Comparison of cardiac surgery with left atrial surgical ablation vs. cardiac surgery without atrial ablation in patients with coronary and/or valvular heart disease plus atrial fibrillation: final results of the PRAGUE-12 randomized multicentre study[†]

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Aims	Surgical ablation procedure can restore sinus rhythm (SR) in patients with atrial fibrillation (AF) undergoing cardiac surgery. However, it is not known whether it has any impact on long-term clinical outcomes.
Methods and results	This multicentre study randomized 224 patients with AF scheduled for valve and/or coronary surgery: group A (left atrial surgical ablation, $n = 117$) vs. group B (no ablation, $n = 107$). The primary efficacy outcome was the SR presence (without any AF episode) during a 24 h electrocardiogram (ECG) after 1 year. The primary safety outcome was the combined endpoint of death/myocardial infarction/stroke/renal failure at 30 days. A Holter-ECG after 1 year revealed SR in 60.2% of group A patients vs. 35.5% in group B ($P = 0.002$). The combined safety endpoint at 30 days occurred in 10.3% (group A) vs. 14.7% (group B, $P = 0.411$). All-cause 1-year mortality was 16.2% (A) vs. 17.4% (B, $P = 0.800$). Stroke occurred in 2.7% (A) vs. 4.3% (B) patients ($P = 0.319$). No difference (A vs. B) in SR was found among patients with paroxysmal (61.9 vs. 58.3%) or persistent (72 vs. 50%) AF, but ablation significantly increased SR prevalence in patients with longstanding persistent AF (53.2 vs. 13.9%, $P < 0.001$).
Conclusion	Surgical ablation improves the likelihood of SR presence post-operatively without increasing peri-operative complications. However, the higher prevalence of SR did not translate to improved clinical outcomes at 1 year. Further follow-ups (e.g. 5-year) are warranted to show any potential clinical benefit which might occur later.
Keywords	Atrial fibrillation • Surgical ablation • Maze • Cardiac surgery

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting 1–2% of the general population. It is associated with increased morbidity and mortality.[1,2] Its prevalence increases with age and with the presence of significant valve or ischaemic heart disease.[1,3] The surgical procedure for the treatment of AF was introduced in 1987 by Dr James L. Cox,[4,5] and for more

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than two decades, the Cox−Maze III procedure represents the standard for AF treatment.[6]

In recent years, patients undergoing cardiac surgery and suffering from AF are more and more frequently indicated for some type of concomitant surgical ablation procedure, with variable lesion sets and energies. However, many surgeons do not routinely treat AF with a concomitant cardiac surgical procedure. Gammie et al.[7] recently reported that in nearly 60% of patients undergoing cardiac surgery, concomitant AF is left untreated. This may be due to the variety of lesion sets and energy sources, but may also be due to the lack of clinically convincing results.

Only a few randomized studies have been published to date and they suffered from relatively small sample sizes, involving various groupings of patients and with inconsistent published data relative to mid- and long-term results.[8−16] These studies enrolled only patients scheduled for mitral valve surgery—thus, the efficacy of surgical ablation in patients undergoing other types of surgery, e.g. coronary artery bypass graft (CABG) or aortic valve replacement (AVR), is even less well established, with one study showing an increased rate of peri-operative complications in the ablation group.[12] Most studies were able to demonstrate sinus rhythm (SR) restoration rates, but whether this has any (positive or negative) impact on major clinical events is not known.

Thus, a prospective randomized study was designed to estimate the role of surgical ablation procedures in an unselected group of patients with AF who were candidates for coronary and/or valve surgery.

Methods

Study design and patients

The PRAGUE-12 trial was a prospective, open, randomized multicentre clinical trial assessing the outcome of cardiac surgery with left atrial ablation vs. cardiac surgery alone (without ablation) in patients with coronary and/or valve disease and AF. The primary hypothesis was that surgical ablation of the left atrium (LA) would result in a higher incidence of SR in the treated group 1 year after surgery. The primary efficacy endpoint was SR presence (without any AF episodes) during a 24 h electrocardiogram (ECG) after 1 year. The primary safety endpoint was a composite of death, myocardial infarction (MI), stroke, or new onset renal failure (with the need for haemodialysis) at 30 days. The major secondary endpoint was a composite of death, major bleeding, stroke, or hospitalization for heart failure within 1 year of surgery. The study design also includes a 5-year follow-up.

The trial was approved by the institutional Ethics Committee of each participating centre and was conducted in accordance with the Declaration of Helsinki. All patients provided a written informed consent.

The inclusion criteria were indication for cardiac surgery (CABG, valve replacement or repair, others, or combinations) and AF (paroxysmal, persistent, or long-standing persistent) documented at least twice in the previous 6 months before surgery, a signed informed consent, and an age >18 years. The only exclusion criterion was emergency surgery. Patients who fulfilled these criteria were randomly assigned to surgery combined with left atrial ablation (group A) or to surgery without left atrial ablation (group B). Patient's pre-operative, intra-operative, and early post-operative data were prospectively recorded. After discharge from the cardiac unit, all follow-up data were prospectively recorded in anti-arrhythmic units of participating cardiology departments.

The study was designed and all data (mainly endpoints definitions) were collected and presented in accordance with definitions and recommendations for AF-related trials published by AHA/ACC, STS, EHRA, and AFNET.[17−19] The types of AF were defined according to current ESC guidelines.[1]

Surgical procedure

All patients (groups A and B) underwent a CABG and/or valve surgery through a median sternotomy, using cardiopulmonary bypass (CPB) and cardioplegic heart arrest. The energy source for creating lesions was chosen according to the preference of the lead surgeon and the guidelines of the particular department. In 113 (96.6%) patients, a surgical cryo-probe with an argon-based cooling system was used (ATS cryomaze 10 cm surgical ablation probe, ATS Medical, Inc., Minneapolis, MN, USA), and the ablation time for each lesion was 90 s; in four (3.4%) patients, a radiofrequency was used. The lesion set was the same for all patients in group A and was performed immediately prior to the valve or CABG procedure, but after placing the patient on CPB and arresting the heart. It included pulmonary vein (PV) ablation (left-sided and right-sided PV pairs separately), left atrial appendage (LAA) surgical resection, and three other lesions—interconnecting lesion between PV pairs, connecting lesion from PV to mitral annulus, and a lesion from the left upper PV to the rim of the LAA (Figure 1). This last mentioned lesion was performed endocardially in all patients after the resection of the LAA. In procedures where the LA was not opened (CABG, aortic/tricuspid valve surgery, or combination), all other lesions were performed epicardially. In procedures where the LA was planned to be opened (operations that included mitral valve surgery), all the other lesions were created endocardially after opening the LA. All procedures were performed using CO_2 insufflation. Lesion lines were not assessed for conduction block so as not to prolong the surgical procedure.

Treatment strategy

Patient medication was maintained until the day of surgery except for anticoagulation or antiplatelet therapy, which was either discontinued 5 days prior to surgery or switched to heparin. Post-operative care was identical for both groups. Unless contraindicated, all patients received
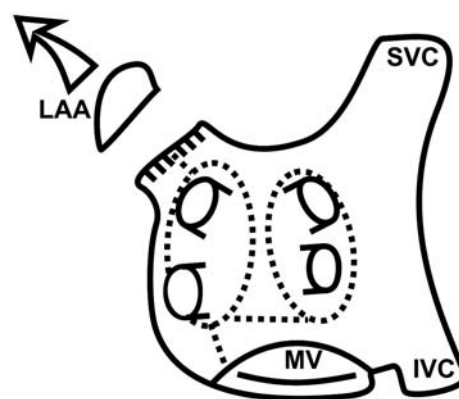
Figure 1 Schematic drawing of the left atrium in a postero-anterior view with the cryo-ablation lesions (dotted lines) and the left atrial appendage resection. LAA, left atrial appendage; SVC, superior vena cava; IVC, inferior vena cava; MV, mitral valve.

anti-arrhythmic drugs (AADs) post-operatively on the day of surgery; amiodarone was the first choice, with propafenone or sotalol as the second choice. All patients were put on warfarin with a target international normalized ratio of 2–2.5. Other medication, including beta-blockers, was adjusted routinely, according to the patient's co-morbidities. It was recommended that AADs be discontinued 3 months after surgery if the patient appears to be AF-free. Unless otherwise contraindicated, warfarin was recommended to be discontinued 6 months after surgery (i.e. 3 months after discontinuation of AADs) if patients remained in stable SR. Direct current cardioversion was strongly recommended if AF was present at the 30-day follow-up. Nevertheless, the actual treatment strategy was left at the discretion of the treating cardiologists (according to patients' CHADS$_2$ score and other characteristics).

Follow-up

Cardiac rhythm was continuously monitored until discharge from hospital. Post-operative follow-ups were scheduled at 1, 3, and 6 months and 1 year after surgery. All of the follow-ups were performed in the participating cardiology centres. The first three follow-ups included clinical examination and ECG, the 1-year follow-up also included a 24 h Holter-ECG and ECHO. At each follow-up, data regarding current medications, recent complications, or hospitalizations were recorded. Since the study was an open design, a blinded clinical events committee (CEC) was not established; nevertheless, the primary endpoint analysis was blinded since the Holter-ECGs were performed and analysed by arrhythmologists who did not have detailed information about the patients.

Power calculation

According to available publications, we assumed that the SR restoration rate 1 year after surgery would be 70% in the ablation group and 30% in the control group. A power analysis revealed that a minimum of 100 patients per group were required to assure at least 90% power for detecting the anticipated between-group differences in SR prevalence at 1-year and 5-year follow-ups and to compensate for the expected drop-out rate.

Statistical analysis

The primary analysis of the study was based on the intention-to-treat principle. Continuous data are presented as arithmetic means and SD for normally distributed variables or as medians and the 25th–75th percentiles range for log-normally distributed variables. Normality was tested using the Shapiro–Wilk test. Comparison of groups was based on Student's two-sample *t*-test and the Mann–Whitney test. Within-subjects comparisons at two time points were done using the paired *t*-test. Categorical data are given as absolute and relative frequencies (percentages). The differences in proportions between groups were analysed using Fisher's exact test and its generalization. Analysis of the major secondary endpoint at one year was based on the log-rank test for interval-censored failure time data. A logistic regression model was used to identify independent predictors of failure to restore SR. All statistical tests were treated as two-sided and evaluated at a significance level of 0.05. Statistical analysis was performed using the statistical software Stata, release 9.2 (Stata Corp LP, College Station, TX, USA).

Results

Patients

A total of 224 patients were enrolled in three university centres between 2007 and 2011. There were 117 patients randomized into group A and 107 patients into group B. Detailed patient characteristics are shown in *Table 1*. Both groups were comparable in all baseline characteristics, except for history of MI and chronic renal disease, which were more frequent in group B.

Peri-operative and post-operative courses

Two patients from group B were contraindicated to surgery after randomization and those were excluded from follow-up. Both groups were similar, comparable with regard to types of operations (*Table 2*). The lesion sets were completely performed in all patients in group A, and there were no intra-operative complications associated with energy application. Cross-clamp time, duration of CPB, and the overall surgical time were significantly prolonged in group A. At the end of surgery, significantly more patients in group A required epicardial stimulation and more patients in group B concluded the procedure in SR (*Table 3*).

Eleven in-hospital deaths occurred, six (5.1%) in group A and five (4.7%) in group B. Five patients died because of multi-organ failure, four because of cardiogenic shock or refractory heart failure, one died of ischaemia, and one died of sepsis. Other post-operative complications (except for those included in the primary safety endpoint) are shown in *Table 4*. Seven patients from group A and one from group B required an in-hospital pacemaker (PM) and/or implantable cardioverter–defibrillator (ICD) implantation to treat second or third degree AV block. The length of hospital stay was comparable in both groups.

At each follow-up, we analysed data from all patients who reached a given scheduled follow-up point (i.e. 1, 3, 6 months, and 1 year). The exact number of ECGs analysed is shown in *Figure 2*. The overall retention relative to clinical follow-ups is shown in the legend of *Figure 2*. At the time of data analysis, the last 13 patients enrolled had not yet reached the 1-year follow-up, which affected the overall retention for the 1-year follow-up. A total of 169 patients were included in the primary endpoint analysis 1 year after surgery (93 Holter-ECGs were recorded and analysed in group A and 76 in group B).

Comparing baseline characteristics of patients who were not included in the primary endpoint analysis (Not-analysed, i.e. died, refused follow-ups, or have not reached the 1-year endpoint yet) with those who were included (Analysed) showed a significantly higher prevalence of the use of angiotensin-converting enzyme-inhibitors (69.8 vs. 51.5%, *P* = 0.026), renal disease (20.8 vs. 8.3%, *P* = 0.022), lung disease (30.2 vs. 13.4%, *P* = 0.005), and hypertension (90.6 vs. 78.1%, *P* = 0.046) in the Not-analysed group. Those patients also had a shorter hospital stay (median of 7 vs. 8 days for the Analysed group, *P* = 0.011).

Primary outcomes

In group A, 56 of 93 patients (60.2%) showed SR (without any AF episodes) on the 24 h Holter-ECG 1 year after surgery, compared

Table 1 Baseline characteristics

Characteristics	Group A (with ablation) (n = 117)	Group B (without ablation) (n = 107)
Demography		
Age (years)	69.9 ± 7.8	71.0 ± 7.9
Female gender, n (%)	50 (42.7)	44 (41.2)
Body mass index (kg/m^2)	29.4 ± 4.6	28.8 ± 4.4
AF		
Duration (months)	15.0 (5.0−64.0)	16.0 (5.0−60.0)
Type of AF, n (%)		
Paroxysmal	26 (22.2)	33 (30.8)
Persistent	30 (25.6)	25 (23.4)
Longstanding persistent	61 (52.1)	49 (45.8)
Pre-operative rhythm, n (%)		
SR, n (%)	24 (20.5)	33 (30.8)
AF, n (%)	91 (77.8)	70 (65.4)
Paced rhythm	1 (0.9)	4 (3.7)
Atrial flutter (typical)	1 (0.9)	0 (0.0)
Pre-operative cardioversion, n (%)	18 (15.4)	15 (14.0)
Pre-operative catheter ablation, n (%)	2 (1.7)	2 (1.9)
Left atrial diameter (mm)	48.7 ± 7.3	47.7 ± 7.1
NYHA functional class, n (%)		
I	7 (6.0)	16 (14.9)
II	66 (56.4)	51 (47.7)
III	43 (36.7)	37 (34.6)
IV	1 (0.9)	3 (2.8)
Mean NYHA functional class	2.3 ± 0.6	2.3 ± 0.7
Comorbidity, n (%)		
Hypertension	95 (81.2)	86 (80.4)
MI	23 (19.7)	37 (34.6)
Stroke/TIA	13 (11.1)	15 (14.0)
Diabetes	41 (35.0)	40 (37.4)
Renal failure	7 (6.0)	18 (16.8)
Bleeding	4 (3.4)	6 (5.6)
Heart failure	29 (24.8)	34 (31.8)
Lung disease	19 (16.2)	19 (17.8)
Thyroid gland disease	10 (8.5)	17 (15.9)
Thrombosis	5 (4.3)	7 (6.5)
PM/ICD	9 (7.7)	15 (14.0)
Ejection fraction (%)	52.6 ± 10.9	49.9 ± 12.5
Logistic EuroSCORE	5.8 (3.2−9.9)	6.8 (4.0−11.6)
Medication, n (%)		
Beta-blocker	90 (76.9)	85 (79.4)
Amiodarone/propafenone	22 (18.8)	19 (17.8)
ACE-inhibitor	65 (55.6)	61 (57.0)
Digoxin	30 (25.6)	24 (22.4)
Statin	53 (45.3)	59 (55.1)
Sodium warfarin	81 (69.2)	69 (64.5)
Aspirin	41 (35.0)	33 (30.8)

Data are presented as mean ± SD or median, with 25th−75th percentile range in brackets, unless otherwise stated. n, number of patients; AF, atrial fibrillation; NYHA, New York Heart Association; TIA, transitory ischaemic attack; ICD, implantable cardioverter−defibrillator; EuroSCORE, European System for Cardiac Operative Risk Evaluation; ACE, angiotensin-converting enzyme; SR, sinus rhythm; MI, myocardial infarction; PM, pacemaker.

Table 2 Types of operations

Characteristics	Group A (with ablation) (n = 117)	Group B (without ablation) (n = 105)
Without mitral surgery, *n*	59	60
CABG	23	31
AVR	19	13
TVP	1	1
AVR + CABG	9	11
AVR + TVP	4	2
TVP + CABG	0	1
AVR + TVP + CABG	3	1
With mitral surgery, *n*	58	45
MVP	3	1
MVR	4	3
MVP + CABG	2	5
MVR + CABG	1	1
AVR + MVP	1	0
AVR + MVR	1	0
MVP + TVP	19	13
MVR + TVP	7	3
AVR + MVP + CABG	2	1
AVR + MVR + CABG	0	1
MVP + TVP + CABG	9	9
MVR + TVP + CABG	2	1
AVR + MVP + TVP	1	6
AVR + MVR + TVP	2	0
AVR + MVP + TVP + CABG	4	1

n, number of patients; CABG, coronary artery bypass graft; AVR, aortic valve replacement; MVP, mitral valve plasty; MVR, mitral valve replacement; TVP, tricuspid valve plasty.

Table 3 Operative characteristics

Characteristics	Group A (with ablation) (n = 117)	Group B (without ablation) (n = 105)	P-value
Duration of surgery (min)	220 (180–255)	200 (165–240)	0.003
CPB (min)	100 (74–121)	72 (46–97)	<0.001
Cross-clamp time (min)	78 (46–96)	51 (31.5–73)	<0.001
End-operation rhythm, *n* (%)			<0.001[a]
SR	69 (59.0%)	79 (75.2%)	
AF	12 (10.3%)	16 (15.2%)	
Epicardial stimulation	36 (30.8%)	10 (9.5%)	
Blood loss (mL)	680 (450–1115)	705 (445–945)	0.565
Hospital stay (days)	8 (7–12)	8 (6–11)	0.307

Data are presented as median, with 25th–75th percentile range in brackets unless otherwise stated. *n*, number of patients; CPB, cardiopulmonary bypass; SR, sinus rhythm; AF, atrial fibrillation.
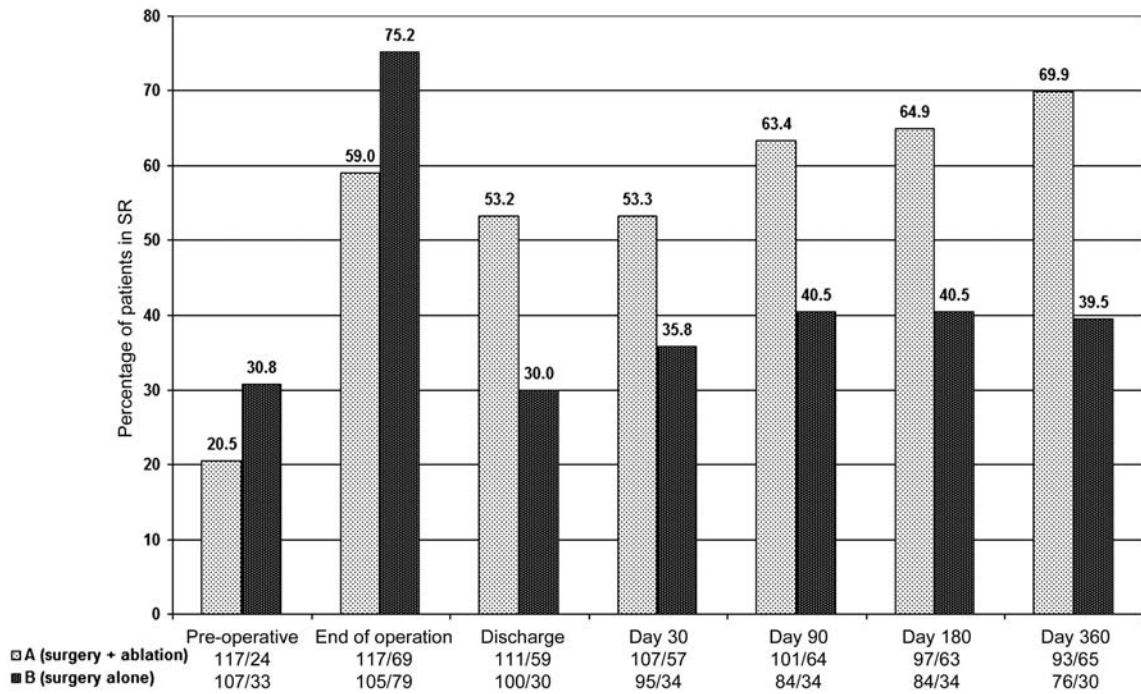[a]Fisher's exact test or generalized Fisher's exact test was used.

Table 4 Other 30 days' complications

Complications	Group A (with ablation) (n = 116)	Group B (without ablation) (n = 102)	P-value
Operative revision for bleeding	10 (8.6%)	9 (8.8%)	1.000
Other bleeding complication	5 (4.3%)	6 (5.9%)	0.759
Pneumothorax	4 (3.4%)	3 (2.9%)	1.000
Pleural effusion with puncture	16 (13.8%)	16 (15.7%)	0.706
Pneumonia	3 (2.6%)	4 (3.9%)	0.708
Respiratory insufficiency with re-intubation	3 (2.6%)	8 (7.8%)	0.119
Sternal wound infection	2 (1.7%)	0 (0.0%)	0.500
Heart failure with rehospitalization	14 (12.1%)	14 (13.7%)	0.840
Multi-organ failure	5 (4.3%)	4 (3.9%)	1.000
PM implantation	7 (6.0%)	1 (1.0%)	0.070

Data are presented as number with percentage in brackets. Fisher's exact test was used. *n*, number of patients; PM, pacemaker.

with 27 patients of 76 (35.5%) in group B (*P* = 0.002). The primary combined safety endpoint at 30 days after surgery did not show any significant difference in any of the followed (serious) post-operative complications (*Table 5*).

Other outcomes (1-year follow-up)

The occurrence of serious complications at the 1-year follow-up was similar in both groups (*Table 6*). The SR prevalence verified by ECGs at each time point is shown in detail in *Figure 2*.

Of the patients in SR 1 year after surgery, 36 (64.2%) in group A were without AADs and 23 (41%) were without warfarin compared with 20 (74%) and 11 (40.7%) in group B, respectively. However, of the remaining 33 anticoagulated patients in group A, 14 received a mechanical valve and 2 had other indications for chronic anticoagulation. Details regarding anti-arrhythmic therapy during follow-up are presented in *Table 7*.

Except for the early PM implantations mentioned above, another 4 patients in group A and 11 in group B required PM implantation between day 30 and the 1-year follow-up. Overall, the

number of PM implantations in the first post-operative year was 11 (9.9%) in group A and 12 (13%) in group B, (*P* = 0.512).

There was no significant change in mean left ventricular ejection fraction; in group A, it increased by 0.7 ± 9.1 vs. $1.1 \pm 11.3\%$ in

Figure 2 Electrocardiogram-verified sinus rhythm prevalence graph. The numbers below each column represent the number of electrocardiograms analysed/the number of electrocardiograms with sinus rhythm. Overall completeness of clinical follow-up (patients who died were included) was 97.8% at 1 month, 94.6% at 3 months, 95.1% at 6 months, and 91.4% at 1 year.

Table 5 Primary safety endpoint (30 days)

Complications	Group A (with ablation) (n = 116)	Group B (without ablation) (n = 102)	P-value
Primary combined safety endpoint	12 (10.3%)	15 (14.7%)	0.411
Death	9 (7.8%)	9 (8.8%)	0.809
Myocardial ischaemia	2 (1.7%)	2 (2.0%)	1
Stroke	2 (1.7%)	4 (3.9%)	0.422
Renal failure with HD	1 (0.9%)	4 (3.9%)	0.188

Data are presented as number with percentage in brackets. Fisher's exact test was used. HD, haemodialysis.

Table 6 One-year complications

Complications	Group A (with ablation) (n = 111)	Group B (without ablation) (n = 92)	P-value
Death	18 (16.2%)	16 (17.4%)	0.800
Bleeding	11 (9.9%)	9 (9.8%)	0.654
Stroke	3 (2.7%)	4 (4.3%)	0.319
Heart failure	26 (23.4%)	24 (26.1%)	0.680
Combined	45 (40.5%)	37 (40.2%)	0.785

Fisher's exact test was used. The groups were compared using the log-rank test for interval-censored data. n, number of patients.

group B ($P = 0.825$). The mean LA diameter enlarged non-significantly by 1.3 ± 7.3 mm in group A ($P = 0.085$) and significantly by 1.5 ± 6.0 mm in group B ($P = 0.037$); however, comparisons of means differences were non-significant ($P = 0.887$). In patients with successfully restored SR 1 year after surgery, the mean LA size increased by 0.5 ± 7.4 mm compared with 2.2 ± 5.8 mm in patients who remained in AF ($P = 0.112$). Patients in both groups (A and B) exhibited a similar improvement in the New York Heart

Association functional class; the mean decrease was 0.76 ± 0.9 in group A vs. 0.58 ± 0.85 in group B ($P = 0.174$).

Analysis of SR prevalence 1 year after surgery according to the type of pre-operative AF revealed that SR presence was much more common in group A compared with group B for all AF types. The difference (A vs. B) was significant in patients with pre-operative long-standing persistent AF (53.2 vs. 13.9%, $P < 0.001$). In intermittent pre-operative types of AF, the difference was non-significant (61.9 vs. 58.3%, $P = 1.000$ in paroxysmal; 72 vs. 50%, $P = 0.194$ in persistent AF). The overall group-by-AF type

Table 7 **Anti-arrhythmic therapy during follow-up**

Medication	Group A (with ablation)	Group B (without ablation)	P-value
Discharge, *n* (%)	*n* = 111	*n* = 100	
Beta-blockers	64 (58%)	67 (67%)	0.162
Anti-arrhythmics	91 (82%)	76 (76%)	0.285
Digitalis	9 (8%)	7 (7%)	0.761
Day 30, *n* (%)	*n* = 107	*n* = 93	
Beta-blockers	74 (69%)	69 (74%)	0.431
Anti-arrhythmics	80 (75%)	62 (67%)	0.207
Digitalis	10 (9%)	6 (7%)	0.451
Year 1, *n* (%)	*n* = 93	*n* = 76	
Beta-blockers	67 (72%)	59 (78%)	0.406
Anti-arrhythmics	29 (31%)	17 (22%)	0.200
Digitalis	10 (11%)	12 (16%)	0.333

Anti-arrhythmics: amiodarone, sotalol, or propafenone. Fisher's exact test was used. *n*, number of patients.

Table 8 **Sinus rhythm prevalence at 1 year according to the type of surgery**

Complications	Group A (with ablation) (*n* = 93)	Group B (without ablation) (*n* = 76)	P-value
Without MS			
Overall	27/46 (58.7%)	15/41 (36.6%)	0.053
CABG alone	9/18 (50%)	7/21 (33.3%)	0.342
AVR alone	8/14 (57.1%)	5/11 (45.5%)	0.695
With MS			
Overall	29/47 (61.7%)	12/35 (34.3%)	0.025
With CABG	10/13 (76.9%)	7/13 (53.9%)	0.411
Without CABG	19/34 (55.9%)	5/22 (22.7%)	0.026

Data are presented as number of patients in sinus rhythm/total number of patients (with percentage in brackets). Fisher's exact test was used. *n*, number of patients; MS, mitral surgery; CABG, coronary artery bypass graft; AVR, aortic valve replacement.

interaction *P*-value was 0.093. Detailed information regarding SR prevalence 1 year after surgery, relative to the type of surgery, is presented in *Table 8*. The overall group-by-mitral surgery interaction *P*-value was 0.725.

Multiple logistic regression analysis identified a longer pre-operative AF history as the only significant independent risk factor ($P = 0.024$). An association between failure and the degree of dilatation seen in the LA was different between groups A and B ($P = 0.039$) and was more pronounced in group B only ($P = 0.047$).

Discussion

The original Cox-Maze III operation had a 95% success rate in restoring SR that persisted 5 years after surgery.[20,21] Its significant effect on the reduction in the rate of cerebrovascular accidents and transient ischaemic events has also been described.[22,23] However, this method has not expanded a lot, mainly because it is a technically difficult and demanding procedure. A systematic review published in 2005 by Khargi *et al.*[24] reports comparable efficacy rates for the cut-and-sew Maze III surgery and ablation procedures using alternative energy sources; however, the limitation of that review was that rhythms were evaluated at a fairly short time of 6 months following procedure.

In the 2008 edition of *Cardiac Surgery in the Adult*, Voeller *et al.*[25] strongly recommend a concomitant Cox-Maze procedure to all patients with AF who were scheduled to undergo elective cardiac surgery.[25] Despite all the facts, a large data registry study shows that <50% patients receive some type of concomitant AF ablation when undergoing cardiac surgery.[7] We believe that this fact is strongly related to the lack of convincing results based on randomized studies with long-term follow-ups.

The aim of our trial was to assess the long-term efficacy and safety of surgical ablation compared with pharmacological treatment in non-selected, typical, realistic population of patients undergoing CABG and/or valve surgery. Cryo-energy (in most cases) and the left atrial lesion set were used, as they represented the standard ablation procedure used in the participating centres.

Our results show a significant improvement in restoring SR in the ablation group relative to the control group (60% in group A vs. 35.5% in group B, $P = 0.002$). Camm *et al.*[26] published a review of the nine most relevant papers, which reported efficacy of cryo-ablation in concomitant cardiac surgery. They found the SR prevalence at 1 year to be between 60 and 82%, which is very similar to our ablation group results. Similar comparisons can be made with trials that describe the efficacy of LA ablation procedures to be between 58 and 95%.[25]

A significant distinction was found when we analysed the SR prevalence at 1 year relative to the type of pre-operative AF. Many studies reported better results for ablation in patients with intermittent forms of AF compared with the continuous form.[26] Gammie *et al.*[27] reported an SR prevalence of 85% in intermittent AF and 47% in continuous AF 3 years after cryo-ablation. In our trial, the SR prevalence was found in 61.9% of those with paroxysmal, 72% of those with persistent, and in 53.2% of those with long-standing persistent AF, but compared with SR prevalence in the control group (B), a significant difference was found only in long-standing persistent AF ($P < 0.001$). Our explanation is that in intermittent forms of AF, the efficacy in both groups (but probably more in the group without ablation) was partly received due to ECG-unrecognized episodes of AF, that camouflage the real effect in the ablation group. Therefore, with one 24 h Holter recording, the real effect of the ablation procedure is more objectively shown in patients with long-standing persistent AF and that is why a significant difference could be obtained in this group even

with a single ECG-Holter after 1 year. Additionally, our results show an overall difference in SR prevalence in both groups when we compared results based on ECGs (shown in *Figure 2*) with Holter-ECGs (primary endpoint). Therefore, the efficacy of usage of single ECG-Holter monitoring seems to be arguable for correct evaluation of efficacy of heart rhythm after ablation procedures, whereas the total deficiency of monitoring using only an ECG has already been demonstrated.[28] In our study, we preferred this 'patient-friendly' monitoring strategy, because we felt that it gave us better compliance compared with Holter-ECGs that were scheduled more frequently.

Another interesting feature was noted when we analysed patients according to the type of concomitant surgery. In patients in whom the mitral valve was not involved, the overall difference of SR prevalence in group A compared with B was very close to the level of significance ($P = 0.053$), but was non-significant in patients who underwent CABG alone ($P = 0.342$) or AVR alone ($P = 0.695$). In patients in whom the mitral valve was involved, the effect was significant ($P = 0.025$), but when we divided those patients based on coronary artery disease (CAD), significance was found only in patients without CAD ($P = 0.026$). This might support a finding by the authors of the SWEDMAF trial,[12] who speculated that CAD could be a risk factor for failed cryo-ablation. It is worth mentioning that both divisions were found to be without a statistically significant relationship ($P = 0.249$).

Our peri-operative results were in agreement with the fact that the addition of surgical ablation was not associated with increased operative risk.[29] Blood loss and duration of hospital stay were equivalent. Occurrence of early serious post-operative complications did not differ in any of the conditions that we monitored, including death, MI, stroke, or renal failure with a need for haemodialysis. There were more patients who needed a PM implantation in group A—the difference was close to a level of significance ($P = 0.070$), but did not reach it although significance was reached in other publications.[7,28]

An important aim of our study was to assess the long-term effects of ablation. Our 1 year results did not show any significant clinical benefit for patients who received concomitant AF ablation. Overall 1-year mortality was 16.2% in group A and 17.4% in group B ($P = 0.800$). Occurrences of serious complications were similar in both groups, including major bleeding events, incidence of stroke, and hospitalization for signs of heart failure. This combined endpoint was positive in 40.5% of patients in group A and 40.2% in group B ($P = 0.785$). Even though the effect of ablation on the decreased incidence of strokes or stroke-related deaths are often reported,[23,30] we found remarkable, but non-significant, differences in stroke rates in favour of the ablation group at both the 30-day and 1-year follow-ups.

More significant ablation effects, relative to mortality and morbidity, are expected in the long term[31]; therefore, a 5-year follow-up is planned. Analysis of left atrial cryo-ablation failure risk factors found age, size of the LA, and pre-operative duration of AF to be risk factors of failure-to-restore SR in the whole set of patients; this was in accordance with other publications.[32–34]

Limitations of the study

This study has several limitations. First, the rhythm monitoring by ECGs and by single 24 h Holter-ECG may fail to detect certain recurrences of AF. This is an inherent limitation in all AF studies without implantable devices. Therefore, the actual SR prevalence could be overestimated, especially in patients with pre-operative paroxysmal or persistent AF; nevertheless, this mistake would most likely be equally distributed in both groups. Second, follow-ups were not completed in all patients. In addition to the expected drop-outs, the last 13 patients to enter the study had not reached the 1-year follow-up when the data were analysed, which partially skewed the retention rates for the 1-year follow-up. Third, differences (described in the Results section) were found between patients who were analysed for the primary endpoint and patients who were not analysed for the primary endpoint; however, in our opinion, those differences show mainly the corollary between higher pre-operative morbidity and post-operative mortality in the Not-analysed group. Fourth, as our study was focused mainly on the clinical impact of ablation, some other issues that are useful to follow (mainly data on atrial function) were not part of our focus. Fifth, since a blinded CEC was not established, the events were not evaluated in a blinded manner. Sixth, as the expected impact of ablation was not seen during the first year following surgery, a longer follow-up period seems to be necessary. We plan a 5-year follow-up with the possibility of a 1-week Holter-ECG as the final follow-up evaluation.

In conclusion, this prospective randomized study showed that adding left atrial cryo-ablation of AF to a cardiac surgery is safe and increases the SR prevalence at 1 year after surgery, although a benefit in peri-operative and 1-year mortality or morbidity was not found.

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