

EFFECT OF THE SIZE OF THE LEFT ATRIUM ON SUSTAINED SINUS RHYTHM IN PATIENTS UNDERGOING MITRAL VALVE SURGERY AND CONCOMITANT BIPOLAR RADIOFREQUENCY ABLATION FOR ATRIAL FIBRILLATION

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SUMMARY – Atrial fibrillation is associated with systemic embolization and complications due to anticoagulant therapy. Radiofrequency ablation has been established as an effective and safe method for the treatment of atrial fibrillation. The aim of this study was to evaluate the effect of the size of the left atrium on the outcome of surgical radiofrequency ablation. Forty patients scheduled for elective mitral valve surgery and radiofrequency ablation were enrolled in the study. Group 1 consisted of patients with a left atrium diameter ≤ 5 cm and group 2 of patients with left atrium diameter >5 cm. The primary endpoint of the study was stable sinus rhythm 6 months postoperatively. At 6 months postoperatively, sinus rhythm was present in significantly more group 1 patients as compared with group 2 patients, i.e. 15 (75%) vs. 8 (40%), $p=0.025$. Multivariate analysis proved the size of the left atrium to be an independent predictor of the radiofrequency ablation outcome. Accordingly, the size of the left atrium was demonstrated to be an important predictor of the outcome of radiofrequency ablation for atrial fibrillation. A lower cut-off value of surgical reduction of the atria than previously reported should be considered in order to improve the radiofrequency ablation outcome.

Key words: *Atrial fibrillation; Anticoagulants; Catheter ablation; Heart atria; Cardiac surgical procedures; Multivariate analysis*

Introduction

Atrial fibrillation (AF) is found in about 4% of the general population aged >60 and in about 9% of those aged >80 , which makes it the most common cardiac arrhythmia in the general population¹. It is a global healthcare problem and with the ongoing aging of the general population, its prevalence and incidence is estimated to double in the next 50 years²⁻⁴. It has major

medical and economic implications, as it is associated with compromised cardiac function, systemic embolization, and complications associated with anticoagulant therapy, resulting in higher mortality, morbidity, and prolonged hospital stay⁴⁻⁸. The traditional anti-arrhythmic medications for AF are limited in long-term efficiency and have significant and sometimes fatal adverse events⁹.

Depending on the cardiac pathology, over 58% of patients with mitral valvular heart disease had electrocardiographically documented AF with adverse hemodynamic effects before cardiac surgery^{10,11}. Although the Cox-Maze III cut-and-sew procedure provides excellent short- and long-term results both in convert-

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ing AF to sinus rhythm and preventing thromboembolic complications, it is not widely accepted among surgeons due to its technical complexity and long duration¹²⁻¹⁵. As a consequence, bipolar radiofrequency ablation (RFA) has been established as a simple, effective and safe alternative method capable of creating fast transmural tissue lesions of the atrial myocardium^{16,17}. It provides a shorter time of surgery and reduces the risk of perioperative complications^{6,7,12,13}.

Risk factors such as the size of the left atrium (LA)¹⁸⁻²⁰, AF duration²⁰, persistent *vs.* paroxysmal AF^{18,19,21}, female gender²², higher CHADS₂ score^{23,24}, presence of hypertension^{18,25}, coronary artery disease¹⁹, and metabolic syndrome²⁶ have all been correlated with a less favorable success of ablation. Among them, larger LA size remains one of most cited predictors of long-term ablation outcome^{18-21,27,28}. However, the results of these studies have so far been contradictory and rather inconclusive. Furthermore, there are no clear recommendations at what atrial size an LA reduction procedure should be considered. The aim of this study was therefore to evaluate the effect of the 5-cm threshold LA size on the outcome of surgical RFA in patients undergoing elective mitral valve surgery.

Patients and Methods

The study was conducted in patients scheduled for elective mitral valve surgery and concomitant RFA for permanent atrial fibrillation between September 2008 and December 2009. The study protocol was approved by the institutional medical ethics committee and in full accordance with the World Medical Association Declaration of Helsinki.

Exclusion criteria included emergency surgery, AF lasting for less than 6 months, and severe systolic dysfunction of the left ventricle (ejection fraction <25%). Once the patient was considered eligible for enrolment, she/he was informed about the study protocol and a written informed consent was obtained. The patients were divided into two groups regarding the LA diameter. Group 1 consisted of patients with LA diameter ≤ 5 cm and group 2 consisted of patients whose LA diameter was greater than 5 cm. The LA diameter was measured echocardiographically as the end-systolic anteroposterior linear dimension obtained from the parasternal long axis view. Twenty consecutive patients were included in each group.

In addition to the preoperative echocardiogram, basic demographic, laboratory, and medical data were obtained and recorded before surgery. Patients in both groups received the same preoperative medical premedication and underwent the same anesthesia protocol. All patients underwent standard full sternotomy and cardiopulmonary bypass with mild hypothermia. Antegrade and retrograde cold blood cardioplegia was used for cardiac protection. The ablation procedure was performed with the Medtronic Cardioblate bipolar RFA clamp.

Radiofrequency ablation around the right and left pulmonary vein orifices, as well as around the base of the LA appendage was usually performed before clamping the aorta. After the aortic cross-clamping, two connecting lesions were made on the LA posterior wall between both islands of pulmonary veins (box lesion). The LA appendage was closed from the atrial side using a running polypropylene 4/0 suture.

Intraoperatively, surgical data such as cardiopulmonary bypass time, aortic cross-clamp time and type of surgery on mitral valve were recorded. Postoperatively, both groups underwent the same routine postoperative intensive care unit (ICU) and ward care. All patients received amiodarone intravenously 300-600 mg b.i.d. for the first 3 postoperative days. Afterwards, or when the patient's condition allowed, amiodarone was continued orally in a dose of 200 mg daily. In case of a relapse of AF, electroconversion was performed after a thrombus in the LA was excluded with transesophageal echocardiogram (TEE). In case of severe bradycardia (<50/min), amiodarone was discontinued. A permanent pacemaker was implanted in case of long-standing bradycardia (>10 days). All patients received oral anticoagulation therapy with warfarin for 6 months regardless of their heart rhythm, with a target INR 2.5-3.5.

All patients underwent a 6-month follow-up. Postoperative electrocardiograms (ECGs) were used to assess heart rhythm. They were performed routinely before discharge from the hospital and afterwards at 3 and 6 months after the surgery. Additional ECGs were performed at the discretion of the referring physicians. If the patient was found to be in AF, conversion to sinus rhythm was attempted with electroconversion. A TEE was performed prior to conversion if the patient was not adequately anticoagulated for the last 6 weeks. In addition to ECG, a transthoracic echocardiogram

was performed 6 months after the surgery. To declare a patient to be in normal sinus rhythm, in addition to an ECG, sinus rhythm had to be confirmed echographically as well.

The primary endpoint of the study was the percentage of patients who were in sinus rhythm 6 months after the surgery.

Continuous variables were compared using the Student's t-test for parametric and Mann-Whitney U test for nonparametric data. A paired-sample t-test was used to compare preoperative and postoperative echocardiogram data. Categorical variables were analyzed using χ^2 -test or Fisher exact test, as appropriate. Additionally, a binary logistic regression model was constructed using factors found to be significant in univariate analyses ($p < 0.05$) to assess the independent correlates to sinus rhythm after 6-month follow-up. All statistical analyses were performed using the SPSS 22.0 software (IBM Corporation, Armonk, NY, USA).

Results

A total of 40 patients were included in the study, with 20 patients in each study group. The results are reported as mean \pm standard deviation for continuous data and frequencies (percentages) for categorical data. The groups were well matched for baseline demographics, preoperative medications, and comorbidities (Table 1). The mean LA diameter difference between the study groups was 15.8 mm (mean diameter was 45.6 \pm 4.6 mm in group 1 and 61.4 \pm 6.8 mm in group 2; $p < 0.001$).

Both groups had similar intraoperative characteristics with no significant differences regarding cardiopulmonary bypass time, aortic cross-clamp time, and the ratio of mitral valve repair/replacement (Table 2).

The postoperative heart rhythm is shown in Table 3. No significant differences between the study groups could be detected regarding the heart rhythm at discharge from the hospital. Similarly, no statistically significant differences were identified three months after the surgery. However, after 6 months, significantly more patients were found to be in sinus rhythm in group 1 as compared to group 2 (15 (75%) *vs.* 8 (40%); $p = 0.025$).

The binary logistic regression analysis demonstrated the LA size larger than 5 cm to be an independent predictor of the success of surgical RFA. In addition to

Table 1. Preoperative patient characteristics

	Group 1 (LA \leq 50 mm)	Group 2 (LA $>$ 50 mm)	p value
LA diameter (mm)	45.6 \pm 4.6	61.4 \pm 6.8	<0.001
Age (yrs)	67.7 \pm 11.8	71.8 \pm 6.9	0.197
Male sex	13 (65%)	11 (55%)	0.519
Smoking	6 (30%)	8 (40%)	0.507
Body mass index (kg/m ²)	25.6 \pm 4.0	27.5 \pm 12.5	0.766
Diabetes mellitus	4 (20%)	2 (10%)	0.376
LVEF (%)	49.2 \pm 9.6	49.6 \pm 10.1	0.886
Mitral valve stenosis	7 (35%)	7 (35%)	0.999
Preoperative β -blocker	14 (70%)	17 (85%)	0.451
Preoperative ACEI/ARB	17 (85%)	18 (90%)	0.633
Preoperative digoxin	12 (60%)	12 (60%)	0.999

LA = left atrium; LVEF = left ventricular ejection fraction; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker

Table 2. Intraoperative data

	Group 1 (LA \leq 50 mm)	Group 2 (LA $>$ 50 mm)	p value
CPB time (min)	145 \pm 53	154 \pm 46	0.534
Aortic cross-clamp time (min)	100 \pm 34	118 \pm 43	0.211
MV repair/replacement	11/9 (55%/45%)	12/8 (60%/40%)	0.342
Concomitant procedure			
TV annuloplasty	19 (95%)	19 (95%)	>0.999
AVR	3 (15%)	5 (25%)	0.347
CABG	3 (15%)	4 (20%)	0.500

LA = left atrium; CPB = cardiopulmonary bypass; MV = mitral valve; TV = tricuspid valve; AVR = aortic valve replacement; CABG = coronary artery bypass grafting

the LA size, patient age and preoperative left ventricular ejection fraction (LVEF) also proved to be independent predictors of the success of surgical RFA (Table 4).

Table 3. Postoperative sinus rhythm

	Group 1 (LA ≤50 mm)	Group 2 (LA >50 mm)	p value
SR at discharge	16 (80%)	13 (70%)	0.288
SR at 3 months	16 (80%)	11 (55%)	0.091
SR at 6 months	15 (75%)	8 (40%)	0.025

LA = left atrium; SR = sinus rhythm

Table 4. Final step of binary logistic regression

Variable	B	Exp(B)	95% confidence interval for exp(B)	p value
Age (yrs)	-0.144	0.966	0.756-0.992	0.039
LA size >5 cm	-1.939	0.144	0.024-0.863	0.034
Preoperative LVEF	0.106	1.112	1.008-1.227	0.034

LA = left atrium; LVEF = left ventricular ejection fraction

Table 5. Postoperative course and complications

	Group 1 (LA ≤50 mm)	Group 2 (LA >50 mm)	p value
ICU stay (days)	4.6±2.9	5.6±3.3	0.371
Length of hospital stay (days)	13.6±7.0	13.4±5.8	0.817
Stroke	0	0	
Sternal wound infection	0	0	
Lethal outcome	0	0	

LA = left atrium; ICU = intensive care unit

Regarding the echocardiogram 6 months after the surgery, a significant decrease in the LA diameter compared to the preoperative values was detected in both groups (Fig. 1). However, there were no significant differences when comparing the mean LVEF before the surgery to the values 6 months after the surgery in either group (group 1: 49.2±9.6% *vs.* 47.4±8.8%, $p=0.205$; and group 2: 49.6±10.1% *vs.* 47.9±8.5%; $p=0.157$).

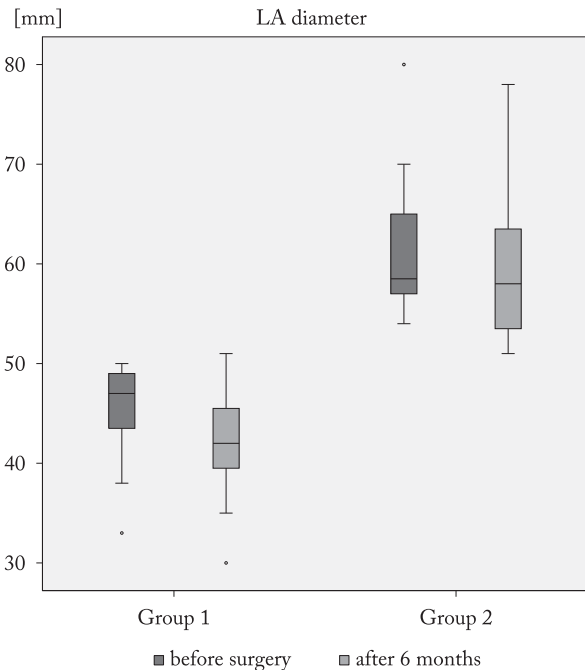


Fig. 1. Left atrium diameter: preoperative *vs.* 6 months postoperatively.

Group 1: 45.6±4.6 mm *vs.* 42.4±5.3 mm, $p<0.001$;
group 2: 61.4±6.8 mm *vs.* 59.1±6.8 mm, $p=0.008$.

Eventually, as summarized in Table 5, analysis of the postoperative course and complications did not show any differences between the groups. The length of ICU stay and overall hospitalization time did not differ between the groups. No lethal outcomes and neurologic adverse events were observed in the study. There were no sternal wound infections either.

Discussion

Chronic volume and pressure overload due to mitral valve disease results in dilatation and structural LA changes. Although the exact mechanisms remain unclear, mechanical stretching itself, along with consequent histologic changes such as fibrosis, necrosis and atrophy alter the electrical characteristics of the atrial myocardium. Unidirectional conduction blocks, prolonged circuit lengths, non-homogeneous repolarization, and altered refractory periods are the underlying electrophysiological substrates for triggering and maintaining the re-entrant circuits of AF^{28,29}.

It has been shown that AF and LA size are mutually interdependent. Many studies have confirmed LA

dilatation as the cause of AF^{30,31}, and *vice versa*, AF was also shown to be the cause of LA enlargement³². Although mitral valve surgery is mandatory to eliminate the pressure and volume overload of the LA, it is by itself inadequate to induce spontaneous conversion to sinus rhythm³³. These findings indicate irreversible underlying histologic and electrophysiological changes in the atrial myocardium. Therefore, an additional ablative procedure is necessary to efficaciously restore sinus rhythm.

In this study, the mean LA size at 6 months after the surgery was significantly smaller compared to the preoperative values in both groups. As we did not perform any surgical reduction of the left atria, we assume that this was due to a combined effect of both mitral valve surgery and the ablative procedure. However, the clinical consequence of this size reduction is questionable as the mean postoperative reduction of the LA diameter in groups 1 and 2 was only 3.2 mm and 2.3 mm, respectively.

In general, the reported long-term success rate of RFA for AF in patients with AF and mitral valve surgery varies from 65% to 90%^{34,35}. The results of our study are consistent with these reports, however, only in the group of patients with the left atria smaller than 5 cm. In the group with the larger left atria, we observed a significantly worse outcome as only 40% of the patients remained in sinus rhythm at the 6-month follow-up period. These results highlight the importance of good and consistent long-term follow-up of these patients. This is particularly important in patients with larger atria. In the group of patients with the left atria larger than 5 cm, the number of patients with stable sinus rhythm 6 months after the procedure nearly halved compared to the number of patients who were in sinus rhythm at the time of discharge from the hospital (8 *vs.* 13 patients).

Left atrial size is certainly one of the most cited predictors of the outcome of RFA for AF¹⁸⁻²¹. However, despite a large body of data and studies currently available, the results are often contradictory and inconclusive. In many cases, it is still difficult for a surgeon to foresee the success of a concomitant RFA procedure and to recognize the circumstances where prolonged procedure time, the risk of potential complications, and additional financial burden are warranted.

Many clinical investigators have set thresholds of the LA diameter in order to predict the efficacy of sur-

gical treatment of AF. Melo *et al.*³⁶ report the boundary of 5.5 cm, Yin *et al.*³⁷ set the threshold at 5.8 cm and Cao *et al.*³⁸ at 6.8 cm. Similarly, Isobe *et al.*³⁹ recommend LA reduction procedure only in patients with an LA diameter larger than 80 mm and a chest x-ray cardio-thoracic ratio greater than 70%.

However, with regard to the results of our study, a lower threshold value of the LA diameter is to be considered where additional measures for improving the outcome of RFA should be considered (biatrial lesion set, atrial reduction procedure).

Numerous studies have reported better results of RFA using both left- and right-sided atrial lesion^{40,41}. However, isolated LA ablation is still widely used and extensively studied worldwide, both in open and especially in minimally invasive procedures⁴²⁻⁴⁵. Furthermore, many recent studies report that the limited, left side-only lesions are not only effective⁴³, but may provide equivalent results as biatrial lesion sets⁴⁶⁻⁴⁸.

There also are some important limitations of this study, which need to be mentioned. Firstly, it was a relatively small, single-center study with only 40 included patients and a follow-up period of only 6 months. The identification of sinus rhythm relied on repetitive ECG recordings; no 24-hour Holter or continuous subcutaneous monitoring was implemented to detect potential paroxysms of AF. Furthermore, several different ablation technologies exist nowadays that use different energy sources to create tissue lesions; among them, radiofrequency and cryoablation are the most widely used. Because the present study focused only on (bipolar) RFA, the results may at least partially be also dependent on the ablation technology used.

In conclusion, although with some limitations, our study suggests that a suboptimal outcome of RFA is to be expected in mitral valve patients with larger LA. A lower cut-off value for reduction of the atria, as previously reported, may therefore be considered. Future research is warranted to better determine this threshold and to evaluate if additional right atrial lesions and/or an atrial reduction procedure could improve the outcomes of RFA in patients with LA diameter larger than 5 cm.

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Sažetak

UTJECAJ VELIČINE LIJEVOG ATRIJA NA PERZISTENTNI SINUSNI RITAM
KOD BOLESNIKA KOJI SE PODVRGAVAJU KIRURGIJI MITRALNOG ZALISTKA
I KONKOMITANTNOJ BIPOLARNOJ RADIOFREKVENTNOJ ABLACIJI

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Atrijska fibrilacija je povezana sa sistemskom embolizacijom i komplikacijama povezanim s antikoagulantnom terapijom. Radiofrekventna ablacija se preporuča kao učinkovita i sigurna metoda za liječenje atrijske fibrilacije. Cilj ove studije bio je procijeniti učinke veličine lijevog atrija na ishod operativne radiofrekventne ablacije. Studija je provedena na 40 bolesnika predviđenih za elektivno operativno liječenje bolesti mitralne valvule i radiofrekventne ablacije zbog trajne atrijske fibrilacije. Bolesnici su podijeljeni u dvije skupine prema veličini lijevog atrija. U prvoj skupini bili su bolesnici s lijevim atrijem promjera ≤ 5 cm, dok su u drugoj skupini bili bolesnici s promjerom lijevog atrija preko 5 cm. Primarni cilj studije bio je postotak bolesnika u stabilnom sinusnom ritmu 6 mjeseci nakon operacije. Rezultati zabilježeni 6 mjeseci nakon operacije pokazali su značajno više bolesnika u sinusnom ritmu u prvoj skupini u usporedbi s drugom skupinom: 15 (75%) prema 8 (40%), $p=0,025$. Multivarijantna analiza je dokazala veličinu lijevog atrija kao neovisan prediktor za uspjeh operativne radiofrekventne ablacije. Zaključuje se da je veličina lijevog atrija važan čimbenik o kojem ovisi uspješnost operativne radiofrekventne ablacije. Za poboljšanje rezultata ablacije trebalo bi u obzir uzeti niže vrijednosti za operativnu redukciju atrija od onih preporučenih u prijašnjim izvješćima.

Ključne riječi: *Atrijska fibrilacija; Antikoagulansi; Kateterska ablacija; Srčane pretkljetke; Kardiokirurški zahvati; Multivarijantna analiza*