Short-term sinus rhythm predicts long-term sinus rhythm and clinical improvement after intraoperative ablation of atrial fibrillation

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Aims Our aim was to compare the long-term effects on rhythm and quality of life (QoL) after left atrial epicardial radiofrequency (RF) ablation vs. no ablation in patients undergoing cardiac surgery.

Methods and results Thirty-nine patients with ECG documented atrial fibrillation (AF) scheduled for coronary artery bypass grafting (CABG) with or without concomitant valve surgery were consecutively elected for epicardial RF ablation. Thirty-nine age- and gender-matched patients scheduled for CABG with or without concomitant valve surgery only and with documented AF served as controls. The follow-up after ablation was 32 ± 11 months. The percentage of patients in sinus rhythm (SR) at long-term follow-up was 62 vs. 33% (P = 0.03) after ablation and no ablation, respectively. SR at 3 months was highly predictive of that at 32 months (sensitivity 95%, positive predictive value 86%). Long-term SR was associated with better QoL, fewer symptoms, higher ejection fraction, and smaller left and right atria than AF.

Conclusion SR at 3 months was highly predictive of long-term SR that was associated with clinical improvement when compared with patients still in AF. AF at 3 months did not preclude a later stabilization to SR.

KEYWORDS
Ablation; Atrial fibrillation; CABG; Quality of life

Introduction

The first reports of a cure for atrial fibrillation (AF) related to the maze I surgery that was introduced by Cox et al.1 In spite of encouraging results, the technique was not widely used; instead, the complicated surgical technique was modified and performed with variations, sometimes referred to as 'mini-maze', but they had little in common with the surgical maze procedure and did not show the same efficacy. Meanwhile, progress was made in the catheterization laboratory after detection of arrhythmogenic pulmonary vein potentials.2–4 Taking advantage of this new knowledge, devices inducing myocardial injury by means of energy sources, such as radiofrequency (RF) energy, microwaves, ultrasound, laser, and cryothermal energy, were developed to be used during open heart surgery.5–7 Reports of successful treatment of AF in patients undergoing intraoperative ablation as a concomitant procedure during coronary artery bypass grafting (CABG) or valve surgery have usually comprised small non-randomized or non-controlled patient materials with short follow-up periods.

In the present study, we aimed at comparing the long-term clinical effects on rhythm and quality of life (QoL) after left atrial epicardial RF ablation vs. no ablation in patients who were to undergo CABG and had a history of AF.

Patients and methods

Thirty-nine patients were included between September 2001 and September 2004. The indication for surgery was the underlying ischaemic heart disease. Concomitant valve pathology was allowed. Patients were consecutively identified on the waiting list for CABG and were eligible for ablation if they had a history of AF with ECG documentation. Atrial fibrillation was classified according to the ACC/AHA/ESC guidelines8 and then divided into two groups: paroxysmal/persistent and permanent AF. Patients with unstable angina pectoris, hypertrophic cardiomyopathy, and re-operations

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Long-term effects on rhythm and quality of life

were excluded. The patients underwent CABG with or without concomitant valve surgery, and, in addition, epicardial RF ablation. Thirty-nine age- and gender-matched patients with AF undergoing CABG with or without concomitant valve surgery only treated during the same time period served as controls. All patients gave their written informed consent to participate in the study. The study protocol was approved by the Ethics Committee of Sahlgrenska University Hospital (Dno S-131-01). All patients underwent 24 h Holter monitoring the day before surgery, and a transthoracic echocardiography was performed to examine aortic, mitral, and tricuspid valve function, left ventricular ejection fraction (LVEF), and atrial dimensions.

Intraoperative radiofrequency ablation

A thorough dissection was made to expose the left atrium to optimize the contact with the ablation probe. A disposable monopolar radiofrequency probe (Cobra, Boston Scientific Corporation, San José, CA, USA) was used, delivering a maximum of 150 W over a period of 120 s at a preset temperature of 70°C at each lesion site. The ablation procedure was performed before valve surgery and CABG so as not to expose sutures and foreign materials to hyperthermia. The ablation lesion set consisted of two semicircles forming a full circle around each pair of right and left pulmonary veins with a connecting line in between. Connecting lines from the superior part of the left circle to the base of the left atrial appendage (LAA) and from the inferior part of the left circle to the mitral valve annulus were added (Figure 1). The LAA was closed from the outside with a purse string suture in all ablated patients and checked with transesophageal echocardiography for the absence of residual flow after declamping the aorta. Following the CABG routines at the time, the LAA was not closed in the control group. No tests were performed to confirm that the ablation lines were continuous or transmural.

Post-operative management and clinical follow-up

All patients were monitored with telemetry until hospital discharge. Amiodarone and/or sotalol was given to all patients in the ablation group for at least 3 months. Control patients were treated with antiarrhythmic drugs as needed. All patients with an indication for anticoagulation according to the ACC/AHA/ESC guidelines received warfarin. In the case of AF recurrence during the hospital stay, at least one DC cardioversion was attempted both in ablated and control patients. After discharge, all patients were followed by their referring cardiologist. DC cardioversion of recurrent AF was recommended for all ablated patients during the subsequent 3 postoperative months, and, for control patients, at the discretion of the patient’s physician. A 12-lead ECG was obtained at 3, 6, and 12 months in all patients. After 32 ± 11 months, a long-term follow-up was made using a 12-lead ECG, a 48 h Holter recording, and a transthoracic echocardiography. Any AF period exceeding 30 s on 48 h Holter monitoring was noted. At long-term follow-up, all patients completed the generic Quality of Life questionnaire Short Form-36 Health Survey and the Toronto Symptoms Checklist for Frequency and Severity in order to compare the patients who were then in sinus rhythm (SR) and AF.

Statistical analysis

Data are presented as mean ± SD or percentages, unless otherwise stated. For comparisons between groups, Fisher’s exact test was used for dichotomous variables and Mann-Whitney U-test for continuous/ordered variables. A two step strategy was applied to identify predictors of SR at long-term follow-up. First, 15 baseline factors were tested in a univariate analysis for association with success at long-term follow-up. These factors were age, sex, body mass index (BMI), previous hypertension, diabetes, stroke/transient ischaemic attack (TIA), angina pectoris, myocardial infarction, hyperlipidaemia and chronic obstructive pulmonary disease, type of AF, concomitant valve replacement, and treatment with ACE-inhibitors and lipid lowering drugs at index hospital discharge. Of these factors, those with a univariate P < 0.30 were tested in a second step for inclusion in a logistic regression model (forward stepwise selection, P < 0.30 for entering and P < 0.05 for staying in the model). All P values are two-tailed and considered significant if below 0.05. The log-rank test was used to test for differences between groups regarding freedom from documented AF/flutter during follow-up, from 3 months after operation and onwards. The corresponding Kaplan-Meier curves were calculated. Hazard ratios and corresponding confidence intervals were calculated using the Cox proportional hazards model.

Results

Pre-operative patient characteristics are given in Table 1. The prevalence of risk factors for AF was similar in both groups with the exception of a larger BMI in the control group (P = 0.02). Echocardiographically, there were no significant differences in the LVEF, or left or right atrial areas. Perioperative data are given in Tables 1 and 2. A full lesion pattern was performed in all patients. In one patient in the ablation group, CABG was not performed because the coronary artery was unsuitable for grafting. The additional extracorporeal circulation time in the RF ablation group was 24 ± 6 min. There was one in-hospital death in each group. In the ablation group, an 80-year-old male had an aortic valve replacement and CABG and died 18 days post-operatively of cerebral anoxia. In the control group, an 82-year-old male underwent aortic valve replacement, a tricuspid valvuloplasty, and CABG. Seventeen days post-operatively he needed a re-operation due to tricuspid valve insufficiency and died of pneumonia 54 days after the first operation. None of the complications was related to the ablation procedure. The slightly longer stay in the intensive care unit in the control group (Table 1) can be explained by logistic problems in maintaining an ideal patient flow.

Figure 1 Schematic representation of left atrial lesion set. LAA, left atrial appendage; LPV, left pulmonary veins; MV, mitral valve; RPV, right pulmonary veins.
Post-operative medication

During the post-operative hospital stay, four patients in the ablation group and two in the control group needed DC cardioversion. At the time of discharge, the ablated patients were on amiodarone (n = 34), sotalol (n = 10), digoxin (n = 5), beta-blockers (n = 9), and calcium-channel blocker (n = 1) vs. amiodarone (n = 1), sotalol (n = 6), digoxin (n = 9), beta-blockers (n = 24), and calcium-channel blocker (n = 1).
CHADS2 score of 1, 2, and 3, respectively, developed respectively. In the control group, three patients with CHADS2 score 1 and 2, respectively, developed embolic stroke 2 and 3 years post-operatively, adverse events are shown in survivors. Complete data were retrieved for 61 patients. Late complications, n

<table>
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<th>In-hospital Complications</th>
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Late complications, n

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<th>Complications</th>
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<tr>
<td>Death</td>
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TIA, transient ischaemic attack; ICD, implantable cardioverter defibrillator. In the control group, the same patient who got a permanent pacemaker post-operatively due to slow AF alternating with nodal rhythm, later received an ICD. In the ablation group, two permanent pacemakers were implanted 2 years post-operatively, one because AV block II on exertion and one before the planned His-ablation.

Morbidity and mortality

The long-term follow-up period was $32\pm11$ months. From a total of 78 patients, follow-up was attempted in the 69 survivors. Complete data were retrieved for 61 patients. Late adverse events are shown in Table 2. In the ablation group, two patients with CHAD$_S^2$ score 1 and 2, respectively, developed embolic stroke 2 and 3 years post-operatively, respectively. In the control group, three patients with CHAD$_S^2$ score of 1, 2, and 3, respectively, developed embolic stroke at 3 months, 1 year, and 1 month post-operatively. Remarkably, four of them were in SR at all rhythm control ECGs. Four of them, two in each group, had been given aspirin, whereas the fifth patient had alcohol abuse and was not capable of handling warfarin treatment. In addition, one patient with atherosclerotic plaque in the carotid artery in the ablation group had a TIA 3 years post-operatively and one patient in the control group had a peripheral arterial embolus in a leg 3 months post-operatively. During the follow-up period, there were three deaths in the ablation group, due to B-cell lymphoma, pneumonia, and one of unknown cause, and four deaths in the control group, two of heart failure, one of myocardial infarction, and one of sepsicaemia and multiorgan failure.

Rhythm and prediction of rhythm

The cumulative freedom from documented AF or atrial flutter was significantly higher in the ablated patients, $P=0.002$ (Figure 2). The first rhythm follow-up, at 3 months, was highly predictive of the rhythm at subsequent controls. In the ablation group, all but three patients with SR at 3 months had SR at 32 months [sensitivity 95%, positive predictive value (PPV) 86%, Figure 3A]. One patient in SR at 12 months refused long-term follow-up. Consistent with this, all but 2 of the 24 patients in the control group with AF at 3 months also had AF at long-term follow-up (sensitivity 91%, PPV 91%, Figure 3B). One patient with AF at 3 months died during follow-up and one patient with AF at 12 months refused long-term follow-up. The proportion of patients in SR at 3 months was 61% in the ablation group vs. 32% in the control group ($P=0.02$). The PPVs of the results at 3 months vs. $32\pm11$ months were 82–86% and the negative predictive values 90–91%, regardless of whether all patients, ablated patients, or control patients were counted. Thus, AF at 3 months after ablation did not preclude a later stabilization to SR, whereas SR, when found 3 months after ablation, was a good predictor of long-term SR. Long-term SR was, in turn, associated with higher LVEF and smaller left and right atria than AF.

Patients with paroxysmal or persistent AF had a higher chance of regaining and maintaining SR than those with permanent AF. In patients with paroxysmal/persistent AF, 82% were free from documented AF/flutter at $32\pm11$ months follow-up when compared with 53% in the control group ($P=0.005$, refers to all follow-up). In patients with permanent AF, the corresponding figures were 26 and 0% ($P=0.008$).
The following drugs were used for rhythm or rate control at the long-term follow-up: sotalol \((n = 3)\), amiodarone \((n = 2)\), beta-blockers \((n = 19)\), digoxin \((n = 3)\), and calcium channel blockers \((n = 1)\) in the ablation group and sotalol \((n = 1)\), amiodarone \((n = 1)\), beta-blockers \((n = 26)\), and digoxin \((n = 4)\) in the control group. We do not know how many had been given their beta-blockade and digoxin for other reasons than rhythm or rate control.

Multiple logistic regression analysis identified two variables independently predictive of success/SR at long-term follow-up. These were paroxysmal/persistent AF at baseline \((OR 16.7; 95\% CI 3.6, 78.5; P = 0.0004)\) and BMI \((OR 0.79; 95\% CI 0.63, 0.98; P = 0.03)\).

Quality-of-life assessment

Thirty-four patients in the ablation group and 30 patients in the control group completed the QoL assessment at the long-term follow-up \((Figure 4)\). There were no significant differences in SF-36 scores between the ablation and the control group at 32 months. However, when all patients in SR were compared with all patients in AF, irrespective of their original groups, those in SR scored better than those in AF with respect to bodily pain \((P = 0.002)\) and general health \((P = 0.005)\), whereas vitality was close to reaching statistical significance in spite of low numbers \((P = 0.07)\).

Figure 3 Flow chart of rhythm development during follow-up in (A) the ablation group and (B) the control group.

Figure 4 Comparison of quality-of-life scores (SF-36) between patients in sinus rhythm and atrial fibrillation at long-term follow-up. The scale is 0–100; higher is better. *\(P < 0.05\).

Symptoms

There was a significant difference for the better in the ablation group vs. the control group when symptoms check list scores for severity of symptoms were compared \((P = 0.03)\), but not for frequency of symptoms \((P = 0.08)\) \((Figure 5A)\).
When a comparison was made between patients in SR vs. AF, significant differences were seen in both scores, for severity \( P = 0.0004 \) and for frequency \( P = 0.0009 \) (Figure 5B).

**Discussion**

Restoration and maintenance of SR were associated with an improvement of clinical measures and QoL. Patients with pre-operatively diagnosed paroxysmal or persistent AF had a higher chance of regaining and maintaining SR than those with permanent AF, independent of the pre-operative occurrence of symptoms caused by AF. The difference in QoL is notable since very few of the patients had complained of symptoms of AF or had received pre-operative treatment for AF, and 14 patients actively negated symptoms when questioned pre-operatively. This implies that the symptoms of coronary artery disease may have dominated and/or were perceived to be more important. Our study demonstrated that, when AF can be treated, the future well-being of these patients exceeded that of those undergoing CABG, with or without valve surgery alone. Thus, our strategy to include patients on a consecutive basis rather than on the basis of selective symptoms was proved justified.

An antiarrhythmic agent (AA) was routinely administered during a period of 3 months post-operatively in the ablation group, but not in the control group, most frequently amiodarone \( n = 34 \), sotalol \( n = 2 \), and amiodarone + sotalol \( n = 8 \). In reality, 36 patients received AA, whereas two did not. It was an emerging concept that AAs would be beneficial in the early stabilization of SR by facilitating reverse remodelling. This aggressive policy to restore and maintain SR also included multiple DC cardioversions when necessary. It has since been our policy and was recently added to the current guidelines.\(^8\) To our knowledge, there is no randomized study that has compared the use of AAs or not during the first 3 post-operative months. Further to support the use of AAs, none of the deaths in the present study was caused by proarhythmia.

Pre-operatively, AF was categorized into paroxysmal, persistent, and permanent, according to the guidelines at the time.\(^9\) However, in some patients, a known, untreated, and accepted AF proved possible to treat. Consistent with this, the Cox maze III procedure, catheter ablation, and, now, intraoperative ablation have all provided evidence that AF that is no longer amenable to pharmacological and electrical treatment means can be cured, completely or partially, with good clinical benefit. Strictly defined, a permanent AF is no longer convertible or has been accepted, and ablation success in this group can be anticipated to be low. However, results from others as well as our own results show that patients with ‘permanent’ AF may benefit from ablation. Thus, among patients with permanent AF, there are long-standing persistent AF episodes that are still susceptible to treatment. Success rates in permanent AF are variable and some report better results than ours, most likely due to differences in patient populations as well as in ablation technique and lesion sets.\(^10\)

The post-operative period after intraoperative ablation is characterized by electrical instability with a stabilization of rhythm over time, and the clinical evaluation of rhythm usually starts after a period of stabilization of 3 months. Careful rhythm surveillance before and after catheter ablation shows the same pattern in many patients, expressed first as shorter and then fewer episodes, and finally as a reduction of the total AF burden. In the present study, we found a high predictive value of a 12-lead ECG at 3 months for SR at 32 ± 11 months. This was associated with clinical improvement, such as a reduction of symptoms, reduction of echocardiographic atrial dimensions, improvement of ventricular function, and better QoL, when compared with those still in AF.

In our study, owing to the consecutive enrolment practice, symptoms and QoL were never criteria for inclusion or exclusion, leading to inclusion of quite a number of patients who had not complained of AF or who perceived themselves not to have symptomatic AF. It is therefore notable that differences in QoL could be demonstrated at long-term follow-up and that this finding was corroborated by a reduction of symptoms. It can also be concluded that a pre-operative evaluation of symptoms may not give true information about the post-operative benefit of AF ablation.

The proportion of patients in SR was much higher as a result of the additional use of intraoperative ablation than after CABG with or without valve surgery alone. However, intraoperative ablation does not reach the same success rate as the Cox maze III procedure. Several factors may play a role: transmurality can be achieved at surgery by transmural cutting in a way that is difficult to ascertain during RF ablation. When ablation lines are long, it may be difficult to get a continuity of lines. Furthermore, the long-term predictive value of acute confirmation of transmurality and completeness of lines is not yet proven, and we do not know whether it would persist in the long-term, after the scar has developed.

![Figure 5](https://example.com/figure5.png)
The evaluation made with the Short Form-36 Health Survey QoL questionnaire at the end of the follow-up distinguished those who achieved long-lasting SR from those who did not. Since there was no validated disease-specific QoL instrument for AF, we added, over and above the generic SF-36, the Toronto Symptoms Checklist for Frequency and Severity. Significantly reduced severity of AF-related symptoms was noted, but not their frequency, when the ablation group and control group were compared. Comparison between patients in SR and AF showed highly significant differences in the cases of both frequency and severity.

In patients with AF, QoL can be significantly impaired by symptoms of palpitations, exercise intolerance, and fatigue. Patients with paroxysmal AF have significantly impaired health-related QoL when compared with healthy controls and commensurate with that in patients with significant cardiac disease. The reduction of scores in the physical and psychological domains of the generic SF-36 has been shown to be similar in patients with ischaemic heart disease undergoing percutaneous coronary intervention and after recent myocardial infarction when compared with patients with AF. QoL improves when AF is medically treated. According to the AFFIRM, RACE, and PIAF studies, there was no difference in QoL between patients who were treated with rhythm and those treated with rate control strategies. A possible explanation could be that antiarrhythmic drugs have potential side effects and do not prevent relapses of AF necessitating potential cardioversions. Lönnelholm et al. evaluated Cox maze III surgery in highly symptomatic patients refractory to antiarrhythmic drugs and found that the SF-36 scores were significantly improved after surgery and reached levels seen in the general population.

Warfarin was prescribed according to the ACC/AHA/ESC guidelines. Nevertheless, the number of early and late thromboembolic complications seems to be high. One stroke and one peripheral arterial embolism occurred during AF in the control group, but two strokes and one TIA in the ablation group and two strokes in the control group occurred in patients who regained long-lasting SR. The peripheral embolism occurred during warfarin treatment and the TIA during no thromboembolic treatment. All five strokes occurred during treatment with aspirin after treatment with warfarin had been terminated in four and never started in one because of ethylism. The results imply that the thrombogenicity remained in spite of restored SR and that long-term anticoagulation should be prescribed post-operatively and onwards in patients with a CHADS2 score >1 on a routine basis rather than be directed by the post-operative rhythm.

Limitations

Atrial fibrillation is present in ~10% of patients on the waiting list for open heart surgery. As we did not know who would benefit most, or at all, we abstained from selection and included eligible patients on a consecutive basis, then creating a control group of eligible patients who were matched for age and sex. We cannot exclude that the results concerning differences between the two groups might have been different if a randomized study protocol had been used. Rhythm control verification was made with repeated resting ECGs and 48 h Holter recordings. More continuous recordings with an implantable event recorder for automatic detection of AF might have yielded more, especially asymptomatic AF episodes, but this option was not available when the study was carried out.

Conclusion

Our results suggest that patients with not only long-standing AF but also paroxysmal AF may routinely be offered intraoperative ablation for AF as a concomitant procedure while being operated for coronary artery bypass surgery with or without valve disease. They also suggest that patients with long-standing SR have a better QoL than those who remain in AF.

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