablation, the thermal conductivity and temperature of the tissue, and the choice of cooling agent. Commercially available sources of cryothermal energy employ either nitrous oxide (Atri-Cure, Cincinnati, Ohio) or Argon (like in this study). Although the nitrous oxide technology has a well-defined efficacy and safety profile, some degree of late intimal hyperplasia of the coronary arteries after cryoablation has been shown. Potential drawbacks of cryoablation are the relatively long time it requires (1–3 min for each lesion), the difficulty encountered in creating transmural lesions on the beating heart, and the risk of thromboembolism when the blood is frozen during epicardial ablation on the beating heart. Yet, despite several studies on the topic, no hypothetical superiority of cryothermal energy over bipolar radiofrequency, or vice versa, has been proven. The last two disadvantages of cryoablation do not apply to the present on-pump surgical experience where the cryo-lesions were performed on cardioplegic and totally unloaded hearts. Also, as all of the lesions were carried out during only two probe applications (in total 4 min), the time of ablation was minimized. In cardiac surgery, as well as for every surgical discipline, prolonged times of surgery are associated with increased risk of poor outcomes. Consequently, brief operative times (when possible) are recommended for every surgical procedure, both for MV operation and ablation of AF. Obviously, as to concerns surgery of AF, quality of the lesions should be top priority.



**Fig. 1.** Nonparametric curves of freedom from (A) AF at follow-up, (B) AF at follow-up according to the presence of preoperative pulmonary hypertension, (C) AF at follow-up according to cardiac rhythm at hospital discharge, and (D) recurrent AF at follow-up according to the presence of preoperative pulmonary hypertension. The number of patients at risk was reported. The 95%CI was shown. The 1, 5 and 10-year nonparametric estimates of freedom from AF at follow-up were: 98.2% (95%CI: 96.9%–99.5%), 89% (95%CI: 85.9%–92.1%), and 55.6% (95%CI: 48.9%–62.3%), respectively. AF = atrial fibrillation; 95%CI = 95% confidence interval; HR = hazard ratio; PAP = pulmonary artery pressure; SR = stable sinus rhythm.

**Table 7**  
Echocardiographic changes during the follow-up period.\*

Variable	Preoperative-to-3-month follow-up			1/4-to-1-Year follow-up			1-to-5-Year follow-up			5-to-10-Year follow-up		
	Preoperative	3-Month	P	3-Month	1-Year	P	1-Year	5-Year	P	5-Year	10-Year	P
No. of patients at risk	111 <sup>†</sup>	111		111	108		108	77		77	23	
Rhythm			<.0001			0.998			0.972			0.964
SR	0	74 (66.7)		74 (66.7)	73 (67.6)		73 (67.6)	51 (66.2)		51 (66.2)	16 (69.6)	
AF	111 (100)	37 (33.3)		37 (33.3)	35 (32.4)		35 (32.4)	26 (33.8)		26 (33.8)	7 (30.4)	
LA diameter (mm)	51.5 ± 9.3	51.6 ± 9.3	0.810	51.6 ± 9.3	51.6 ± 9.3	1.000	51.6 ± 9.3	52.2 ± 9.5	0.708	52.2 ± 9.5	55 ± 10.6	0.241
LAVI (ml/m <sup>2</sup> )	76.3 ± 35.7	77.8 ± 36.3	0.757	77.8 ± 36.3	77.8 ± 36.3	1.000	77.8 ± 36.3	86.4 ± 38	0.300	86.4 ± 38	96.6 ± 43.7	0.464
RAVI (mlm <sup>2</sup> )	31.2 ± 13.4	31 ± 13.7	0.912	31 ± 13.7	31.3 ± 13.7	0.916	31.3 ± 13.7	32.6 ± 14.6	0.686	32.6 ± 14.6	39.8 ± 14.9	0.0016
LVEDVI (ml/m <sup>2</sup> )	56.5 ± 23.7	62.2 ± 26.5	0.442	62.2 ± 26.5	62.2 ± 26.5	1.000	62.2 ± 26.5	62.4 ± 29.5	0.978	62.4 ± 29.5	66 ± 36.3	0.726
LVESVI (ml/m <sup>2</sup> )	25.1 ± 15.9	29.7 ± 21.6	0.127	29.7 ± 21.6	29.7 ± 21.6	1.000	29.7 ± 21.6	30.1 ± 23.5	0.935	30.1 ± 23.5	27.5 ± 16.4	0.711
LVEF (%)	57.1 ± 12.7	54.6 ± 12	0.033	54.6 ± 12	54.6 ± 12	1.000	54.6 ± 12	54.2 ± 12.1	0.819	54.2 ± 12.1	52.1 ± 12.2	0.468
PAP systolic (mmHg)	43.7 ± 16.8	33.3 ± 11.7	0.206	33.3 ± 11.7	33.3 ± 11.7	1.000	33.3 ± 11.7	35.1 ± 12.4	0.626	35.1 ± 12.4	42.2±20.8	0.180

AF = atrial fibrillation; SR = stable sinus rhythm; LA = left atrial; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; PAP = pulmonary artery pressure; SD = standard deviation.

\* Values are number of patients with corresponding percentage in brackets, or mean ± SD.

<sup>†</sup> Of 118 study patients, seven died in hospital following operation and other seven were hospital discharged with PM-induced rhythm.

Throughout the years, simplified sets of atrial lesions have been proposed to treat AF. As the majority of proxysmal foci of AF appear to originate from the pulmonary veins and the LA wall all

around [36], several authors have suggested performing lesion sets confined to only the LA [36–40]. However, there is counteracting evidence on this topic today. While recent studies are providing



increasing evidence that indicates that LA lesion set is as effective as biatrial lesion set in patients with chronic AF undergoing concomitant open-heart surgical procedures [13,16,18], a meta-analysis of the published Literature (in total 69 studies and 5885 patients; period, 1995–August 2005) [41], as well as a propensity score-matched analysis performed on an original series of 284 patients operated on from 2006 through 2009 [42], have shown that biatrial lesion set results in a significantly higher late freedom from AF when compared with LA lesion set alone ( $P = 0.05$  and  $0.005$ , respectively). This fact would be not surprising considering that some studies of intraoperative mapping of patients with AF have shown that AF originates from the LA in approximately 80% of cases [43,44]. Actually, the importance of the LA lesions of the traditional Cox-Maze procedure is difficult to define and, to date, there are no randomized trials of biatrial versus LA ablation in the surgical population. It should also be kept in mind that recurrent atrial flutter or tachycardia is a well-known complication of performing only the LA lesions that have been reported in as many as 13%–21% of patients undergoing the procedure [37,45]. On the other hand, there is some consensus that the addition of right atrial lesions to a lesion set limited to only the LA would be associated with an increased risk of sinus node dysfunction and PPM implantation [13,46]. Moreover, it is complicated to establish the specific weight of each LA lesion of the Cox-Maze procedure in preventing late recurrence of AF. While all of the surgeons agree on the importance of isolating the pulmonary veins, there is no unanimous consensus on the role of the LA isthmus, though Gillinov and colleagues have shown the importance of the LA isthmus in a retrospective study [47]. In the aforementioned randomized trial [36], Gaita and colleagues have shown the superiority of two alternate lesion sets that included the ablation of the LA isthmus over pulmonary vein isolation alone ( $P < 0.0006$ ). In the present experience, both bilateral encircling of the pulmonary veins and ablation of the LA isthmus were carried out. However, there was only one connecting line for the two pulmonary veins boxes, and the line connecting the left box to the LA appendage was waived. Consequently, the LA lesion set was simplified with respect to that of the standard Cox-Maze procedure [6]. Nevertheless, the 1 and 5-year freedom from AF at follow-up of this experience (98.1% and 89.2%, respectively) were comparable (or compared favorably) with those of other studies of Literature [10–32] where either biatrial (75% to 91% and 80.2%, respectively) or isolated LA ablation (57.8% to 95% and 72% to 81.1%, respectively) was performed. The present authors have no convincing arguments to give reason of these good results, which were consistent with the higher rate of dismissal of any anti-arrhythmic drug of this experience with respect to other experiences (97.3% vs. 63% to 88.4%, at 1 year from hospital discharge) [10–32]. These results were even more unexpected considering that the line connecting the left pulmonary veins box to the LA appendage was waived and that an endocardial purse-string suture was used to perform the LA appendage obliteration (when performed). The LA appendage may play indeed an important role in patients with (especially persistent) AF. In contrast to LA appendage clipping (with specific automatic stapler) or amputation (cut and sew), endocardial closure has been reported to be associated with a higher risk of residual leakage (especially in MV patients) and do not result in electrical isolation of the LA appendage. Despite these considerations, however, the rates of embolic stroke and recurrent AF of this study were both not higher than those of other experiences. Actually, in the literature, there is a relative lack of information concerning specifically the ablation of AF in isolated MV surgery (i.e., not combined with aortic valve operations), and it is known that the probability of success of surgery of AF in the case of concomitant correction both of mitral and aortic valvulopathy is higher than that of concomitant treatment of mitral valve disease alone [21]. Also the higher rate of

patients of the study who died in-hospital (5.9% [5.3% ± 5.2% by EuroSCORE II] vs. 0–3% of Literature [10–32]), and the fact that these high-risk subjects were (obviously) excluded from the calculation of the nonparametric estimates of freedom from AF at follow-up, may have improved the results significantly. Incidentally, the increased rate of in-hospital deaths of the present study was ascribed by the authors to the frequent (21.2%) presence of ischemic heart disease among the causes of MV disease, to the high rate of urgent surgical priority (25.4%), and to the prolonged time of surgery (an average of 5 h). No in-hospital death was directly or indirectly due to ablation of AF.

According to this analysis, higher preoperative values of PAP systolic and hospital discharge on AF were associated with an increased risk of AF at follow-up; higher preoperative levels of PAP systolic were associated with an increased risk of recurrent AF. However, older age and comorbidities such as systemic hypertension, chronic obstructive pulmonary disease, and morbid obesity, as well as rheumatic etiology of MV disease, MV disease alone, cardiac (or MV) reoperation, permanent AF, long duration of AF (>10 years), LA dilation (>50, 50.5, or 70 mm), left ventricular dysfunction (LVEF < 37.5%), the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and EuroSCORE II, the type of MV surgery, and residual/recurrent significant MV disease were not risk factors for AF at follow-up; the role of preoperative use of  $\beta$ -blockers as a predictor of success was not confirmed; the role of C-reactive protein (>12 mg/dl) and F-wave in V1 < 0.1 mV as predictor of failure was not evaluated because of the lack of the data [10–32]. The present authors have no convincing arguments to explain this fact, even though the limited number of patients enrolled in the study, the low frequency of the event of interest (recurrence of AF), the brief interval between AF-onset and cryoablation (median, 3 years), as well as the wide range of LA size could all have contributed significantly to the results. The 1-year freedom from stroke was the same as that of other investigations (99.1% vs. 94–100%) [10–32]. The higher rate of dismissal of oral anticoagulation of the study (97.3% vs. 21.7–75% at 1 year) may explain the low rate of major hemorrhagic events (0.9% at 5 years and 10.2% at 10 years) [10–32].

The rate of hospital discharge on stable SR of this study (70.3%) was comparable with that of other studies of literature (66.2–91.2% for isolated LA ablation, 29–97.6% for biatrial ablation) [10–32]. Higher preoperative LAVI values and mixed etiology of MV disease were independent predictors of hospital discharge on AF. At the present authors' institution, the rate-control strategy (using drugs) is being preferred in treating AF in the postoperative setting. The three patients who underwent electrical cardioversion for AF suffered from postoperative low cardiac output and electrical cardioversion was performed to achieve hemodynamics improvement.

As expected, also in this study there was a high rate of heart rhythm disorders that needed PPM implantation, in-hospital or during the follow-up period. The actual rate of freedom from PPM at discharge (91.5%) and the actuarial rate of freedom from PPM at 5-year follow-up (84.1%) were comparable with those reported by other authors (95.5% and 82–96.2%, respectively) [10–32]. Indications to PPM were an atrioventricular block or sinus bradycardia/arrest (79.2%) and slow AF (20.8%). Of the patients with PPM, just under half received it before hospital discharge. Based on the results of a recent meta-analysis including 28 studies and 7065 patients, [48] indications to PPM were an atrioventricular block or sinus bradycardia/arrest in 82.9% of patients and bradyarrhythmia in 17.1% of cases; biatrial ablation led to an increased risk of PPM at 30-day follow-up with respect to isolated LA ablation (13.6% vs. 6.3%,  $P = 0.028$ ). Based on the results of a recent randomized trial [49], 14.4% of subjects received a PPM within the first year after surgery and 83% underwent implantation during the index hospitalization; the frequency of PPM implantation was

7.7% in patients randomized to MV surgery alone, 16.1% in MV surgery plus pulmonary vein isolation, and 25% in MV surgery plus biatrial ablation; AF ablation, multivalve surgery, and NYHA functional class III–IV were associated with an increased risk for permanent pacing. Although no specific multivariable analysis was performed in the present study, a trend ( $P = 0.111$ ) towards an increased risk of PPM implantation was found for patients in whom TV annuloplasty had been performed.

#### 4.1. Study limitations

This study suffers from several limitations that deserve to be underlined. First, it is a retrospective study performed on a limited (albeit well-selected) series of patients. Consequently, only a limited number of variables could be included in the Cox regression models and all of the inferences of the study may appear weakened. Second, the series of patients encompasses subjects who were operated on over 13 years by several surgeons. As the field of AF ablation is continually evolving, the techniques and technologies used for surgery and ablation have evolved significantly during such a long period. There may have been unrecognized changes also in clinical practice. Despite these considerations, however, there was no significant difference on the rate of AF at hospital discharge between the study patients enrolled in 2005 and those enrolled in 2016–2017 (Suppl. Table S6). Actually, according to the univariable (but not the multivariable) analysis, operation carried out between 2013 and 2017 was a risk factor for AF at discharge. Third, no comparisons between sources of energy for ablation of AF, or sets of atrial lesions, or concomitant surgical procedures could be performed. Cryothermal energy is indeed the only source of energy that was used at the present authors' institution during the study period, and the described LA lesions set is the only set that was adopted. No other sets of atrial lesions were used. Biatrial lesions were performed only in the rare cases of documented episodes of atrial flutter or supraventricular paroxysmal tachycardia; however, these cases were excluded *a priori* from the study. Thus, the comparison regarding outcomes after surgery was carried out with those of (rare) studies of Literature reporting results of concomitant ablation of AF in conventional MV surgery alone. Fourth, as patients undergoing concurrent aortic valve operations were ruled out from this study, which included only patients having CABG and/or TV annuloplasty as concomitant procedures, the observed arrhythmias might also be attributed to the last two procedures in addition to LA ablation and MV operation. Fifth, as continuous rhythm monitoring was not performed until discharge, patients with silent AF episodes may be missed. Finally, paroxysmal and persistent AF were both considered in the study. However, human mapping data has not shown significant differences in mechanism between the two types of AF. Because of these limitations, the present results should be considered in no way conclusive and should be verified on a prospective and multicenter basis.

#### 4.2. Insights from the study

The following insights might derive from the study: (1) the patients with MV disease of mixed etiology and severe preoperative LA dilation ( $LAVI > 85 \text{ ml/m}^2$ ) should be continuously monitored for heart rhythm until hospital discharge to miss no silent AF episodes; (2) electrical cardioversion (at least one attempt) should be performed before hospital discharge in all subjects with residual/recurrent AF; (3) the patients with SR at hospital discharge but severe preoperative LA dilation and/or pulmonary hypertension (PAP systolic  $> 60 \text{ mmHg}$ ) should undergo strict heart rhythm monitoring during the follow-up period; (4) for these patients, more complete sets of LA ablation that include the con-

necting line to the LA appendage, LA appendage clipping (or suture), as well as biatrial sets of lesions should be considered; (5) biatrial ablation should be considered also for patients with significant right atrial dilation (with or without TV disease, pulmonary hypertension, or right heart failure), even in the absence of prior episodes of atrial flutter or supraventricular paroxysmal tachycardia; finally, (6) as the increased risk of PPM implantation, a strict heart rhythm monitoring should be recommended during the follow-up period when a concomitant TV annuloplasty is performed.

#### 4.3. Conclusions

To treat AF during conventional MV surgery, a cryo-lesion set limited to only the LA may give good, early and late outcomes. The outcomes were also comparable with those of studies of Literature that explore results of biatrial ablation. Preoperative LA dilation and mixed etiology of MV disease were predictors of hospital discharge on AF. As AF at discharge and preoperative pulmonary hypertension combined with an increased risk of AF at follow-up, restoring SR before discharge is of the utmost importance to gain success of surgery even on a long-term basis. Further prospective multicenter studies are needed either to strengthen or to weaken the evidence of these findings.

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None.

#### Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

#### Appendix A. Supplementary data

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