Routine ganglionic plexi ablation during Maze procedure improves hospital and early follow-up results of mitral surgery

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Objective: Ganglionic plexi are claimed to be potentially responsible for atrial fibrillation. We evaluated whether ganglionic plexi isolation improves the results of the Maze procedure during mitral valve surgery.

Methods: A total of 75 patients with atrial fibrillation underwent radiofrequency ablation during mitral valve surgery without (group A) or with (group B) ganglionic plexi ablation with bipolar radiofrequency plus fat pad resection along the Waterston groove, left pulmonary veins, and Marshall's ligament. Ganglionic plexi were intraoperatively mapped, and fat pad specimens were sectioned and analyzed. Hospital and follow-up results were recorded. Amiodarone was discontinued at the sixth month.

Results: Active ganglionic plexi were mainly located in the upper parts of fat pads. Active specimens demonstrated more ganglionic plexi than inactive specimens ($P \leq .015$ at different levels) but did not correlate with atrial fibrillation recurrence ($P =$ not significant). Atrial fibrillation was higher in group A at aortic declamping ($P = .03$) and discharge ($P = .03$). Early events were comparable ($P = .565$). At 16.7 ± 0.95 (standard error) months, the cumulative freedom from atrial fibrillation, atrial flutter, and atrial tachycardia with antiarrhythmic therapy was $63.2\% \pm 7.3\%$ and proved higher in group B ($83.9\% \pm 7.9\%$ vs group A $52.8\% \pm 8.7\%$; $P = .035$). However, after the sixth month, at 12.8 ± 0.80 months, freedom from atrial fibrillation, atrial flutter, and atrial tachycardia without antiarrhythmic therapy was $72.5\% \pm 7.7\%$ and proved higher in group B ($92.9\% \pm 6.9\%$ vs $62.5\% \pm 9.4\%$; $P = .023$). A higher proportion of patients in group B showed normalized E/A ratio (61.3% vs group A 36.4% ; $P = .029$). No differences were detected in follow-up freedom from congestive heart failure (group A: $83.4\% \pm 7.0\%$ vs group B: $93.5\% \pm 4.4\%$; $P = .978$) and hospital readmission (group A: $84.2\% \pm 5.9\%$ vs group B: $92.6\% \pm 5.1\%$; $P = .376$).

Conclusion: Ganglionic plexi isolation can improve hospital and follow-up results during mitral valve surgery and possibly ameliorate echocardiographic recovery of atrial function during follow-up.

Since Cox proved that atrial fibrillation (AF) could be treated by means of surgery,¹ a growing number of modified "mini-Maze" procedures have been proposed to overcome the problems of complexity and prolonged operating time of the Cox-Maze III technique.^{2,3} Along with the demonstration by Haissaguerre and colleagues⁴ of the key role of ectopic triggers localized in the pulmonary veins, recent literature data also have shown a role of epicardial ganglionic plexi (GP), which are primarily found in the epicardial fat tissue of the upper half part of the heart, in determining or inducing AF.^{5,6} Accordingly, some articles from electrophysiologic groups have addressed the safety, feasibility, and efficacy of sinus rhythm (SR) recovery after GP catheter ablation in paroxysmal AF.^{7,8} Furthermore, it was recently confirmed with electrophysiologic mapping that active GP are clustered around the interatrial groove and the ligament of Marshall, and that cardiac response to GP stimulation

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Abbreviations and Acronyms

AF	= atrial fibrillation
AFL	= atrial flutter
AT	= atrial tachycardia
CHF	= congestive heart failure
GP	= ganglionic plexi
NYHA	= New York Heart Association
RF	= radiofrequency
SR	= sinus rhythm

can be eliminated with surgical bipolar radiofrequency (RF) isolation.⁹ On the other hand, Alex and Guvendik¹¹ failed to demonstrate any role of cardiac denervation on AF recurrences after surgery. Different techniques aimed at reducing postoperative autonomic imbalance (eg, thoracic epidural anesthesia) also failed to reduce postoperative AF.¹¹ Therefore, despite the postulated role for surgical GP isolation, there is no general agreement on the efficacy of strategies targeting the autonomic nervous system on postoperative AF.⁷⁻¹⁰ Although surgical AF ablation with modified “mini-Maze” procedures is now considered curative for the majority of patients referred to surgery,² it still carries the risk for AF recurrence, estimated to range from 10% to 40% in the different series, during the short- and mid-term follow-ups.^{11,12} We hypothesized that GP isolation with bipolar RF ablation may increase freedom from AF in patients undergoing persistent/long-standing persistent AF ablation during concomitant mitral valve surgery. The present study analyzes the hospital and short-term follow-up outcomes of patients undergoing 2 different surgical strategies (mini-Maze vs mini-Maze + GP isolation) used in the last 2.5 years to treat AF in patients undergoing mitral valve surgery.

Materials and Methods

From January of 2005 to October of 2007, 75 patients with persistent or longstanding persistent AF who required mitral valve surgery were enrolled in this prospective study after the approval of the institution's (Cardiac Surgery Unit Magna Graecia University) ethical committee/institutional review board and informed consent had been obtained. The study design was set to enroll patients undergoing the mini-Maze during mitral valve surgery in the first period (January of 2005 to September of 2006) and to compare hospital outcome and short-term follow-up with that of patients undergoing the combined mini-Maze + GP isolation and mitral valve surgery during the second period of the study (September of 2006 to October of 2007). AF was defined as persistent or longstanding persistent according to the Heart Rhythm Society, European Heart Rhythm Association, and European Cardiac Arrhythmia Society.¹⁴ The demographics are reported in Table 1.

Surgery

Cardiopulmonary bypass was standardized.¹³ Cardiac arrest was achieved with intermittent antegrade plus retrograde blood cardio-

TABLE 1. Demographic and intraoperative data

	Group A (44 patients)	Group B (31 patients)	P
Age (y)	64.6 ± 10.3	64.2 ± 9.8	.849
Age > 65 y	21 (47.7%)	21 (67.7%)	.068
Sex (male)	33 (75.0%)	23 (74.2%)	.572
Diabetes mellitus	14 (31.8%)	11 (35.5%)	.465
Hypertension	33 (75.0%)	22 (71.0%)	.448
Dyslipidemia	24 (54.5%)	13 (41.9%)	.200
COPD	19 (43.2%)	10 (32.3%)	.238
>90 kg (weight)	12 (27.3%)	6 (19.4%)	.306
Mitral disease	44 (100%)	31 (100%)	-
Aortic disease	22 (50.0%)	11 (35.5%)	.156
Tricuspid disease	16 (36.4%)	14 (45.2%)	.299
Coronary heart disease	5 (11.4%)	4 (12.9%)	.556
Longstanding persistent AF	38 (86.4%)	27 (87.1%)	.605
Persistent AF	6 (13.6%)	4 (12.9%)	.605
AF duration (mo)	29.1 ± 10.7	27.5 ± 11.4	.548
Preoperative NYHA	3.68 ± 0.47	3.58 ± 0.62	.425
Preoperative heart failure state	14 (31.8%)	11 (35.5%)	.465
Previous pharmacologic cardioversion	44 (100%)	31 (100%)	-
Previous electric cardioversion	17 (38.6%)	8 (25.8%)	.181
Preoperative LVEF	45.6 ± 10.4	44.8 ± 9.6	.738
Preoperative LVEF < 45%	26 (59.1%)	17 (54.8%)	.448
Preoperative transverse LAD	53.7 ± 6.7	53.5 ± 7.6	.906
Preoperative longitudinal LAD	57.3 ± 9.9	59.2 ± 12.6	.553
Mitral valve replacement (mechanical)	7 (15.9%)	8 (25.8%)	.222
Mitral valve replacement (biologic)	4 (9.1%)	-	.112
Mitral valve plasty	33 (75.0%)	23 (74.2%)	.572
Aortic valve replacement (mechanical)	7 (15.9%)	4 (12.9%)	.493
Aortic valve replacement (biologic)	5 (11.4%)	2 (6.5%)	.384
Aortic valve plasty	3 (6.8%)	5 (16.1%)	.182
Tricuspid valve plasty	16 (36.4%)	14 (45.2%)	.299
CABG	5 (11.4%)	4 (12.9%)	.556
Crossclamp time	60.2 ± 15.1	59.1 ± 11.3	.730
Cardiopulmonary bypass time	83.7 ± 12.5	81.2 ± 14.1	.407

AF, Atrial fibrillation; COPD, chronic obstructive pulmonary disease; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; CABG, coronary artery bypass grafting.

plegia. Mitral valve surgery was performed through a longitudinal atriotomy. Mitral valve replacement was always achieved by implanting prostheses in the intra-annular position. When tricuspid disease was encountered, longitudinal intercalval right atriotomy was used as the surgical access. Intraoperative data and concomitant procedures are also shown in Table 1.

With regard to arrhythmia surgery, 2 different surgical strategies were adopted: A total of 44 patients underwent the isolated “left + right mini-Maze” procedure (group A) as previously reported,¹² preferentially during the first phase of the study, and the remaining 31 patients (group B) underwent the “left + right mini-Maze”

procedure plus GP isolation, preferentially during the second phase of the study. Briefly, left-sided lesions were in the pulmonary veins and left atrial appendage bipolar RF isolation, with the bipolar clamp (Medtronic, Minneapolis, Minn) and Cardioblate surgical ablation generator (Medtronic) as the power source. The left isthmus lesion was always performed with a unipolar RF pen (Cardioblate surgical pen; Medtronic). The left lesion set was completed by bipolar RF lesion connecting the left upper pulmonary vein to the left atrial appendage. Right-sided ablation lines were created as previously reported, always using a bipolar clamp.¹² Briefly, a purse-string suture stitched in front of the coronary sinus was used to insert the bipolar clamp, which was first directed between the inferior vena cava and the coronary sinus, and then rotated toward the atrioventricular groove, between the coronary sinus and the tricuspid valve, to ablate the cavo-tricuspid isthmus. The clamp was subsequently rotated upward to create a transmural ablation line, connecting the purse string to the right appendage. Finally, an additional purse-string suture was stitched on the tip of the right atrial appendage (for venous drainage), through which the bipolar clamp was introduced to first allow an ablative line connecting the superior vena cava to the inferior vena cava and then to ablate the terminal crest. Off-pump ablation of the right appendage completed the procedure.¹² Because of the risk of incomplete right septal isthmus ablation, patients with a large right atrium (≥ 7.0 cm) undergoing tricuspid valvuloplasty also underwent further monopolar RF septal isthmus ablation. Left and right appendages were always excluded by external ligation or internal stitching.¹²

Ganglionic Plexi Isolation

In patients undergoing GP isolation, intraoperative epicardial electrophysiologic mapping was performed at the time of operation, starting from the right-sided pulmonary veins, moving from the area of the superior right pulmonary vein to that of the inferior right pulmonary vein, and then moving in the same manner to the left-sided pulmonary veins. Intraoperative epicardial electrophysiologic mapping was performed using a standard 6F catheter (FIAB SpA, Florence, Italy). The catheter was connected to an external pulse generator (St Jude Medical Inc, St Paul, Minn) to deliver high-frequency stimulation (at a rate of 800/min, amplitude of 12 to 16 mA, with a pulse duration of 9.9 ms) to the above-mentioned areas. The electrocardiogram was monitored, and stimulation that resulted in a doubling of the R-R interval indicated an active GP.⁹ A bipolar RF lesion encompassing the right-sided interatrial fat pad of Waterston's groove, as suggested by Mehall and coworkers,⁹ was then made. This lesion was created with 1 jaw of the bipolar clamp posterior to the right-sided pulmonary veins and the other jaw on the right atrium, medial to the interatrial fat pad, to encompass part of the left atrium, right atrium, and interatrial septum. Another bipolar RF clamping was made jawing the ligament of Marshall.⁹ GP areas that had preablation activity were then restimulated to confirm the isolation. Both lesions involving GP locations were made off pump and at least twice to achieve isolation. Extended fat pad resection along Waterston's groove, the ligament of Marshall, and the left-sided pulmonary veins was then executed to demonstrate GP with pathologic analysis on the specimens. Each right- and left-sided fat pad specimen was divided into 3 portions (superior, middle, and inferior), and active ganglia were localized in each specimen. To differentiate ganglia from nerves, specimens were stained with hematoxylin/eosin and antibodies to S100 protein and neurofilaments.

However, except for the surgical AF ablation technique, preoperative, intraoperative, and postoperative management techniques were standard during the entire study period.

Postoperative Care

Inotropic support was defined as low dose when enoximone was administered at a dosage of 5 $\mu\text{g/kg/min}$ or less, medium dose when enoximone was administered at a dosage of 6 to 10 $\mu\text{g/kg/min}$ or dobutamine was added from 5 to 10 $\mu\text{g/kg/min}$, and high dose when enoximone or dobutamine was administered at a dosage of 10 $\mu\text{g/kg/min}$ or epinephrine at any dose was added.

An intravenous amiodarone bolus (150 mg), followed by continuous intravenous infusion at 1 mg/kg/h for 12 hours and then 0.5 mg/kg/h until patients tolerated oral intake, was routinely administered intraoperatively. Patients then underwent oral amiodarone (200 mg twice per day for 1 week, then 200 mg daily) until the sixth postoperative month. Patients with postoperative persistence of AF, as well as those with new-onset AF, did not undergo electrical cardioversion but were treated with intravenously and orally administered amiodarone. The international normalized ratio was maintained between 2.5 and 3.5 for the first 6 months in all patients and lifelong in patients receiving mechanical valves or with AF persistence.

Assessment of Cardiac Rhythm and Follow-up

Twelve-lead electrocardiographic recordings were performed preoperatively, on admission to the intensive therapy unit, and daily thereafter until hospital discharge or whenever necessary. All patients underwent continuous electrocardiographic monitoring for the first 72 hours postoperatively. The incidence of arrhythmias, both atrial and ventricular, was recorded during hospitalization and follow-up. The mean follow-up time was 16.7 ± 0.95 (standard error) months (confidence limit 14.9–18.6 months), and no patient was lost during follow-up (100% complete). An initial post-ablation blanking period of 3 months was considered according to the Heart Rhythm Society, European Heart Rhythm Association, and European Cardiac Arrhythmia Society: The reported recurrences during the post-ablation blanking period were defined as “early events.”¹¹ Follow-up data were collected by routine examination in our outpatient clinic (7 days, 14 days, 1 month, 3 months, 6 months, and 1 year after surgery, and then once per year or whenever requested by the patient). Phone contacts with patients and cardiologists were made whenever necessary. One month after surgery, patients underwent 24-hour Holter electrocardiography, which was repeated at least once during the first 6 months of follow-up. According to the Heart Rhythm Society, European Heart Rhythm Association, and European Cardiac Arrhythmia Society, 6- and 12-month follow-ups were recorded. Follow-up was closed on November 30, 2007.

End Points

The primary efficacy end point was freedom from AF, atrial flutter (AFL), and atrial tachycardia (AT) of at least 30 seconds duration in the absence of antiarrhythmic drug therapy 3 months after stopping amiodarone.¹¹ The prevalence of AF at 6 and 12 months postoperatively were also recorded. Secondary end points were freedom from AF, AFL, and AT in the presence of antiarrhythmic therapy, prevalence of “early events” during the post-ablation blanking period of 3 months, in-hospital electrophysiologic results, and freedom from episodes of congestive heart failure (CHF) and hospital readmission. CHF was defined as any episode of cardiac

decompensation during follow-up requiring adjustment of the therapy or hospitalization; hospital readmission was defined as any hospital admission for any cardiac cause and requiring more than a 6-hour stay. As a surrogate outcome of cardiac compensation, the need and dose of furosemide were registered preoperatively, at hospital discharge, and at the end of follow-up.

Echocardiography

The echocardiographic examinations were performed preoperatively, postoperatively, and at 6 months follow-up using a VIVID 7 Pro ultrasound machine (GE Technologies, Milwaukee, Wis). Atrial and ventricular remodeling (longitudinal and transverse atrial diameters, diastolic ventricular diameter), systolic pulmonary arterial pressure, indexed left ventricular mass, and E/A ratio recovery were investigated.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ standard deviation, and categoric data are expressed as proportions. Comparisons of continuous variables were made with the Student unpaired *t* test, and categoric variables were compared with the chi-square test or Fisher exact test. Comparison between and within groups was made using 2-way analysis of variance for repeated measures.

Freedom from AF, AFL, AT, CHF, and hospital readmission was determined by means of the Kaplan–Meier life-table analysis. Log-rank test was performed to ascertain differences during follow-up between patients undergoing the isolated left + right mini-Maze procedure and those undergoing combined GP isolation. All statistical analyses were performed with the Statistical Package for the Social Sciences 13.0 (SPSS Inc, Chicago, Ill).

Results

Hospital Mortality, Morbidity, and Drug-related Complications

There were no hospital deaths during hospitalization or ablation device-related complications. Hospital morbidity is reported in Table 2. No differences were registered in perioperative inotropic support (Table 2).

TABLE 2. Hospital morbidity and perioperative inotropic support

	Group A (44 patients)	Group B (31 patients)	<i>P</i>
Morbidity	7/44 (15.9%)	6/31 (19.4%)	.464
LOS	2/44 (4.5%)	2/31 (6.5%)	.551
ARF	3/44 (6.8%)	2/31 (6.5%)	.664
Pneumonia	2/44 (4.5%)	2/31 (6.5%)	.551
LD inotropic support	24/44 (54.5%)	18/31 (58.1%)	.474
MD inotropic support	16/44 (36.4%)	11/31 (35.5%)	.567
HD inotropic support	4/44 (9.1%)	2/31 (6.5%)	.516
ITU stay (h)	51.6 $\pm$ 9.6	50.2 $\pm$ 6.5	.481
Hospital stay (d)	9.0 $\pm$ 12.5	7.3 $\pm$ 0.8	.481

LOS, Low output syndrome; ARF, acute renal failure; LD, low dose; MD, medium dose; HD, high dose; ITU, intensive therapy unit.

When chronic amiodarone therapy was considered, only 1 patient in group A (2.3%; *P* = .587) experienced optic neuropathy at 4 months after surgery, with partial improvement after drug discontinuation. However, all other patients continued amiodarone until the sixth month. Finally, no warfarin-related complications were registered during the study.

Pathologic Analysis

The details of the site and number of GPs detected at pathology are shown in Table 3. As evidenced, GPs are generally clustered in a higher number on the upper right and left fat pad specimens. No GP can be demonstrated in 1 superior, 6 middle, and 12 inferior right fat pad specimens, and in 11 superior, 4 middle, and 7 inferior left fat pad specimens (Table 3). Obviously, none of these specimens were active at intraoperative electrophysiologic analysis. A mean of 3.09 $\pm$ 1.13 GP (range 0–5) in the superior, 1.70 $\pm$ 1.04 GP (range

TABLE 3. Number of ganglionic plexi found at pathologic analysis in each patient

	Superior right FPS	Middle right FPS	Inferior right FPS	Superior left FPS	Middle left FPS	Inferior left FPS
Patient 1	4.00	3.00	3.00	3.00	3.00	3.00
Patient 2	3.00	2.00	2.00	3.00	3.00	2.00
Patient 3	3.00	2.00	3.00	2.00	3.00	2.00
Patient 4	4.00	2.00	2.00	2.00	2.00	2.00
Patient 5	4.00	3.00	2.00	4.00	2.00	1.00
Patient 6	4.00	2.00	3.00	3.00	2.00	1.00
Patient 7	3.00	2.00	2.00	2.00	2.00	1.00
Patient 8	3.00	2.00	1.00	2.00	2.00	1.00
Patient 9	3.00	3.00	1.00	3.00	1.00	1.00
Patient 10	3.00	2.00	0.00	3.00	1.00	1.00
Patient 11	3.00	2.00	2.00	1.00	1.00	1.00
Patient 12	3.00	2.00	1.00	1.00	1.00	1.00
Patient 13	4.00	1.00	2.00	0.00	1.00	0.00
Patient 14	3.00	3.00	2.00	0.00	1.00	2.00
Patient 15	3.00	3.00	2.00	0.00	1.00	1.00
Patient 16	3.00	1.00	0.00	0.00	1.00	1.00
Patient 17	3.00	2.00	0.00	0.00	1.00	1.00
Patient 18	4.00	2.00	0.00	0.00	1.00	1.00
Patient 19	4.00	0.00	1.00	0.00	1.00	0.00
Patient 20	5.00	2.00	1.00	1.00	1.00	1.00
Patient 21	4.00	3.00	2.00	1.00	1.00	1.00
Patient 22	4.00	3.00	1.00	1.00	1.00	1.00
Patient 23	5.00	2.00	1.00	1.00	1.00	1.00
Patient 24	3.00	2.00	0.00	1.00	1.00	1.00
Patient 25	3.00	1.00	0.00	1.00	1.00	1.00
Patient 26	3.00	1.00	0.00	0.00	1.00	1.00
Patient 27	1.00	0.00	0.00	2.00	1.00	0.00
Patient 28	1.00	0.00	0.00	0.00	0.00	0.00
Patient 29	0.00	0.00	0.00	1.00	0.00	0.00
Patient 30	1.00	0.00	0.00	0.00	0.00	0.00
Patient 31	2.00	0.00	0.00	0.00	0.00	0.00

FPS, Fat pad specimen.

0–3) in the middle, and 1.09 ± 1.04 GP (range 0–3) in the inferior right fat pad specimens were demonstrated. Similarly, a mean of 1.22 ± 1.20 GP (range 0–4), 1.22 ± 0.80 GP (range 0–3), and 0.96 ± 0.70 GP (range 0–3) were detected in the superior, middle, and inferior left fat pad specimens, respectively.

On the other hand, the prevalence of active sites along the fat pad specimens, as demonstrated by intraoperative electrophysiologic mapping, is shown in Figure 1. Inactive zones did not undergo further electrophysiologic stimulation with different frequencies, pulse durations, or amplitudes. Active sites were found bilaterally in 16 patients, unilaterally right sided in 8 patients, and left sided in 7 patients. When active fat pad specimens were compared with inactive fat pad specimens, a significantly higher number of GP were detected by the pathologist in active specimens (superior right: 3.54 ± 0.65 vs 1.57 ± 1.13 in inactive specimens, $P = .003$; middle right: 2.16 ± 0.61 vs 1.07 ± 1.18 , $P = .008$; inferior right: 2.42 ± 0.53 vs 0.70 ± 0.80 , $P = .0001$; superior left: 2.70 ± 0.67 vs 0.52 ± 0.60 , $P = .0001$; middle left: 2.37 ± 0.51 vs 0.82 ± 0.38 , $P = .0001$; inferior left: 2.0 ± 0.70 vs 0.76 ± 0.51 , $P = .015$). All patients in whom AF recurrences developed during follow-up demonstrated at least 1 active fat pad zone. However, no differences were found in the number and site of GP in patients demonstrating AF recurrences during follow-up compared with patients maintaining SR (superior right: AF 3.00 ± 1.41 vs SR 3.11 ± 1.12 , $P = .859$; middle right: 1.25 ± 1.25 vs 1.78 ± 1.01 , $P =$

$.352$; inferior right: 1.25 ± 1.50 vs 1.07 ± 0.99 , $P = .759$; superior left: 1.00 ± 1.41 vs 1.25 ± 1.19 , $P = .695$; middle left: 1.25 ± 1.26 vs 1.22 ± 0.75 , $P = .950$; inferior left: 1.00 ± 1.41 vs 0.96 ± 0.58 , $P = .962$).

Cardiac Rhythm

On aortic declamping, 51 patients (68.0%) recovered SR, 14 patients (18.7%) were in junctional rhythm, and 10 patients (13.3%) displayed persistence of AF. Only 1 case of AF persistence was registered at aortic declamping in group B, and 9 cases were registered in group A (20.5% vs group B 3.2%; $P = .030$). No differences were recorded between the 2 groups in SR (30/44 [68.2%] vs group B: 21/31 [67.7%]; $P = .581$) and junctional rhythm requiring temporary pacemaker stimulation (5/44 [11.4%] vs group B: 9/31 [29.0%]; $P = .052$). Of these, only 1 patient (1.3% of the global population) in group A (2.3% vs group B 0%; $P = .587$) required definitive pacemaker implantation.

All patients were treated with amiodarone postoperatively; thus, 64 patients (85.3%) recovered and were discharged in SR, and 10 patients (13.3%) were discharged in AF. With regard to AFL, postoperative transient AFL developed during hospitalization in 11 patients (14.7%), without differences between the 2 groups (group A: 7/44 [15.9%] vs group B: 4/31 [12.9%]; $P = .493$). On discharge, a significantly higher prevalence of AF was noted in group A (9/44 [20.5%] vs group B: 1/31 [3.2%]; $P = .030$), together with a lower prevalence of SR (group A: 34/44 [77.3%] vs group

Figure 1. A, Electrophysiologic mapping of active GP. GP demonstration on fat pad specimen stained with hematoxylin/eosin (B) and antibodies to neurofilaments (C). LA, Left atrium; RA, right atrium; PA, pulmonary artery; LV, left ventricle.

B: 30/31 [96.8%]; $P = .01$). No differences were recorded in “early events” during the post-ablation blanking period of 3 months between the 2 groups (group A: 5/44 [11.4%] vs group B: 3/31 [9.7%]; $P = .565$). After antiarrhythmic therapy discontinuation, no differences in the prevalence of AF, AFL, and AT were registered at 6 months (group A: 4/36–11.1% vs group B: 1/29–3.4%; $P = .252$), but a significantly lower AF, AFL, and AT prevalence was recorded in group B at 12 months (1/11 [9.1%] vs group A: 14/33 [42.4%]; $P = .044$). At a mean of 11.7 ± 5.9 months follow-up (range 1–22 months), 57 patients (76.0%) were in SR. Actuarial freedom from AF, AFL, and AT recurrence with antiarrhythmic therapy after 16.7 ± 0.95 (standard error) months was $63.2\% \pm 7.3\%$ (Figure 2, A) and proved higher in group B (Figure 2, B). However, after the sixth month, 12.8 ± 0.80 (standard error) months, freedom from AF, AFL, and AT without antiarrhythmic therapy was $72.5\% \pm 7.7\%$ (Figure 2, C) higher in group B (Figure 2, D).

When AF-surgery related complications were considered, no cases of cardiac tamponade, pulmonary vein stenosis, esophageal injury, phrenic/vagal nerve injury, coronary occlusions, or thromboembolism were registered.

Hemodynamic Status, Congestive Heart Failure, and Hospital Readmission

New York Heart Association (NYHA) class improved significantly after surgery within the 2 groups (group A preoperative: 3.68 ± 0.47 vs discharge: 1.45 ± 0.58 , $P = .0001$; group B preoperative: 3.58 ± 0.62 vs discharge: 1.35 ± 0.48 , $P = .0001$) and further ameliorated during follow-up (group A follow-up NYHA: 1.16 ± 0.48 , $P = .0001$; group B follow-up NYHA: 1.19 ± 0.40 , $P = .0007$; statistical significance between groups: $P = .517$). On the other hand, patients with AF displayed less improvement in NYHA class than those with SR at discharge and during follow-up (preoperative NYHA of patients with AF: 3.70 ± 0.46 vs NYHA on

Figure 2. Cumulative freedom from AF, AFL, and AT with antiarrhythmic therapy (A), freedom from AF, AFL, and AT with antiarrhythmic therapy between the 2 groups (B), cumulative freedom from AF, AFL, and AT without antiarrhythmic therapy (C), and freedom from AF, AFL, and AT without antiarrhythmic therapy between the 2 groups (D). AF, Atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia.

discharge: 1.76 ± 0.66 vs follow-up NYHA: 1.52 ± 0.62 , statistical probability within subjects $P = .040$; preoperative NYHA of patients with SR: 3.62 ± 0.55 vs NYHA on discharge: 1.31 ± 0.46 vs follow-up NYHA: 1.06 ± 0.31 , statistical probability within subjects $P = .0001$; statistical probability between groups $P = .001$). When furosemide therapy was considered, of 42 patients in group A (95.5%) and 31 patients in group B (100%; $P = .341$), who were taking diuretics on hospital admission, 41 patients in group A (93.2%) and 29 patients in group B (93.5%; $P = .664$) were discharged with furosemide. Of these, 22 patients in group A (50.0%) and 17 patients in group B (54.8%; $P = .430$) continued to take diuretics at the end of follow-up. However, a significantly higher diuretic dose was necessary in group A (preoperative: 51.7 ± 24.8 mg/d vs discharge: 55.1 ± 20.1 mg/d vs follow-up: 19.6 ± 16.6 ; $P = .070$ within group) compared with group B (preoperative: 70.2 ± 26.1 mg/d vs discharge: 32.2 ± 16.6 mg/d vs follow-up: 13.7 ± 13.8 ; $P = .0001$ within group; statistical significance

between groups: $P = .0001$). Moreover, patients maintaining SR at discharge and during follow-up needed less diuretics than patients experiencing AF recurrence, either in group A (SR at discharge: 36.3 ± 22.2 mg/d vs AF at discharge: 100.0 ± 51.1 ; $P = .0001$; SR at follow-up: 9.6 ± 11.9 mg/d vs AF at follow-up: 43.2 ± 34.8 ; $P = .0001$; statistical significance between groups: $P = .0001$) or group B (SR at discharge: 28.7 ± 13.3 mg/d vs AF at discharge: 56.2 ± 12.5 ; $P = .001$; SR at follow-up: 11.1 ± 12.2 mg/d vs AF at follow-up: 31.2 ± 12.5 ; $P = .005$; statistical significance between groups: $P = .003$).

Seven patients in group A had episodes of CHF during follow-up, giving a global actuarial freedom from CHF of $84.0\% \pm 6.4\%$ (Figure 3, A). However, no differences were recorded between the 2 groups in follow-up freedom from CHF (Figure 3, B). On the other hand, 8 patients were readmitted to hospital during follow-up, meaning that cumulative actuarial freedom from hospital readmission was $87.3\% \pm 4.3\%$ (Figure 3, C). Again, no differences were detected

Figure 3. Cumulative freedom from CHF (A), freedom from CHF between the 2 groups (B), cumulative freedom from hospital readmission (C), and freedom from hospital readmission between the 2 groups (D). CHF, Congestive heart failure.

between group A and B in follow-up freedom from hospital readmission (Figure 3, D).

Echocardiographic Results

Echocardiography documented a normalized E/A in 35 patients (46.7% of global population, 61.4% of patients with SR) at the end of follow-up. Patients undergoing GP isolation demonstrated a higher prevalence of normalized E/A (group B: 19/31 [61.3%] vs group A: 16/44 [36.4%], $P = .029$; 19/27 patients with SR [70.4%] vs 16/30 patients with SR [53.3%], $P = .148$).

When groups A and B were compared, no differences in follow-up echocardiographic parameters were detected; both groups showed significant reverse remodeling of longitudinal and transverse atrial diameters, recovery of systolic pulmonary arterial pressure and indexed left ventricular mass, and follow-up reverse remodeling of diastolic left ventricular diameter (Table 4).

However, patients who recovered SR displayed significant reverse remodeling of left atrial longitudinal and transverse diameters on follow-up echocardiography (Table 4). Such reverse remodeling was not detected in patients in whom AF persisted (Table 4). Only patients in SR showed significant reverse remodeling of left ventricular diastolic diameter during follow-up, as well as a significant improve-

ment in systolic pulmonary arterial pressure and indexed left ventricular mass (Table 4). In contrast, patients with AF only showed a significant improvement in follow-up indexed left ventricular mass (Table 4).

Discussion

Although it has long been ascertained that AF is frequently associated in patients with underlying heart disease, inasmuch as it is estimated to be present in 50% of patients with mitral valve disease, routine ablation of AF in these patients is a recent phenomenon.² The Cox maze III operation is considered the gold standard for surgical treatment of AF, and other approaches to AF ablation should be measured against it.¹⁻³ In this surgical procedure, multiple left and right atrial incisions are placed to interrupt the multiple reentrant circuits of AF.¹ However, the Cox-Maze procedure is a technically demanding operation with a prolonged operative time, so that a number of modified “mini-Maze” procedures with alternative energy sources, other than the cut-and-sew technique, have been proposed to overcome such matters.^{2,11} However, if the Cox-Maze technique allows an SR restoration rate of 70% to 95% in the different experiences,^{2,14,15} the modified so-called mini-Maze procedures have a similar success rate ranging from 65% to 90%, regardless of the ablative pattern, patient populations, and energy sources.^{2,16-18}

All of these data imply that AF recurrences developed during the follow-up in approximately 25% of patients undergoing surgical AF ablation, limiting the primary surgical success rate. Therefore, despite the fact that Haissaguerre⁴ demonstrated the importance of ectopic triggers of the pulmonary veins, different mechanisms can be involved in AF initiation and recurrence. In the last few years, different studies have demonstrated a significant role of parasympathetic autonomic tone in determining AF.^{5-9,19} Active GP are usually located in epicardial fat pads along the right-sided interatrial groove and along the ligament of Marshall on the left.⁹ Therefore, their location is often outside the areas traditionally isolated when pulmonary vein isolation alone is performed.⁹ In particular, it has been demonstrated that GP play a synergistic role with ectopic vein foci, thus decreasing the threshold of inducibility for AF.⁶ GP activation resulted in a progressive decrease in atrial refractoriness, which remains active even after extracardiac denervation.²⁰ Accordingly, the destruction of GP rendered 96% of patients noninducible to AF.²¹ Chiou and Zipes⁸ obtained selective vagal denervation of the atria, sinus, and AV nodes, with preserved ventricular innervation, with RF ablation of the atrial fat pad in a dog model. Moreover, Pappone and colleagues²² suggested that patients undergoing AF catheter-based RF ablation with “vagal” response, who demonstrated higher freedom from AF during follow-up, had GP destruction with loss of the GP function during the interventional procedure. Chen and coworkers²³ demonstrated that a disturbed atrial electrophysiology mediated by higher vagal reflexes could play an

TABLE 4. Echocardiographic results stratified by cardiac rhythm and surgical treatment

		Discharge	Follow-up	P^a	P^b
Longitudinal LAD	SR	58.4 ± 7.0	51.7 ± 7.4	.0001	.0001
	AF	61.5 ± 9.4	60.8 ± 9.5	.120	
Transverse LAD	SR	53.5 ± 7.7	47.9 ± 8.1	.001	.001
	AF	54.4 ± 7.5	54.0 ± 8.2	.181	
PAPs	SR	33.2 ± 2.5	27.4 ± 3.2	.008	.005
	AF	32.7 ± 3.8	31.4 ± 3.2	.521	
LVMi	SR	146.9 ± 31.3	130.1 ± 29.3	.0001	.08
	AF	135.8 ± 26.2	125.4 ± 25.6	.001	
LVDd	SR	5.6 ± 1.3	5.2 ± 1.2	.0001	.001
	AF	5.5 ± 1.0	5.4 ± 1.2	.171	
Longitudinal LAD	Group A	53.4 ± 11.4	51.0 ± 9.2	.0001	.465
	Group B	54.9 ± 10.8	52.9 ± 8.8	.0001	
Transverse LAD	Group A	52.5 ± 9.4	51.3 ± 7.7	.004	.543
	Group B	53.8 ± 9.9	51.0 ± 8.0	.009	
PAPs	Group A	32.6 ± 8.4	28.6 ± 9.9	.015	.426
	Group B	33.4 ± 9.2	30.4 ± 10.4	.034	
LVMi	Group A	144.6 ± 31.2	123.9 ± 28.1	.0001	.454
	Group B	142.5 ± 29.1	125.8 ± 27.4	.0001	
LVDd	Group A	5.4 ± 1.0	5.0 ± 1.4	.0001	.377
	Group B	5.5 ± 1.3	5.2 ± 1.0	.0001	

LAD, Left atrial diameter; PAPs, systolic pulmonary arterial pressure; LVMi, indexed left ventricular mass; LVDd, diastolic left ventricular diameter. ^aStatistical significance between discharge and follow-up echocardiography (within groups). ^bStatistical significance between patients with SR and patients with AF (first part) and between group A and B (second part) (between groups).

important role in the genesis of paroxysmal AF and supraventricular tachycardias. Finally, Mehall and colleagues⁹ recently reported that autonomic GP are clustered around the interatrial groove and the ligament of Marshall, and that cardiac response to GP stimulation can be eliminated with surgical bipolar RF isolation, suggesting the potential for an increased freedom from AF with the addition of GP isolation to bilateral pulmonary vein isolation.⁹ However, there is no general agreement on the efficacy on postoperative AF of strategies targeted on autonomic nervous system: Alex and Guvendik¹⁰ demonstrated that ventral cardiac denervation was not effective in reducing AF recurrences, whereas Jideus and colleagues¹¹ showed thoracic epidural anesthesia to have no effects on postoperative AF. However, the resulting dominating vagotonic status induced by epidural anesthesia, reported by Jideus and colleagues, can explain the results of their study. We reported our experience with the combination of GP isolation to traditional RF mini-Maze procedure, and, as expected, we found a higher, but not significant, freedom from AF in those patients who underwent combined mini-Maze plus GP isolation.

It is well known that the topography of cardiac ganglia in the adult human heart is not common basic or clinical knowledge, due in part to limited or inconsistent reports.²⁴ Moreover, contradictory results are reported in the literature: Singh and colleagues²⁴ showed 2 large populations of cardiac ganglia, the first lateral to the right pulmonary veins and inferior to the superior vena cava, near the sinoatrial node, and the second at the interatrial groove and coronary sulcus junction, near the AV node, but only small populations lateral to the left pulmonary veins.²⁴ On the other hand, Leonhardt²⁵ reported similar cardiac ganglia densities near the sinoatrial node and on the superior left atrial surface, also lateral to the right pulmonary veins. When pathologic-clinical correlations were investigated, Mehall and colleagues⁹ reported active GP preferentially located in the upper right and left fat pads along the pulmonary veins, with bilateral activity in the majority of patients.⁹ As did Leonhardt,²⁵ we found GP clustered along the left pulmonary veins, although according to Singh and coworkers,²⁴ the highest number of GP can be demonstrated on the fat pad of Waterston's groove, either on electrophysiologic stimulation or histologic analysis. Accordingly, our data agree with that of Mehall and colleagues,⁹ showing bilateral activity in the majority of patients, followed by unilateral right-sided GP activity. Moreover, on electrophysiologic study, we found active GPs to correlate with a higher number of clustered GPs detectable at histology. However, we did not found AF recurrences to correlate with a specific histologic pattern.

In-hospital results were significantly better in patients undergoing GP ablation because of the lower AF persistence at aortic declamping or hospital discharge. Our results suggested that GP function may affect the results of the AF ablation in the postoperative course, confirming the findings

of Mehall and coworkers,⁹ who suggested that a persistent activity of unisolated active GP may explain the 10% to 40% recurrence rate of AF after the Maze procedure alone. Moreover, the impact of GP isolation in early postoperative SR recovery can be attributed to the elimination of the vagal reflexes and atrial susceptibility to AF, secondary to different "fibrillogenic" stimuli commonly encountered in the early postoperative phase, such as electrolytic imbalance, systemic inflammation, and hypovolemia.²⁶

Fluid retention was one of the earliest recognized complications of the Maze procedure, related to biatrial appendectomy, lower atrial natriuretic peptide secretion, increased plasma arginine vasopressin and aldosterone levels, and temporary lack of response of the atrial baroreceptors.²⁷ Ad and colleagues²⁸ suggested that the abrupt cardioversion to SR decreases postoperative atrial natriuretic peptide levels, thus determining fluid retention. Despite the fact that biatrial appendectomy was performed in both groups, we found a lower need for furosemide at discharge and during follow-up in patients undergoing GP isolation. It can be hypothesized that the lower AF recurrences during hospitalization and the reduced AF, AFL, AT recurrences during follow-up after GP isolation, with a resulting better hemodynamic status, may explain the lower need for furosemide in this group. Accordingly, we found patients maintaining AF during follow-up to require more furosemide than patients converted to SR. Moreover, the reduced incidence of AF, AFL, and AT with and without antiarrhythmic therapy may favor the recovery of atrial function, thus resulting in a higher or earlier recovery of E/A ratio (as found in group B) at echocardiographic follow-up. However, more studies exploring hormonal response and correlations between electrophysiology and echocardiography are needed to substantiate such hypotheses.

Finally, it can be argued that a more aggressive approach with atrial denervation may favor the development of postoperative junctional rhythm or impair the heart rate autonomic control and reflexes.^{7,22} When junctional rhythm was considered, no differences were recorded in its prevalence in the 2 groups either at aortic declamping or during hospitalization, so no differences were recorded between the 2 groups in postoperative need for definitive pacemaker implantation. When autonomic imbalance was considered, it is well known from literature studies^{7,22} that RF AF ablation modifies heart rate variability and reduces baroreflex sensitivity in the early postoperative course.²² However, we did not study heart rate variability; therefore, further studies are welcome to clarify this topic.

When echocardiographic findings are considered, previous literature studies have demonstrated that restoration of the SR is consistent with a reverse remodeling of the atrial diameters, volumes, and function.^{29,30} However, if the entity of such remodeling is due to the restoration of the rhythm or to the restoration of the underlying valve disease, the evaluation is still challenging. We confirmed our previous findings¹²

that patients undergoing mitral valve surgery demonstrated a significant reverse remodeling of atrial and ventricular diameters only in case of SR restoration, which correlates with a higher prevalence of E/A recovery at follow-up. Therefore, patients with persistence of AF do not undergo a reverse atrial remodeling or ventricular reverse remodeling, despite the relief of the underlying valve pathology, which may only ameliorate echocardiographic indexed left ventricular mass. Therefore, ventricular remodeling is demonstrated during follow-up only when SR maintenance is guaranteed.¹² These findings correlated with the evidence that despite a comparable early postsurgical recovery of NYHA class in the 2 treatment groups, patients demonstrating AF persistence showed a lesser degree of symptomatic improvement during follow-up.¹² However, no differences can be detected in atrial and ventricular remodeling between the 2 surgical treatments, demonstrating that GP isolation did not further affect reverse remodeling of the heart chambers. Finally, given the comparable atrioventricular remodeling and the absence of significant differences in follow-up freedom from AFL, it is not surprising that patients undergoing GP isolation + mini-Maze have similar follow-up freedom from acute heart decompensation and a comparable freedom from hospital readmission when compared with patients undergoing the left + right mini-Maze alone.

Extended GP isolation during AF ablation in mitral valve surgery improves SR recovery during hospitalization and adds a beneficial effect on follow-up freedom from AF and the recovery of atrial function during echocardiographic follow-up.

Study Limitations

The main limitation of the study is the limited number of patients enrolled in different periods; the lack of randomization to treatment is another limitation. Moreover, the type and duration of AF were heterogeneous. All of these limitations stem from the single-center design of the study, which, on the other hand, guaranteed uniformity of the perioperative management of the patient population throughout the experimentation. Certainly, further randomized studies or prolonged follow-up would be required to confirm the beneficial role of GP isolation during AF surgery.

The strengths of our study include its prospective design and the sequential echocardiographic assessment of both atrial and ventricular size and function before and after surgery. Furthermore, there are few literature data with which to compare the isolated Maze procedure with the Maze procedure plus GP isolation.

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