

# Effect of Cryothermic and Radiofrequency Cox-Maze IV Ablation on Atrial Size and Function Assessed by 3D Echocardiography, A Randomized Trial. To Freeze or to Burn

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## Research Article

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# Abstract

## BACKGROUND

Cox-maze procedures are safe methods of restoring sinus rhythm (SR) in patients with atrial fibrillation (AF), and are often performed concomitant with mitral valve (MV) surgery. Atrial linear scars are achieved using Cryotherapy (Cryo) or radiofrequency (RF) techniques. It is unclear how these energy sources differ in terms of effects on late left atrial (LA) reverse remodeling. We used 3-dimensional echocardiography (3DE) to compare the impact of Cryo and RF procedures on LA size and function one year after Cox-maze IV ablation concomitant with MV surgery.

## METHODS

Seventy-two patients with MV disease and AF were randomized to Cryo (n = 35) or RF (n = 37) ablation. Another 33 patients were enrolled according to the protocol without ablation (NoMaze). All patients underwent echocardiogram before and one year after surgery. Between-group differences were evaluated using the Student's paired t-test. Fisher's analysis was used for categorical data.

## RESULTS

Forty-two ablated patients recovered sinus rhythm (SR) one year post-surgery, and had comparable left and right systolic ventricular function and a mean LA size reduction of 23% (LA volume index decreased from  $66 \pm 24$  to  $54 \pm 13$  ml/m<sup>2</sup>; p = 0.004). The 3DE extracted reservoir and booster function were higher after RF ( $37 \pm 10\%$  vs.  $26 \pm 6\%$ ; p < 0.001) than Cryo ablation ( $18 \pm 9$  vs.  $7 \pm 4\%$ ; p < 0.001), while passive conduit function was comparable between groups ( $24 \pm 11$  vs.  $20 \pm 8\%$ ; p = 0.17). Compared to maze groups, patients with restored SR without ablation (7 patients) had similar LA size reduction but more preserved systolic atrial function. The level of LAVI reduction depended on AF duration. Up to 30% reduction in 60% of patients with documented AF less than 6 months compared to 11% in those with AF for more than 5 years.

## CONCLUSIONS

SR restoration after mitral surgery and maze resulted in LA size reduction, irrespective of the applied energy source. Using 3DE, we demonstrated that compared to RF, Cryo produced an extended ablation area that implies LA structural remodeling affecting LA systolic function. Reduced reverse size remodeling was associated with longer AF history.

## TRIAL REGISTRATION

## Introduction

Atrial fibrillation (AF), the most encountered arrhythmia in clinical practice, carries a significantly increased risk of thromboembolic events and heart failure, which are an important cause of comorbidity and mortality worldwide. It occurs with a high prevalence in patients with mitral regurgitation (MR), presenting in over half of those referred for mitral surgery (1). The original surgical ablation technique is generically referred to as cut-and-sew Cox-maze III treatment. The Cox-maze IV procedure is a simplified alternative method of creating atrial lesions using different energy sources, which can be added to mitral surgery to restore SR in cases of AF. The maze procedure is now a Class I recommendation for selected patients, as it has reduced AF recurrence in randomized controlled trials (2) and decreased early and late mortality in risk-adjusted cohort studies (3). Two available techniques to achieve linear scars in the atria are: cryotherapy (Cryo) (freezing the myocardium) and radiofrequency (RF) (heating the myocardium). Several studies demonstrate that the efficacy of sinus rhythm restoration is quite similar with the two energy sources; however, when studying the impact of ablation on the myocardium, cryo procedures are associated with broader lesion width and higher degree of myocardial injury in both open surgery and catheter ablation patients (4, 5, 6). There is a growing interest in the assessment of LA remodeling following mitral valve surgery and after maze procedures, as LA size and function have an impact on long-term clinical outcome (7, 8)

Two-dimensional echocardiography (2DE) and three-dimensional echocardiography (3DE) are the most commonly used noninvasive imaging techniques for assessing atrial size and function. Compared to 2DE, current 3DE allows more accurate volume definition, providing volumes during the three atrial phases: reservoir (filling), conduit (passive emptying), and booster pump phase (active emptying) (9). The 3DE technique shows less interobserver variability and is ideal for serial measurements (10)

In the present study, we aimed to use 3DE to evaluate the impact of the two different energy sources, Cryo and RF, on left atrial size and function in patients with restored SR one year after the ablative procedure concomitant with mitral valve surgery.

## Methods

**STUDY POPULATION.** We performed a prospective, parallel, single-center study with three groups, of which two were randomized. We consecutively screened 105 patients with preoperative AF scheduled for mitral valve surgery between Sept 2013 and July 2018 at Linköping University Hospital (Fig. 1). In the context of a multidisciplinary conference, an arrhythmia group, comprising cardiologists and cardiac surgeons, discussed the indications for whether to add surgical ablation. A total of 72 patients were considered eligible for mitral surgery and maze IV treatment, and were randomly assigned, at a 1:1 ratio in blocks of 10, to undergo concomitant AF ablation with either a Cryo device (Cryo group, n = 35) or RF device (RF group, n = 37). The remaining patients were enrolled in the protocol but did not undergo

concomitant ablation and were thus not randomized (NoMaze group, n = 33). These patients had a low AF burden (one to two verified AF episodes), had severe comorbidities or the guidelines (11) indicated that additional aortic cross clamp time (and the associated prolonged ischemia) was too hazardous. In addition to mitral valve surgery, some patients underwent aortic surgery (10 patients; 9%), tricuspid surgery (76 patients; 72%), and/or coronary revascularization (25 patients; 24%). All patients underwent transthoracic echocardiography within 24 hours before the procedure. One year after surgery, the patients were offered an echocardiogram and medical survey. This study was approved by the Regional Ethical Review Board (2012/371 – 31). Patients were enrolled after providing written informed consent the day before surgery. This study is part of the registered clinical trial: DOI 10.1186/ISRCTN14454361.

**ABLATION METHODS.** Cryoablation was performed using the argon-powered Cardioblate® CryoFlex™ Surgical Ablation Probe (Medtronic Inc., Minneapolis, MN). The probe was applied for 120 s, and the temperature fell rapidly (Joule-Thompson effect) to between – 130°C and – 150°C at each ablation line. The left atrial lesions comprised three lines for the left atrium, and three for the right atrial wall, according to the Cox IV pattern (12).

RF ablation was performed using the Cardioblate® BP2 Irrigated Bipolar Surgical Ablation System (Medtronic Inc., Minneapolis, MN). This system uses irrigation and impedance-based power adjustments to reach tissue temperatures of between 50°C and 80°C during ablation. Each line was subjected to three complete ablation periods. The right and left pulmonary vein orifices were isolated pairwise and epicardially on bypass. The remaining lines were performed endocardially upon cardioplegic arrest, according to the Cox IV pattern (13). The biatrial lesion set was similar for both procedures.

**ECHOCARDIOGRAPHIC PROTOCOL.** All transthoracic echocardiography examinations were performed by the same technician using the Vivid E95 ultrasound system (GE Medical system, Horten, Norway). Stored images were analyzed offline by an experienced reader, blinded to the type of surgery. Echo parameters were measured following the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (14).

**TWO-DIMENSIONAL ECHOCARDIOGRAPHY.** Left ventricular (LV) volumes and ejection fraction (EF) were calculated using the biplane Simpson's method. We extracted the peak velocity of the early mitral inflow (E) and the late inflow caused by atrial contraction (A). The mean value of peak early diastolic tissue velocity from the septal and lateral wall (E') on tissue Doppler imaging (TDI) was used to calculate the E/E' ratio. The LA volume index (LAVI) was measured at end ventricular systole (ES) from the 4-chamber and 2-chamber views, using the biplane Simpson method, and indexed for body surface area (BSA). We also determined the right ventricular (RV) size and function based on tricuspid annular plane displacement (TAPSE) and systolic tissue Doppler velocity (S').

Strain analysis was performed based on 2D speckle tracking, to measure global longitudinal LV strain by automated functional imaging (AFI) in the 4-, 3-, and 2-chamber views. Atrial septal and lateral wall strain were assessed from the 4-chamber view, and calculated as the average over six atrial segments. For atrial strain, the zero reference was set at LV end-diastole. We extracted the LA longitudinal strain during the

reservoir phase (LASr) and the contraction (LASct) (Fig. 2). Image acquisition and analysis were performed according to EACVI/ASE Taskforce (14). All measurements were performed during SR, and averaged over three cardiac cycles. Heart rhythm, height, and weight for BSA calculation were collected at the echocardiography examination.

**THREE-DIMENSIONAL ECHOCARDIOGRAPHY.** The acquisition of a multibeam dataset (2–4 consecutive beats), at a resolution of > 20 frames per second, was performed from the apical view using a real-time 3DE system. We extracted the LA maximum volumes at end systole (ES), minimum at end diastole (ED), and preceding atrial contraction (pre-A). We then calculated the reservoir fraction (ResF); ES-ED/ES, conduit (CF); ES-preA/ES and booster fraction (BF); preA-ED/PreA. Full-3D image acquisition was performed only at the follow-up examination, one year after surgery.

Image analysis and measurement were performed offline using standard software (EchoPAC 202, GE Healthcare). A recently developed LA-dedicated software package was used for LA 3D analysis (Echopac 4D Auto LAQ, GE Health).

**STATISTICAL ANALYSIS.** Statistical analysis was performed using Statistica v.13 (Statsoft Inc., Tulsa, OK, USA). Results are expressed as mean and standard deviation (SD) for echocardiographic continuous variables, which were reasonably normally distributed. Categorical variables were presented as median [25th to 75th percentile] or count (percentage). Between-group differences were evaluated using the Student's paired t-test. Fisher's analysis was used for categorical data. A p value of < 0.05 was considered statistically significant. The correlation between echocardiography measurements was assessed using Pearson's correlation coefficient. No corrections were performed for multiple comparisons.

The intraclass correlation coefficient (ICC) and 95% confidence interval based on two-way mixed average measures were used to assess the reliability of 3D volume measurements performed by two observers (JK and MÅA) and by the same observer (MÅA) two times on separate occasions 3 weeks apart, in a random sample of 10 patients.

## Results

**DEMOGRAPHY.** Of the 105 patients included in this study, 89 underwent echocardiographic examination at the one-year follow-up ( $384 \pm 24$  days). Ten patients declined examination, and six patients died before the one-year follow-up (3 in the RF group, 2 Cryo group, and 1 NoMaze group). Ten patients declined examination. We excluded nine patients (three in each group) who required postoperative implantation of a Dual-Chamber permanent pacemaker device, as well as those who were in junctional rhythm ( $n = 4$ ). At follow-up, 27 patients were in atrial fibrillation (5 in the Cryo group, 6 RF group, 16 NoMaze group). The final analysis included 49 patients in sinus rhythm (20 in the Cryo group 20; 22 RF group, and 7 NoMaze group). The need for mitral valve replacement or repair was evenly distributed.

**CLINICAL CHARACTERISTICS OF PATIENTS WITH RESTORED SR ONE-YEAR POSTOPERATIVELY.** All groups had comparable preoperative clinical characteristics, except for the slightly older age in the Cryo

group compared with the RF group (Table 1). Of the 49 patients, 11 were women (22.4%): 5 in the Cryo group, 4 RF group, and 2 NoMaze group. Mitral valve replacement was performed in one patient in each maze group and two patients in the NoMaze group. Tricuspid valve repair was performed in 29 patients in the maze groups and 4 in the NoMaze group. Aortic valve replacement was performed in two patients in each maze group (Table 1).

Table 1  
Baseline and Perioperative Characteristics for the Study Population.

|                                    | Total<br>(n = 49) | NoMaze<br>(n = 7) | Maze<br>op<br>(n = 42) | p    | Cryo<br>(n = 20) | RF<br>(n = 22) | p           |
|------------------------------------|-------------------|-------------------|------------------------|------|------------------|----------------|-------------|
| Age, y                             | 66.7 ±<br>0.4     | 71.4 ±<br>6.5     | 65.9 ±<br>9.4          | 0.14 | 69.1 ±<br>6.8    | 63 ±<br>10.6   | <b>0.04</b> |
| Height, cm                         | 177 ±<br>11       | 176 ±<br>15       | 177 ± 10               | 0.74 | 177 ±<br>10      | 179 ±<br>10    | 0.48        |
| Weight, kg                         | 84 ± 16           | 79 ± 18           | 85 ± 16                | 0.43 | 81 ± 15          | 88 ± 17        | 0.20        |
| BMI, kg/m <sup>2</sup>             | 26.5 ± 4          | 25.3 ±<br>2.7     | 26.7 ±<br>4.2          | 0.40 | 26 ± 3.8         | 27.3 ±<br>4.5  | 0.31        |
| AF duration < 6 months             | 10                | 3                 | 7                      |      | 5                | 2              |             |
| AF duration > 6 months < 5<br>y    | 30                | 4                 | 26                     |      | 11               | 15             |             |
| AF duration > 5 y                  | 9                 | 0                 | 9                      |      | 4                | 5              |             |
| Paroxysmal, % (n)                  | 26.5<br>(13)      | 42.8 (3)          | 23.8<br>(10)           |      | 20 (4)           | 27.3 (6)       |             |
| Left atrial appendage<br>resection | 40                | 3                 | 37                     |      | 16               | 21             |             |
| ECC, min                           | 171 ±<br>47       | 147 ±<br>53       | 175 ± 45               | 0.15 | 175 ±<br>56      | 175 ±<br>34    | 0.98        |
| CCT, min                           | 107 ±<br>30       | 99 ± 32           | 109 ± 30               | 0.44 | 116 ±<br>37      | 103 ±<br>21    | 0.16        |
| Diabetes                           | 2                 | 0                 | 2                      |      | 1                | 1              |             |
| COPD                               | 8                 | 1                 | 7                      |      | 4                | 3              |             |
| NYHA (III-IV)                      | 37                | 5                 | 32                     |      | 17               | 15             |             |
| Heart failure                      | 30                | 5                 | 25                     |      | 14               | 11             |             |
| Hypertension                       | 18                | 5                 | 13                     |      | 6                | 7              |             |
| Euroscore                          | 5.3 ± 1.9         | 6.1 ± 1.2         | 5.2 ± 2                |      | 5.7 ±<br>1.5     | 4.8 ±<br>2.3   |             |

Patients in sinus rhythm assigned to different groups according to the intervention with or without ablation (Maze, NoMaze groups) and according to the applied ablation strategy (Cryo, RF).

ECC = extracorporeal circulation; CCT = cross clamp time; COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association functional classification.

**Preoperative echocardiographic findings.** Preoperative left and right ventricular size and function, and biatrial size, were comparable between patients who underwent maze ablation and those in the NoMaze group. Preoperative echocardiography data did not significantly differ when comparing the Cryo and RF ablation groups (Table 2).

Table 2  
Preoperative Echocardiographic Measurements in Maze and NoMaze Groups, and in Cryo and RF Ablation Groups.

|  | Total<br>(n = 49) | NoMaze<br>(n = 7) | Maze<br>(n = 42) | p    | Cryo<br>(n = 20) | RF<br>(n = 22) | p    |
|--|-------------------|-------------------|------------------|------|------------------|----------------|------|
| HR, rpm  | 73 ± 16           | 70 ± 16           | 73 ± 16.0        | 0.41 | 77 ± 15          | 70 ± 16        | 0.16 |
| BSA, m <sup>2</sup>                              | 2 ± 0.2           | 1.96 ± 0.3        | 2.02 ± 0.2       | 0.51 | 1.98 ± 0.2       | 2.06 ± 0.2     | 0.23 |
| LV end diastolic volume index, ml/m <sup>2</sup> | 65 ± 24           | 71 ± 29           | 64 ± 23          | 0.50 | 61 ± 15          | 68 ± 28.0      | 0.33 |
| LV ejection fraction, %                          | 57.3 ± 11.6       | 53.9 ± 10         | 57.8 ± 11.8      | 0.41 | 58.5 ± 12        | 57.5 ± 11      | 0.89 |
| LV global longitudinal strain, %                 | -20.2 ± 3.9       | -19.5 ± 4.8       | -20.4 ± 3.8      | 0.61 | -20 ± 4.7        | -20.7 ± 3      | 0.63 |
| RV inflow tract index, mm/m <sup>2</sup>         | 22 ± 4            | 23 ± 2            | 22 ± 5           | 0.84 | 22 ± 3.0         | 23 ± 6         | 0.62 |
| TAPSE, mm  | 20 ± 5.0          | 19 ± 5            | 20 ± 5           | 0.48 | 19 ± 4.          | 21 ± 6         | 0.32 |
| RV S', cm/s                                      | 10.5 ± 2.5        | 9.3 ± 1.9         | 10.6 ± 2.5       | 0.2  | 10.3 ± 2.5       | 10.9 ± 2.6     | 0.5  |
| Tricuspid regurgitation velocity, m/s            | 2.9 ± 0.5         | 3.2 ± 0.7         | 2.9 ± 0.4        | 0.12 | 2.9 ± 0.4        | 2.8 ± 0.5      | 0.49 |
| RV systolic pressure, mmHg                       | 38.2 ± 14.1       | 45.2 ± 18.9       | 36.6 ± 12.7      | 0.19 | 37.1 ± 11.1      | 36.1 ± 14.9    | 0.85 |
| LA area index, cm <sup>2</sup> /m <sup>2</sup>   | 17 ± 3            | 16 ± 4            | 18 ± 3           | 0.19 | 18 ± 3           | 17 ± 3         | 0.36 |
| LA volume index, ml/m <sup>2</sup>               | 68 ± 22           | 61 ± 31           | 70 ± 20          | 0.36 | 72 ± 24          | 67 ± 16        | 0.47 |
| RA area index, cm <sup>2</sup> /m <sup>2</sup>   | 14 ± 4            | 13 ± 2            | 14 ± 5           | 0.35 | 15 ± 6           | 13 ± 3         | 0.15 |

Data are expressed as mean  $\pm$  SD.

LV = left ventricle; RV = right ventricle; LA = left atrium; RA = right atrium; TAPSE = tricuspid annular plane displacement; S' = systolic tissue Doppler velocity in RV; BSA = body surface area.

**Postoperative echocardiographic findings.** At one-year post-surgery, three cases showed more than moderate mitral valve regurgitation. As this could affect the atrial size and function, these three patients were excluded from post-operative analysis. The analysis of 3-DE acquisition was not possible in 5 patients (2 RF, 2 Cryo and 1 NoMaze). Echocardiographic examination in patients with restored SR at one year after surgery revealed significant LV size reduction, with an LV end-diastolic volume index of  $65 \pm 24$  ml/m<sup>2</sup> before surgery compared to  $54 \pm 13$  ml/m<sup>2</sup> postoperatively ( $p = 0.004$ ). Table 3 displays data from the NoMaze and the maze groups.

**Atrial volume after maze surgery.** LA size was significantly decreased at follow-up examination. LAVI was  $66 \pm 24$  ml/m<sup>2</sup> before surgery compared to  $54 \pm 13$  ml/m<sup>2</sup> postoperatively ( $p = 0.004$ ), with a mean reduction of 23%. Six patients (13%) recovered a normal atrial size ( $< 34$  ml/m<sup>2</sup>), while 27 (59%) still had more than moderate LA enlargement ( $> 48$  ml/m<sup>2</sup>) at follow-up. Enlarged atria at follow-up was significantly correlated with AF duration (Fig. 3). LAVI was significantly larger in the Cryo group than the RF group. Full-volume 3D quantification was possible in almost all patients (44 patients: 90%). The RF and Cryo groups significantly differed in the LA reservoir ( $30 \pm 10$  vs.  $23 \pm 8$  ml;  $p = 0.03$ ) and booster volumes ( $11 \pm 7$  vs.  $5 \pm 4$  ml;  $p = 0.005$ ) but showed comparable LA volumes during the conduit phase ( $16 \pm 10$  vs.  $16 \pm 9$  ml;  $p = 0.9$ ), (Fig. 4).

Table 3 presents additional echocardiographic data.

**Atrial systolic function after maze surgery.** Reservoir and booster function analysis showed a significant difference in favor of the RF procedure (Table 3). The peak A wave velocity was  $0.53 \pm 0.20$  m/s at follow-up. It was close to 0 in 3 patients (7%), and slightly higher in the RF group than the Cryo group ( $0.58 \pm 0.18$  vs.  $0.46 \pm 0.2$  m/s;  $p = 0.06$ ). We observed a moderate correlation between peak A velocity and LA booster function ( $r = 0.41$ ,  $p \leq 0.05$ ). Longitudinal 2D strain analysis revealed no significant difference between groups (Table 3).



Table 3  
Echocardiographic Variables One Year After Surgery

|  | NoMaze<br>(n = 7) | Maze<br>(n = 39)   | p            | Cryo<br>(n = 17)   | RF<br>(n = 22)     | p           |
|--|-------------------|--------------------|--------------|--------------------|--------------------|-------------|
| Interval, days                                     | 377.1 ± 20.5      | 391.7 ± 70.4       | 0.54         | 407 ± 100          | 377.9 ± 13.3       | 0.18        |
| BSA, m <sup>2</sup>                                | 1.95 ± 0.3        | 2 ± 0.2            | 0.40         | 1.99 ± 0.2         | 2.01 ± 0.2         | 0.29        |
| Heart rate, rpm                                    | 70 ± 6            | 70 ± 8             | 0.91         | 70 ± 7             | 70 ± 8             | 0.99        |
| LV end diastolic volume index, ml/m <sup>2</sup>   | 52 ± 16           | 54 ± 13            | 0.7          | 53 ± 12            | 55 ± 14            | 0.62        |
| LV ejection fraction, %                            | 54 ± 3            | 55 ± 7             | 0.82         | 55 ± 8             | 55 ± 5             | 0.99        |
| LV global longitudinal strain, %                   | -16.4 ± 2.8       | -17 ± 3.2          | 0.62         | -17.4 ± 3.4        | -16.7 ± 3.1        | 0.35        |
| E/E'   | 21.2 ± 6.7        | 19.1 ± 6.8         | 0.47         | 21.9 ± 6.7         | 16.7 ± 6.3         | <b>0.01</b> |
| TAPSE, mm  | 13 ± 4            | 13 ± 3             | 0.49         | 14 ± 2             | 15 ± 3             | 0.22        |
| RV S', cm/s  | 7.6 ± 1.6         | 8.6 ± 2.1          | 0.22         | 9.12 ± 2.2         | 8.1 ± 2            | 0.13        |
| TR velocity, m/s                                   | 2.6 ± 0.2         | 2.5 ± 1.2          | 0.85         | 2.7 ± 0.4          | 2.2 ± 1.8          | 0.27        |
| RV systolic pressure, mmHg                         | 27 ± 5            | 32.8 ± 9.9         | 0.31         | 32.1 ± 7.4         | 33.8 ± 13          | 0.70        |
| Atrial size and function by 2D echocardiography, n |                   |                    |              |                    |                    |             |
| LA area index, cm <sup>2</sup> /m <sup>2</sup>     | 15 ± 3            | 143                | 0.46         | 15 ± 2             | 13 ± 3             | <b>0,02</b> |
| LA volume index, ml/m <sup>2</sup>                 | 56 ± 22           | 53 ± 15            | 0.63         | 58 ± 14            | 48 ± 14            | <b>0,04</b> |
| LA Sr, %   | 15.5 ± 4.9<br>(6) | 11.7 ± 4.9<br>(38) | 0.09         | 11.7 ± 4.9<br>(17) | 11.8 ± 5.2<br>(21) | 0.9         |
| LA Sct, %  | 8.6 ± 4.9<br>(6)  | 4.2 ± 2.8<br>(36)  | <b>0.003</b> | 3.4 ± 1.8<br>(15)  | 4.7 ± 3.3<br>(21)  | 0.18        |
| RA area index, cm <sup>2</sup> /m <sup>2</sup>     | 14 ± 7            | 15 ± 8             | 0,79         | 17 ± 10            | 14 ± 6             | 0.20        |
| Atrial size and function by 3D full-volume         |                   |                    |              |                    |                    |             |

|  | NoMaze<br>(n = 7) | Maze<br>(n = 39) | p           | Cryo<br>(n = 17) | RF<br>(n = 22) | p                 |
|--|-------------------|------------------|-------------|------------------|----------------|-------------------|
|  | (n = 7)           | (n = 35)         |             | (n = 16)         | (N = 19)       |                   |
| LA minimum volume index, ml/m <sup>2</sup> | 26 ± 10           | 29 ± 9           | 0.40        | 34 ± 8           | 26 ± 9         | <b>0.008</b>      |
| LA maximum volume index, ml/m <sup>2</sup> | 45 ± 14           | 42 ± 13          | 0.54        | 46 ± 11          | 39 ± 15        | 0.11              |
| LA pre-A volume index, ml/m <sup>2</sup>   | 34 ± 12           | 34 ± 10          | 0.99        | 37 ± 9           | 31 ± 10        | 0.11              |
| LA reservoir function, %                   | 42 ± 16           | 32 ± 10          | <b>0.05</b> | 26 ± 6           | 37 ± 10        | <b>&lt; 0.001</b> |
| LA conduit function, %                     | 24 ± 18           | 22 ± 8           | 0.67        | 20 ± 8           | 24 ± 11        | 0.17              |
| LA booster function, %                     | 22 ± 12           | 13 ± 9           | <b>0.03</b> | 7 ± 4            | 18 ± 9         | <b>&lt; 0.001</b> |

LA longitudinal strain during reservoir phase (LASr) and LA strain during contraction (LASct) were extracted from 2D-speckle tracking analysis.

**Atrial size and function in NoMaze patients with restored SR.** In the NoMaze group, 7 of 23 patients (30.4%) had SR at follow-up. LA volume was not significantly reduced ( $56 \pm 22$  compared to  $61 \pm 31$  ml/m<sup>2</sup> preoperatively;  $p = 0.7$ ). LA function was higher during the contraction phase, expressed as A wave velocity ( $0.9 \pm 0.2$  compared to  $0.5 \pm 0.2$  m/s in the maze cohort;  $p < 0.001$ ), while booster function, 2D strain, and reservoir function were comparable (Table 3).

**PATIENTS WITH ATRIAL FIBRILLATION AT FOLLOW-UP.** Compared to those in SR, the 27 patients who had atrial fibrillation at follow-up were older ( $72 \pm 9$  vs.  $67 \pm 9$  years;  $p = 0.009$ ) and had larger LA size before surgery (LAVI:  $91 \pm 38$  vs.  $68 \pm 22$  ml/m<sup>2</sup>;  $p = 0.001$ ), with comparable LV systolic function (EF:  $55 \pm 8\%$  in AF vs.  $55 \pm 7\%$  in restored SR;  $p = 0.7$ ). At follow-up, compared to patients with restored SR, those with AF had significantly lower LV and RV function (EF:  $49 \pm 9$  vs.  $55 \pm 6\%$ ;  $p = 0.005$ ; TAPSE:  $12 \pm 3$  vs.  $14 \pm 3$  mm,  $p = 0.01$ ).

Patient showed a reduction in LA size after surgery. Preoperative LAVI was  $91 \pm 38$  ml/m<sup>2</sup> compared to  $74 \pm 24$  ml/m<sup>2</sup> after surgery ( $p = 0.01$ ), with no difference between the maze and NoMaze groups.

**REPRODUCIBILITY.** The intraclass correlation coefficient showed the intraobserver variability for 3D LA volume measurements: EDV 0.92 (0.85–0.97), ESV 0.98 (0.96–0.99), and pre-A 0.89 (0.71–0.91). The interobserver correlation was high for LA EDV 0.90 (0.73–0.96), ESV 0.84 (0.53–0.95), and pre-A volume 0.75 (0.70–0.82).

## Discussion

To our knowledge, this is the first prospective and randomized study to compare the effects of Cryo and RF ablation modalities on the atria, assessed using 3D echocardiography. We found that patients who were in SR at one year after maze procedure with concomitant mitral valve surgery presented with 1) a reduction of left atrial size which was more pronounced after RF ablation compared to Cryo; 2) better systolic left atrial function after RF ablation (expressed as booster and reservoir fractions compared to the Cryo cohort); and 3) a lower booster fraction compared to the NoMaze group.

The maze procedure is performed to electrically isolate the atria by generating linear scars through application of a warm or cold energy source. Its safety has been proven by several studies (15, 16, 17), and sinus rhythm restoration after this procedure has positive impacts on long-term clinical outcomes (18, 19), although further investigation is needed to determine the extent of LA reverse remodeling and atrial function improvement. Atria undergo a stunning phase directly after cardioversion (20) and lone (surgical or percutaneous) correction of MR results in LA reverse remodeling (21) during the early postprocedural period (22), with a tendency to subsequently return to baseline levels in patients with untreated AF (23).

The setting becomes more complex when adding surgical ablation distress. Atrial myocardial contraction restoration might be more vulnerable when ablation lines are added to the surgical scars. In patients with preoperative AF and mitral valve disease who undergo lone MV surgery, spontaneous SR recovery occurs in 10–20% of cases (24, 25).

In our cohort, SR was restored in 14% of patients who underwent surgery without AF treatment, compared to 65% in the maze group.

**EFFECT OF RF VS. CRYO ABLATION ON LEFT ATRIAL SIZE AND FUNCTION.** The two maze groups showed, from similar preoperatively indexed values, a significant reduction of LA size, with a greater reduction and better preserved atrial function in the RF group.

We tested the hypothesis that Cryo ablation has greater negative impact on atrial function compared to RF, which is supported by the fact that Cryo lesions seem to cause wider damage on the atrial wall (26).

The result might reflect the different breadth of atrial myocardial injury during the ablative procedure between the two energy sources. Direct application of a cooled probe on the atrial epicardium leads to formation of frozen tissue in which trapped cells become irreversibly damaged and are ultimately replaced by fibrous tissue. The width of this area can vary depending on the atrial wall thickness, the time of application, and the temperature achieved. Our Cryo probe reached temperatures of  $-150^{\circ}\text{C}$ . However, currently available devices that cool down to higher temperatures might have the advantage of causing less damage to the surrounding tissues.

The RF lesion produced by tissue heating is smaller and more distinct upon gross examination. The temperature reached is over  $50^{\circ}\text{C}$ , which generates a central zone of coagulative necrosis, with

denaturation of most intracellular proteins. These areas develop inflammatory infiltrates, which are replaced by fibrosis (27).

Impaired atrial function could indicate an increased fibrotic burden of the atria, resulting from the larger lesions caused by Cryo ablation, which may irreversibly affect atrial mechanical properties. Kim et al. found a higher atrial contractility restoration rate after Cryo than after RF ablation (28). The authors used however, different lesion set in this retrospective study and atrial contraction recovery was analyzed on two dimensional echocardiographic parameters based only on atrial wave velocity.

In our study, the feasibility of LA acquisition and analysis on 3 D echocardiography was good (90%) and at one year after MV surgery and maze, LA volumes were still more than moderately enlarged. This enlargement likely reflects the structural remodeling process in response to the volume and pressure overload caused by the preoperative duration and severity of mitral disease, as well as the AF burden. Left ventricular diastolic function may impact LA size and function. Preoperative assessment of diastolic function is challenging in the presence of severe mitral regurgitation. Postoperatively, we found no difference in diastolic parameters expressed as  $E/E'$ , and the right ventricular systolic pressure was comparable between ablation groups. Furthermore, we found no difference in LA conduit function, which is closely related to passive LV filling and LV compliance (29).

**BOOSTER FUNCTION IN NoMaze COMPARED TO MAZE PATIENTS.** Compier et al. reported that atrial active transport function is not restored in approximately half of patients with post-procedural SR after concomitant surgical limited LA RF ablation, while it was restored in patients who underwent bare pulmonary vein isolation (30).

In parallel, our present study showed that compared to in ablated patients, non-ablated patients with spontaneous SR recovery showed better LA active contraction recovery, when the regurgitation was corrected, and no atrial wall distress was added by freezing or warming.

Despite the complex geometry and the thin atrial wall, the quantification of atrial myocardial deformation using strain analysis to evaluate phasic atrial function, was shown to be feasible, in line with other studies (31, 32).

However, we did not detect a difference in atrial function, expressed by reservoir and booster strain, between the RF and Cryo ablation groups.

LV function has been reported to improve after mitral surgery with concomitant ablation in patients with impaired function at baseline (33).

Most of our patients had good systolic ventricular function before the procedure, and they maintained comparable systolic function postoperatively.

## Conclusions

In patients with restored sinus rhythm one year after concomitant mitral valve surgery and Cox-maze IV ablation, the RF modality had a more positive impact on atrial mechanical function compared to the Cryo method. The availability of 3DE, and measurement of LA phasic function, provide a reliable tool for determining therapy results, and could become a precious technique for assessing LA function in clinical practice.

## **CLINICAL PERSPECTIVES**

LA structure and function are reported powerful predictors of outcome in various cardiac conditions (34).

LA enlargement is a predictor of AF recurrence after an ablation procedure (35),

thereby reflecting the risks of developing heart failure, stroke, and death (36).

The recovery of LA global mechanical function can augment LV filling and LV stroke volume, thus becoming an important factor in the setting of high-risk patients with LV dysfunction (37).

Additionally, LA volume reduction may contribute to the prevention of stroke or thromboembolism by increasing the blood flow velocity in the left atrium. These contributions may be affected in patients treated with Cryo; however, our present trial does not address the possible clinical implications.

## **Study Limitations**

The follow-up period was limited to one year. Further LA evaluation based on a larger number of patients, and with longer follow-up, would be valuable in the future. NoMaze patients were not randomized, in accordance with the guidelines, because of their high baseline risk. We did not perform any electro-anatomic voltage mapping after the ablation procedure was completed. The equipment used have changed over time since the study was carried on

## **Abbreviations And Acronyms**

AF = atrial fibrillation

BSA = body surface area

Cryo = cryotherapy

LA = left atrium

LAVI = Left Atrial Volume Index

LV = left ventricular

MR = mitral regurgitation

MV = mitral valve

RF = radiofrequency

3DE = three-dimensional echocardiography

## Declarations

### Ethical Approval

The regional Ethical Review Board in Linköping Sweden approved the study protocol (Registration numbers, 2014/451-32, 2015/400-32). The study was performed in accordance with the Declaration of Helsinki. All participants gave written informed consent before inclusion in the study.

### Competing interests

The authors declare that they have no conflicts of interest, financial or otherwise.

### Authors' contributions

GB drafted, analysed the data, reviewed and finalized the manuscript, MÅA analysed the echocardiographic data, performed statistical analyses, reviewed and finalized the manuscript, FV planned the study and critically reviewed the manuscript. All authors have had full access and take full responsibility for the data. All authors read and approved the final manuscript

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### Availability of data and materials

The data that support the study findings are available from the corresponding author upon request.

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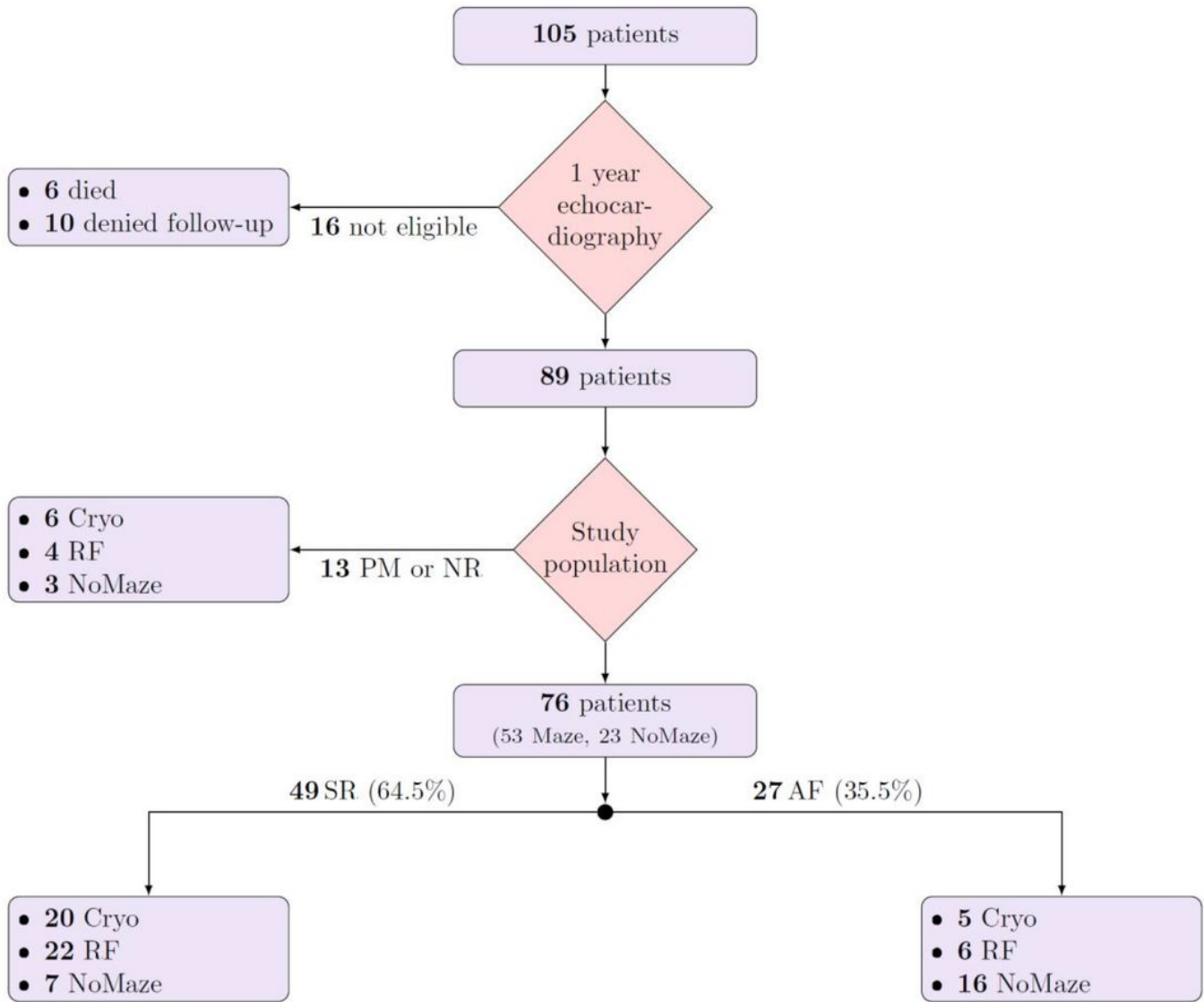
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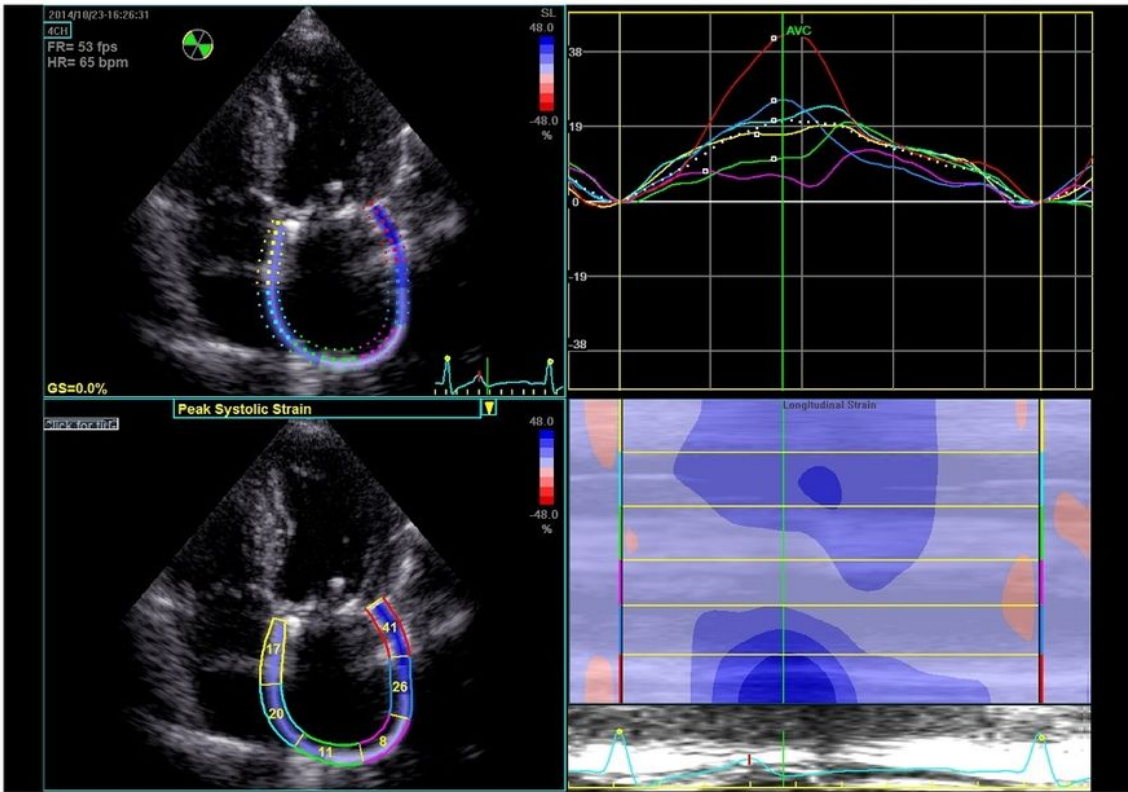
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## Figures



**Figure 1**

Flow Chart of the Patient Cohort Included in this Study



2a

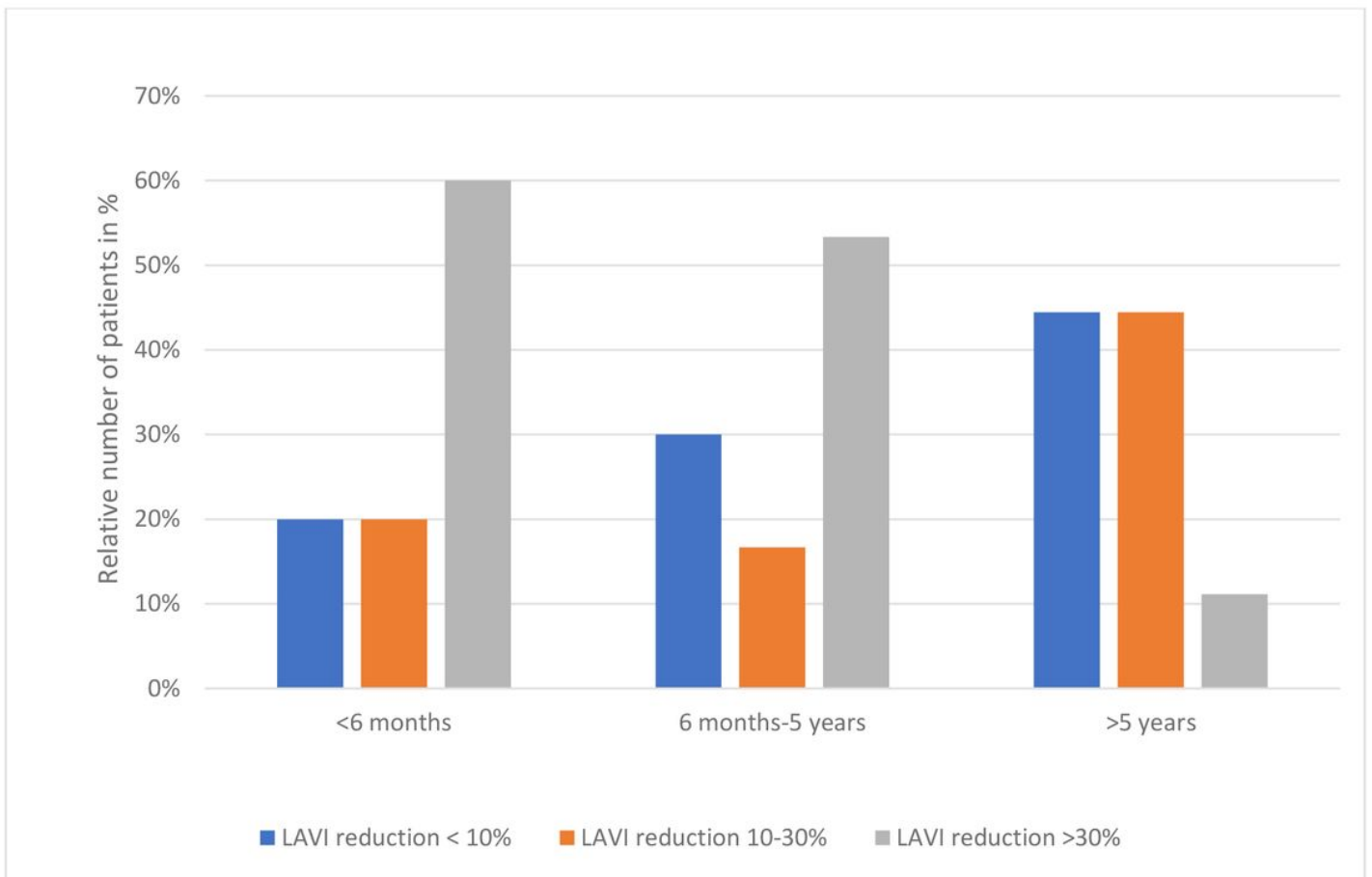


2b

Figure 2

a Left Atrial Function Analysis by 2D Strain

b Left Atrial Volume and Function Using 3D Echocardiography

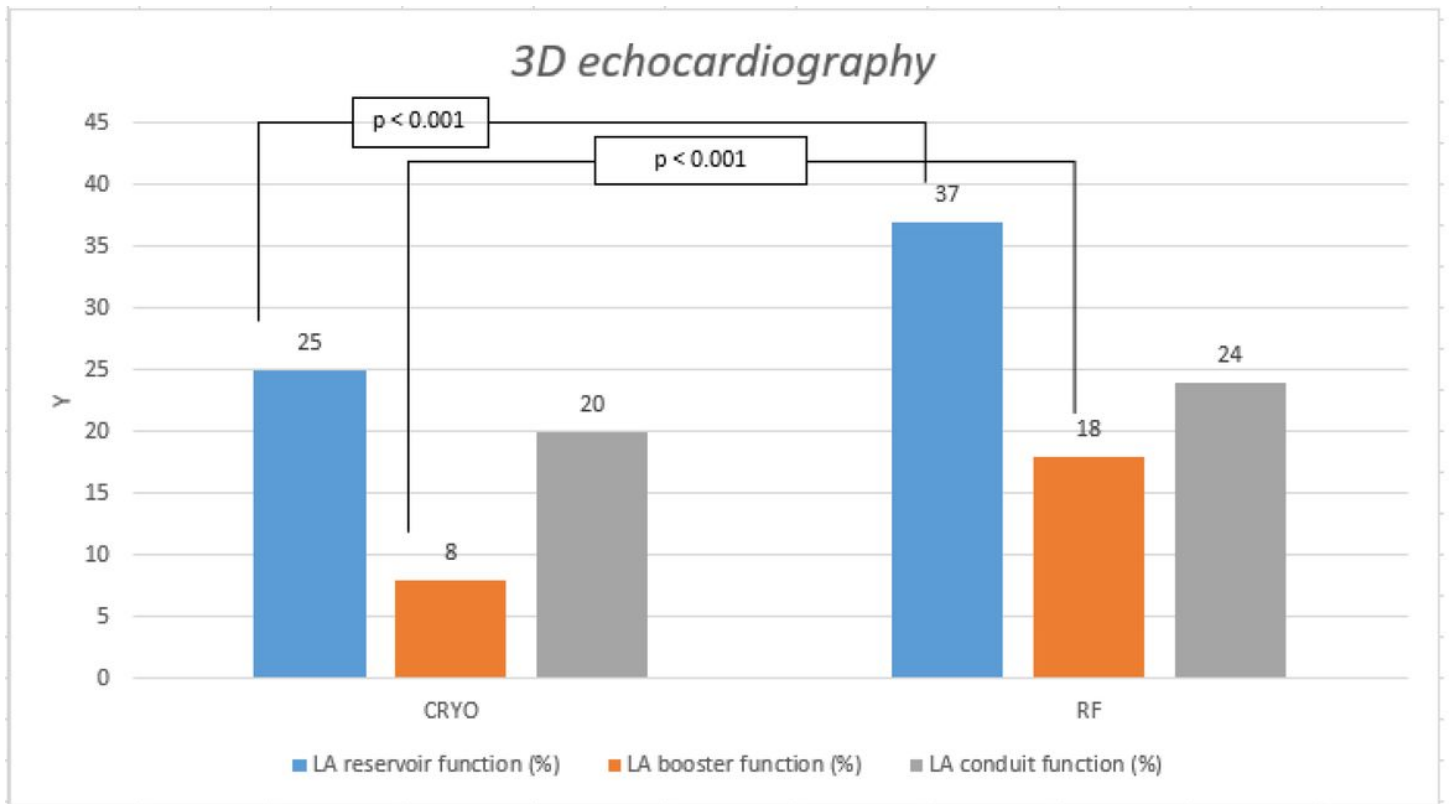


**Figure 3**

Left Atrial Reverse Remodeling After Surgery is Related to the Duration of Atrial Fibrillation.

Left atrial volume index (LAVI) difference between pre- and post-operative measurements.

Y-axis is relative number of patients in %.



**Figure 4**

Left Atrial Reservoir, Conduit, and Booster Pump Function Assessed by 3-Dimensional Echocardiography in Patients with Sinus Rhythm One Year After Cox-Maze IV Concomitant with Mitral Valve Surgery

Y-axis is mean atrial function values expressed in %.