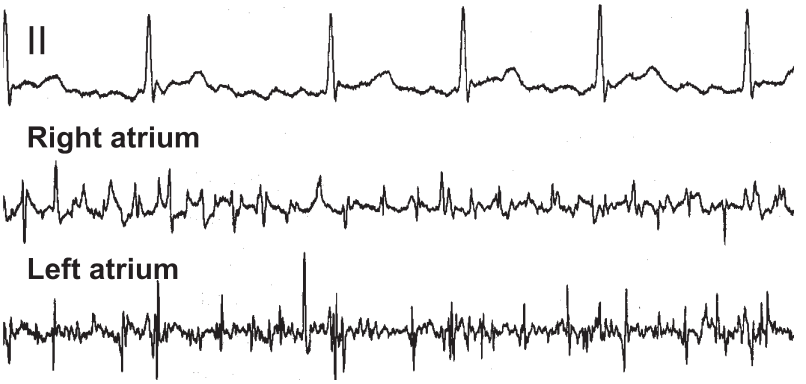
Aspects of Intraoperative Ablation for Atrial Fibrillation



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To my family - Hjalti, Anna and Atli

CONTENTS

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Abstract

Background: Increasing knowledge about mechanisms that trigger and maintain atrial fibrillation (AF) has influenced the possibilities for treatment and even cure of AF. The surgical Cox Maze III procedure is still the gold standard for the curative treatment of AF. The development of new technologies has made it possible to mimic most of the Cox Maze III procedure, including isolation of the pulmonary veins, by means of intraoperative ablation using an epicardial lesion set.

Aim: To assess the efficacy of intraoperative epicardial ablation in patients with a primary indication for cardiac surgery and with documented AF. To assess whether sinus rhythm (SR) after surgery is of clinical benefit to the patient. To identify preoperative factors that can help to predict SR postoperatively.

Method: Intraoperative ablation was performed with radiofrequency energy (RF) in papers I and IV or with cryo energy in II, III and IV. The lesion set was identical in all studies. The study design was randomization in paper II and with age and gender matched controls in papers I and III. Assessment of quality of life (QoL) and symptoms at long-term follow-up was made in paper I and of echocardiographic effects in relation to rhythm before and after coronary artery by-pass grafting (CABG) in paper III. The effects of intraoperative ablation and mitral valve surgery (MVS) were studied in paper II. In paper IV an assessment of potential preoperative echocardiographic predictors for SR after surgery was made in patients from papers I and III.

Results: In papers I, II and III concomitant intraoperative epicardial ablation with RF or cryo energy was significantly more effective in restoring SR than CABG or valve surgery alone. At 32±11 months after heart surgery and intraoperative RF ablation, patients in SR had better QoL and fewer symptoms than patients with AF. In paper III atrial and ventricular function was slightly decreased 22±6 months postoperatively, but still within or close to reference limits for patients in SR before and after surgery. There was a continued deterioration of echocardiographic variables in patients with AF pre- and postoperatively. Preoperative right atrial size and left ventricular diastolic function predicted long-term rhythm outcome (IV). SR at three months was a strong predictor of long-term SR (I and III). Independent preoperative predictors for SR at follow-up were paroxysmal/persistent AF (I), low BMI (I), short duration of AF (II), no coronary artery disease (II), SR before surgery (III) and a small left atrial area (III).

Conclusions: Concomitant intraoperative ablation was significantly more effective than CABG or valve surgery alone in restoring and maintaining SR. Patients with SR at long-term follow-up had better QoL and fewer symptoms. Preoperative predictors for SR postoperatively were right atrial size and left ventricular diastolic function. SR at three months was a strong predictor of long-term SR. The findings speak in favour of offering intraoperative ablation as a concomitant procedure to patients scheduled for CABG or valve surgery and with documented AF.

Key words: atrial fibrillation, radiofrequency, cryo, epicardial, intraoperative ablation, quality of life, atrial function, predictors of rhythm

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LIST OF PAPERS

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Johansson B, Houltz B, Berglin E, Brandrup-Wognsen G, Karlsson T, Edvardsson N
Short-term sinus rhythm predicts long-term sinus rhythm and clinical improvement after intraoperative ablation of atrial fibrillation.
Europace 2008;10:610-617

II. Blomström Lundqvist C, Johansson B, Berglin E, Nilsson L, Jensen S, Thelin S, Holmgren A, Edvardsson N, Källner G, Blomström P
A randomized double-blind study of epicardial left atrial cryoablation for permanent atrial fibrillation in patients undergoing mitral valve surgery: the SWEDish Multicentre Atrial Fibrillation study (SWEDMAF).
Eur Heart J 2007;28:2902-2908

III. Johansson B, Houltz B, Edvardsson N, Scherstén H, Karlsson T, Wandt B, Berglin E
Effects on echocardiographic measures in relation to rhythm before and after intraoperative epicardial cryoablation for atrial fibrillation.
Submitted

IV. Houltz B, Johansson B, Berglin E, Karlsson T, Edvardsson N, Wandt B
Left ventricular diastolic function and right atrial size are important rhythm outcome predictors after intraoperative ablation for atrial fibrillation.
Submitted

ABBREVIATIONS

AF	Atrial fibrillation
ANP	Atrial natriuretic peptide
AV	Atrio ventricular
BMI	Body mass index
BW	Body weight
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CHF	Congestive heart failure
DC	Direct current cardioversion
ECC	Extra corporeal circulation
ECG	Electrocardiogram
FU	Follow-up
GP	Ganglionated plexi
ICD	Implantable cardioverter defibrillator
ICU	Intensive care unit
LA	Left atrium
LAA	Left atrial appendage
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MAM	Mitral annulus motion
MLCV	Maximal longitudinal contraction velocity
MLVLARV	Maximal left ventricular long-axis relaxation velocity
MVS	Mitral valve surgery
NYHA	New York Heart Association
OR	Odds ratio
PCI	Percutaneous coronary intervention
PPV	Positive predictive value
PV	Pulmonary vein
QoL	Quality of Life
RA	Right atrium
RF	Radiofrequency
ROC	Receiver Operating Characteristic Curve
Rx	Randomized
SCL	Symptom Checklist for Frequency and Severity
SF-36	Short form 36
SR	Sinus rhythm
TIA	Transient ischemic attack

BACKGROUND

Definition and classification of atrial fibrillation

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized on the electrocardiogram (ECG) by the absence of consistent P waves before each QRS-complex, while instead there are rapid oscillations or fibrillatory waves that vary in size, shape and timing, resulting in an absence of coordinated atrial systole. The atrial rate is usually in the range of 350-600 impulses/minute. The ventricular rhythm is often irregular and its rate is dependent on the filtering of the AV node [1].

Atrial flutter is a related arrhythmia, in the typical form characterized by a saw-tooth pattern of regular atrial activation called *f*-waves on the ECG, usually at a rate of 280-300 impulses per minute. Atrial flutter may degenerate into AF and AF may convert to atrial flutter, sometimes during treatment of AF with antiarrhythmic drugs [2].

Different classification systems have been used to describe AF [3]. The pattern of the arrhythmia can change over time, but it seems to be of clinical value to classify the arrhythmia at a given time point. When a patient presents with AF for the first time, it is called first detected. When AF is terminated spontaneously, often within 24 hours, it is called paroxysmal and, if sustained beyond seven days, it is designated persistent. Longstanding persistent AF has a duration of more than a year and permanent AF is no longer possible to cardiovert to sinus rhythm (SR) or has been accepted [2]. Paroxysmal AF represents about one-third of all AF cases [4].

Epidemiology

The estimated prevalence of AF is 0.4-1 % in the general population [5, 6]. The prevalence of AF increases with age from 0.5 % at age 50-59 years to almost 9 % at age 80-89 years. The incidence of new onset AF seems to double with each decade of age [7]. The incidence of AF is less than 0.1 % per year in those under 40 years old to exceed 1.5 % per year in women and 2 % in men older than 80 [8, 9, 10]. Men have a 1.5 fold greater risk of developing AF than women, after adjustment for age and predisposing conditions [7]. The estimated lifetime risk for development of AF is 25% for men and women 40 years of age and older. Lifetime risk does not seem to change with increasing age, since the AF incidence rises with advancing age [11]. Secular trends in Europe and in the US point toward a rising prevalence of AF [6] *(Fig 1)*. In the

Framingham study the prevalence of AF in men 65-84 years of age nearly trebled during 1968-1989 [7].

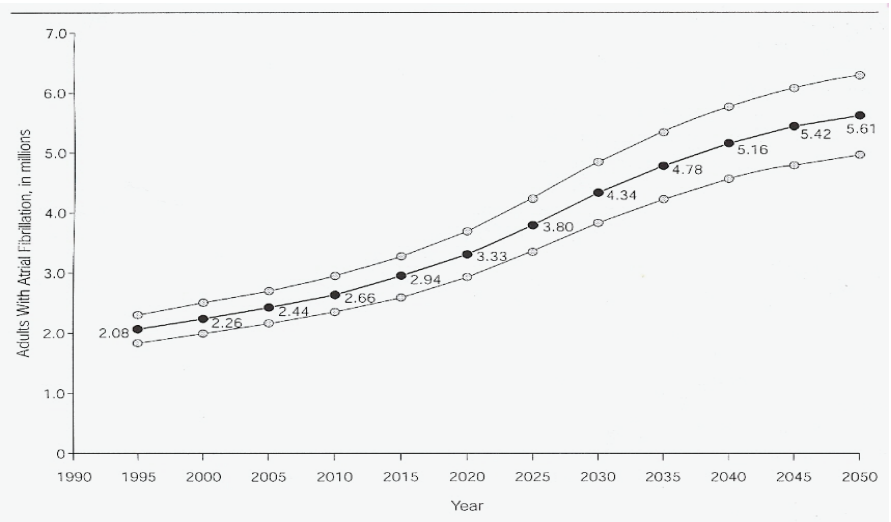

Figure 1. Projected number of adults with AF in the United States between 1995 and 2050. (Reprinted from Go-01 with permission [6] . Copyright © 2001 American Medical Association. All rights reserved.)

Data from the Copenhagen City Heart Study showed a 60 % increase in the rate of first hospital admissions for AF during the last two decades [12]. These data are in agreement with data from Scotland, where a two to three fold increase in the numbers of hospital admissions for AF was found from 1986-1996 [13].

Etiology

AF may be secondary to conditions such as congestive heart failure (CHF), valvular heart disease, hypertension with left ventricular hypertrophy, ischemic heart disease, myo- or pericarditis, hypertrophic or dilated cardiomyopathy, congenital heart disease (especially atrial septal defects), infiltrative disorders (amyloidosis, hemochromatosis) and Wolff-Parkinson-White syndrome. Diseases such as diabetes mellitus, thyreotoxicosis and obesity may also be associated with AF.

AF without associated heart or systemic disease

The prevalence of lone (idiopathic) AF without identifiable underlying disease varies widely between 11.4-31 % in different studies [8, 14]. In persons younger than 60 years with the diagnosis of lone AF and without predisposing structural heart disease, the risk of stroke is very low (0.5 % / year) and survival is not affected by the arrhythmia [15].

Pathophysiology

In 1959 Moe et al. [16] described the multiple wavelet hypothesis as a theory for the genesis and perpetuation of AF. According to this, the conduction of a wave front through the left and right atrium can result in new wavelets with shifting positions, directions and frequency because the "mother wave" becomes fractionated when meeting islets or strands of refractory tissue. The coexistence of multiple wandering wavelets and complex activation will cause the chaotic appearance of AF. In humans, a functional re-entrant wave front is not stationary and is influenced by the structural complexities of atrial tissue [17, 18]. When a wave front meets an area of unidirectional conduction block, it will travel around this obstacle through tissue with slow conduction and, when head meets tail, the reentry circuit is complete. The wave length is dependent on the atrial conduction velocity and refractory period. Short atrial refractory periods, dispersion of atrial refractoriness and atrial conduction delay are significant electrophysiologic findings in the perpetuation of AF that influence the wave length [19]. A trigger or premature atrial contraction is needed for the initiation of AF. In recent years attention has focused on the pulmonary veins and the left posterior atrium. Most (89-94 %) ectopic foci triggering AF originate from the pulmonary veins. Sleeves of atrial myocardial tissue reach 1-3 cm into the pulmonary veins. These zones of transition seem to harbour substrates for triggering activity. Extrapulmonary vein locations of triggering foci have been found in the superior vena cava, crista terminalis, ostium of the coronary sinus, interatrial septum and atrial free wall [20, 21, 22, 23]. In postoperative electrophysiology studies after surgical isolation of the posterior left atrium and pulmonary veins in humans, the pulmonary venous region was still able to sustain spontaneous or induced AF, whereas the rest of left atrium (LA) and right atrium (RA) were not [24].

Both sympathetic and parasympathetic stimulation can induce paroxysmal AF in humans [25]. Ganglionated plexi (GP) as a part of the human cardiac autonomous nervous system, located in the posterior left atrium also seem to play a role in the initiation of paroxysmal

AF. Activation of GP results in a progressive and significant decrease in atrial refractoriness that lowers the threshold for induction of AF [26]. GP are interconnected, and stimulation of one of the plexi will result in effects on others, which is of importance when these plexi are used as targets during ablation [27].

AF, *per se*, is able to induce progressive electrophysiological, contractile and structural changes in the atria that lead to a "domestication" of the arrhythmia ("AF begets AF"), as first shown in a goat model [28]. This process is called remodeling. The first changes are metabolic and appear within seconds/minutes, followed by electrical remodeling, with a shortening of the atrial refractory periods and action potentials, shorter fibrillation intervals and prolonged duration of induced AF episodes coming within hours/days. Electrical remodeling is mainly the result of a down regulation of ion channels with a marked reduction of the inward L type Ca^{2+} current. Other ion channels play a role in this process as well. After weeks in AF, contractile changes of the atria will occur and, finally, structural remodeling after months/years [29, 30, 31]. Electrical remodeling seems to be reversible within a week, whereas atrial contractile function does not recover until several weeks after SR has been re-established. This has clinical implications, as the risks for AF recurrences and stroke are high during the first weeks after cardioversion [32, 33]. It is still not clear whether AF itself or a combination of AF and underlying diseases such as heart failure or hypertension causes structural remodeling. Structural remodeling will not always be reversible [29].

Clinical features of AF

Symptoms and quality of life (QoL)

AF may be recognized as a sensation of palpitations or symptoms caused by its hemodynamic or thromboembolic consequences. AF can reduce cerebral blood flow and cardiac output up to 30 % because of loss of synchronous atrial mechanical activity and an irregular and often fast ventricular response [34, 35]. Symptoms may be aggravated because of impaired coronary arterial blood flow and, when diastolic ventricular filling is impaired e.g. due to hypertension, mitral valve stenosis or hypertrophic cardiomyopathy [2]. Most patients complain of palpitations, dyspnea, fatigue, chest pain, lightheadness or syncope. The arrhythmia may be perceived by the patient as disabling and even life-threatening [36]. Other patients have no or minimal symptoms during AF and may even be unaware of their arrhythmia [37]. Ambulatory ECG

recordings have revealed that an individual may experience both symptomatic and asymptomatic AF [38]. Importantly, initially symptomatic AF may seem to become less symptomatic over time, as patients have a tendency to adapt to their AF symptoms.

QoL refers to the physical, psychological, social and emotional consequences of illness, as well as symptom burden and general well-being. Traditional measurements of how AF influences a patient, that is, frequency, duration, cardiac dysfunction and New York Heart Association (NYHA) class, relate poorly to a patient's subjective QoL impairment [39]. Health-related QoL assessment deals with data that attempt to provide a measurement of a patient´s perception of illness. This is important and influences both the patient and clinician with respect to health care utilization and therapeutic options [40]. Dorian et al. [39] compared QoL in patients with paroxysmal or persistent AF with patients six months after percutaneous coronary intervention (PCI) and with patients after myocardial infarction with significant structural heart disease. They found that AF patients scored worse or the same even though patients after PCI and myocardial infarction were older, had poorer left ventricular function and had required major procedural interventions. The QoL pattern seen in patients with intermittent symptomatic AF is similar to that seen in patients with chronic diseases with an unpredictable course, where not only somatic and psychological domains, but also emotional and social domains, are influenced by the disease. Interestingly, there is as yet no readily available instrument specifically designed to assess QoL in patients with AF. The short form (SF)-36 questionnaire [41] is a generic instrument with eight different domains and has been found to be useful in confirming improvement after interventions for AF e.g. percutaneous catheter ablation [42, 43] and the Cox Maze III procedure [44]. In the AFFIRM-study [45] patients with less symptomatic AF yielded neutral results in QoL measurements using the SF-36 questionnaire.

The Symptom Checklist (SCL), is the most frequently used disease specific questionnaire for assessing symptom frequency and severity in AF symptoms [43, 46].

Atrial and ventricular function

Structural remodeling of the atria secondary to AF may or may not be reversible, and this will depend on the duration of AF and underlying diseases [29, 47]. Different therapeutic options, i.e. antiarrhythmic drugs [48], cardioversions [49], percutaneous [50] or surgical interventions [51] for AF, may also have an influence on atrial function

temporarily or more permanently. Echocardiographic evaluation of atria and ventricles commonly includes the diameter, area and sometimes the volume of the LA and the end-systolic and end-diastolic diameter of the left ventricle (LV) in combination with the left ventricular ejection fraction (LVEF).

The LA serves multiple functions. It operates as a "reservoir" for blood from pulmonary veins during left ventricular systole. During early diastole, it operates as a "conduit" for transfer of blood into the ventricle and, during late diastole, the "active" contraction of the left atrium contributes to the left ventricular stroke volume by 20-30 % [52, 53].

Atrial contractions can be assessed by the pulsed Doppler technique measuring transmitral and transtricuspid inflow velocities. During early diastole, the pressure in the ventricle falls below the atrial pressure; the valve opens and rapid early filling begins (E-wave). At the end of diastole, there is an atrial contraction contributing to the rest of ventricular filling (A-wave), and this reflects global atrial function [54]. The E/A ratio is used as a measure of the diastolic function of the ventricles. If diastolic function is disturbed, the measurement of atrial function through A-wave velocity has to be completed with an assessment of the pulmonary vein flow velocity in order to reveal increased atrial pressure [55].

Another way to measure left atrial function is through M-mode or tissue Doppler recording of the mitral ring motion during atrial contraction. Measurement of the annular motion amplitude or velocity during atrial contraction can be made from septal and lateral parts, and also from anterior and posterior parts of the left atrium. In this way information about *regional* function of the left atrium can be assessed, as well as information about the *global* function if an average of the above mentioned measurements from the four sites is calculated. Atrial contribution is the ratio between amplitude during atrial contraction and total amplitude of the mitral annulus motion (MAM) [56, 57, 58].

AF occurs in about 30-40 % of patients with CHF. There may be an underlying cardiac disease that may cause CHF and/or AF [59, 60]. Rapid ventricular rate as a response to AF may also lead to an impaired ventricular function, often called tachycardia-induced cardiomyopathy [59, 61]. Changes in ventricular function are even seen in patients with a well-regularized ventricular rate during AF. An absence of atrial contractions ("atrial kick"), loss of atrioventricular synchrony and irregular ventricular rhythm with

insufficient diastolic filling have been shown to lead to adverse effects on cardiac output, "AF heart failure" [60, 62].

Tachycardia-induced cardiomyopathy due to AF is associated with systolic dysfunction, elevated ventricular filling pressures, reduced cardiac output and elevated systemic vascular resistence. There is also a neurohormonal activation, including elevated plasma levels of atrial natriuretic peptide (ANP), epinephrine, norepinephrine, plasma renin activity and elevated serum aldosterone levels [63].

Restoration of SR with cardioversion [62] or percutaneous catheter ablation [60, 64], as well as rate or rhythm control with drugs [65] or AV junctional ablation [66, 67], has been shown to restore/improve decreased ventricular function.

The systolic ventricular function measured as the LVEF is usually assessed with 2D echocardiography and M-mode and is frequently reported before and after interventions for AF. Left ventricular systolic and diastolic function can also be assessed by M-mode or pulsed tissue Doppler recording of the MAM during ventricular contraction and relaxation. The amplitude of mitral annulus motion is recorded by M-mode at four sites of the mitral ring about 90º apart [57]. The maximal longitudinal contraction velocity (MLCV) [68] and maximal LV long-axis relaxation velocity (MLVLARV) are recorded from the same sites [69]. The MLCV is thought to be a more sensitive index of systolic function. This measurement is thought to reflect the function of subendocardial fibers that are aligned longitudinally. Impaired function of this layer from subendocardial ischemia and fibrosis in coronary heart disease or other diseases may be a reason for the affected long-axis function early in the development of left ventricular systolic dysfunction [70]. MLVLARV reflects the active relaxation period during early diastole, while increased atrial contribution reflects impaired late diastolic passive properties of the ventricle with decreased compliance. Impaired active relaxation is seen in early stages of diastolic dysfunction. The MLVLARV is independent of the mechanical function of the left atrium [71]. Increased age and hypertension have an inverse correlation to MLVLARV, and recording of MLVLARV is considered a sensitive index of early diastolic dysfunction [69].

Effects on morbidity and mortality

AF is a significant marker for a higher incidence of stroke, presence of other cardiovascular diseases and increased mortality [8]. Between 50 and 59 years of age, the annual attributable risk of stroke in patients with AF is 1.5 %, and the risk increases steeply to 23.5 % at ages of 80-89 years [7]. Approximately 15 % of all strokes are caused by AF [72]. In the Framingham Heart Study, patients who already had an embolic event seemed to be at high risk of further emboli. Ischemic strokes associated with AF were twice as often fatal or accompanied with severe functional deficits among survivors as compared to strokes unassociated with AF [10, 73]. Common risk factors for stroke include increasing age, valvular heart disease, hypertension, ischemic heart disease, CHF, previous ischemic stroke/transient ischemic attack (TIA) and diabetes mellitus [3, 74, 75].

During AF there is a decreased blood flow in the LA and left atrial appendage (LAA) due to markedly decreased or absent mechanical contractions ("stunning"). Stasis with spontaneous echo contrast, endothelial dysfunction and a hypercoaguable state are associated with thrombus formation [76]. Spontaneous echo contrast or "smoke" that can be detected by transesophageal echocardiography relates to fibrinogen-mediated erythrocyte aggregation [77]. Stunning of the left atrium persists even after conversion to SR and can remain up to four weeks. During this time there is a significantly increased risk of thromboembolism [78].

The risk of developing heart failure in AF patients is about three fold compared to patients without AF [9]. The incidence of heart failure among AF patients is about 33 per 1000 person years [79]. On the other hand, the prevalence of AF in heart failure patients varies between 30 and 40 % [59, 60]. About one-third of AF associated heart failure is caused by tachycardia-induced cardiomyopathy without any known structural heart disease [59].

In the Framingham Heart Study, AF was associated with a 1.5 to 1.9 fold mortality risk after adjustment for pre-existing cardiovascular conditions. No distinction was made between paroxysmal or permanent AF, and the investigators also included atrial flutter. Decreased survival was seen in both men and women across a wide range of ages [80]. According to the SCAF study, *paroxysmal* AF was associated with increased mortality

compared both to the general population and to patients with persistent AF. This seemed to be related to a concomitant cardiovascular comorbidity such as myocardial infarction, heart failure and cardiovascular disease. Deaths from cerebral infarction or bleedings were not significantly more common than expected. Survival was better among patients treated with warfarin compared to patients on aspirin or without any anticoagulant treatment. The authors suggested that paroxysmal AF may be a possible indicator of underlying cardiovascular disease [81]. This is in accordance with the results of Ruigómez et al. [82] who found that the most frequent etiology among initially detected paroxysmal AF was ischemic heart disease in both sexes (43 %), but in their study patients with permanent AF had an increased mortality risk (RR 1.5, 96 % CI 0.8-2.9).

Management of atrial fibrillation

Table 1. Vaughan Williams classification of antiarrhythmic drugs

Class IA	Disopyramide Procainamide Quinidine
Class IB	Lidocaine Mexiletine
Class IC	Flecainide Propafenone
Class II	Beta blockers (e.g metoprolol, atenolol)
Class III	Amiodarone Bretylium Dofetilide Ibutilide Sotalol
Class IV	Calcium channel antagonists (diltiazem and verapamil)

Pharmacological treatment

AF is a progressive disease and treatment strategies for a specific patient may change over time. There are three main objectives in the management of AF – symptom relief,

prevention of complications, such as thrombembolism, and prevention of progression of AF. Pharmacological treatment includes rhythm control with the aim of maintaining SR, rate control with adequate ventricular response during AF, and prevention of thromboembolism.

Maintenance of sinus rhythm

Amiodarone is generally perceived to be the most efficacious rhythm control agent and may be given to patients with CHF, but there are limitations as to its safety and tolerability. At the one year follow-up in an AFFIRM substudy, amiodarone prevented recurrence of AF better than class I antiarrhythmic drugs (62 % versus 23 %) and also in comparison to sotalol (60 % versus 38 %). A comparison between class I antiarrhythmic drugs and sotalol did not show any significant difference [83]. In the SAFE-T study, amiodarone again proved to be superior to sotalol [84]. Class IC agents such as flecainide and propafenone may be effective, but are restricted to patients without significant underlying heart disease [85] (Table 1).

Rate control

Rate control may be seen as a complement to rhythm control but may also be what is left to do when rhythm control has failed. In patients with persistent or permanent AF, rate control with adequate ventricular response is important. This allows enough time for ventricular filling, avoids rate-related ischemia and improves hemodynamics. The ACC/AHA/ESC recommendations for rate control at rest range between 60 and 80 beats/ minute and between 90 and 115 beats/ minute during moderate exercise [2]. First line recommendations for rate control include beta blockers or calcium channel antagonists. Digoxin is effective in the regulation of heart rate at rest and in patients with heart failure or left ventricular dysfunction [86]. Digoxin has a vagotonic effect on the AV node but a reduced effect during exercise and in states of high sympathetic tone [87]. A combination of digoxin and beta blockers or calcium channel antagonists can increase the effect on heart rate at rest and during exercise.

Prevention of thromboembolism

According to current guidelines [2] antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except those with lone AF or with

contraindications. Anticoagulation with vitamin K antagonist is recommended for patients with more than one moderate risk factor. Different risk classification schemes have been developed to stratify between high and low risk of stroke. The $CHADS_2$ risk index for patients with non-valvular AF is a point system in which 1 point is assigned for cardiac failure, history of hypertension, age >75 or diabetes mellitus and 2 points for a history of stroke or TIA. Patients with $CHADS_2$ scores 0 - 6 have annual stroke rates of 1.9 %, 2.8 %, 4.0 %, 5.9 %, 8.5 %, 12.5 % and 18.2 % respectively. In randomized trials the anticoagulation is well managed in accordance with current guidelines [88], while in reality compliance is low and several reports from various geographic regions suggest that just about 50% of patients with indications and without contraindications actually receive anticoagulation [89].

Non-pharmacological treatment of AF

AV junctional ablation," His' ablation"

Patients with a high ventricular rate due to AF who do not respond to pharmacological treatment with rate or rhythm control may benefit from the "ablate and pace" strategy for rate control. Patients will have a permanent pacemaker implanted, and an atrio-ventricular block is thereafter created by catheter ablation. Rate control and regularization of ventricular rhythm is achieved. AF is still present and no restoration of atrial contractions or atrio-ventricular synchrony is achieved. After the procedure, patients are dependent on permanent pacing from the right ventricular apex or from biventricular pacing in appropriate cases [90]. After AV junctional ablation in patients with moderately to highly symptomatic AF, most patients do well with respect to ventricular function and QoL [90, 91, 92].

Percutaneous catheter ablation

Here, the term percutaneous catheter ablation is used to describe approaches in the catheterization laboratory that aim to restore SR. The pulmonary veins (PV) play an important role in the initiation and maintenance of AF, and so called PV potentials may be identified in the ostial area where AF is being triggered. At present, there is full agreement that PV isolation is a key factor in catheter ablation approaches, especially for paroxysmal and short-lasting persistent AF. However, by increasing duration of AF and increasing remodeling, isolation at the ostial level may not be sufficient. The ablation

procedure commonly includes circumferential ablation pairwise around the left and right pulmonary veins, in the antrum at a distance of about one centimetre from the ostia, by means of electroanatomic mapping, followed by inspection of the PV ostia.

Radiofrequency (RF) energy has long been the most commonly used, but recent advances have brought to the market cryo balloons and cryo energy catheters [93], high frequency ultrasound balloons [94] and mesh electrodes [95], but long-term results in large groups of patients are not yet available to define their role.

Results of catheter ablation have been better than those of antiarrhythmic drugs in randomized, controlled studies [96, 97, 98]. Results of catheter ablation for AF are as yet better for paroxysmal than for persistent AF, reaching success rates of around 70 % as compared to around 35-50 % [99]. There may be a number of explanations. One would be that AF is a multifactorial condition and that other factors than the pulmonary veins must be taken into consideration. Areas with fractionated electrograms have been ablated with variable success [100], and the importance of GP has become apparent [101]. It seems likely that the areas with fractionated electrograms at least partly coincide with the location of GP. Long-term data from studies including these strategies are largely lacking. It is also likely that different approaches should be used depending on the type of AF and degree of atrial remodeling. In judging the results of catheter ablation it is important to know the follow-up routines. Another important factor is the experience at various sites that can vary substantially depending on the number of ablations per year.

Catheter ablation for AF is mainly indicated for symptomatic paroxysmal and short-lasting persistent AF, when one to two antiarrhythmic drugs have failed, and there is little or no underlying structural heart disease. Serious complications are uncommon, but include pericardial tamponade, pulmonary vein stenosis, oesophageal injury, stroke and death [102, 103, 104].

The Cox Maze III procedure

The golden standard of surgical treatment for AF is the Maze procedure, introduced in 1987 by James L. Cox. The aims of the Maze procedure are to cure AF, restore AV synchrony and restore atrial transport function. Through multiple strategically located transmural incisions in the left and right atrium, macroreentrant circuits responsible for AF can be interrupted. The incisions force the electrical activity of the atria to propagate from the sinoatrial node down to the AV node and further to the ventricles. Multiple

"blind alleys" on the way through the atria are a prerequisite in restoring atrial contractile function. After modifications in the technique, the Cox Maze III procedure was developed. The left and right atrial appendages are surgically removed and all incisions are sutured (*Fig 2).*

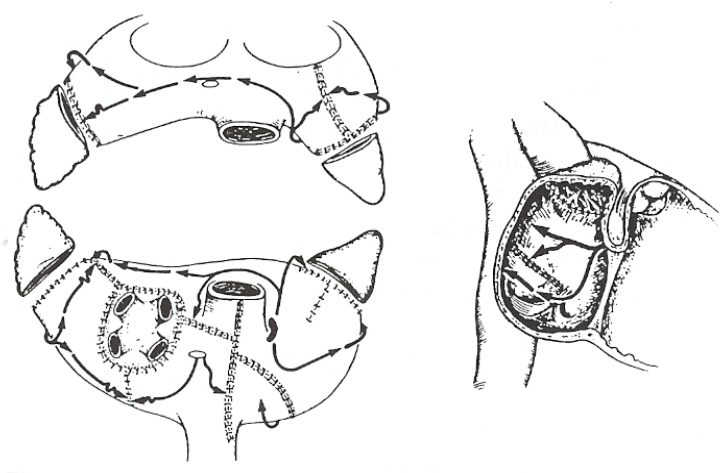

Figure 2. Incisions in the Maze III procedure. The left lower panel is a posterior view of both atria. The right panel is a right lateral view of the atrial septum. The arrows show impulse propagation across the atrial walls. (Printed from Cox with permission [105]).

The indications for Maze surgery are arrhythmia intolerance, drug intolerance or inefficacy, and previous thromboembolism [106].

Long-term follow-up (8 ½ years) after Maze surgery showed freedom from AF/atrial flutter in 93 % of patients. Twenty-four percent needed pacemaker implantation, mainly due to preoperative sinus node dysfunction. Ninety-four percent had documented left atrial function and 98 % had right atrial function [106]. Pasic et al. [107] documented progressive improvement of sinus node function and atrial contractions during the first postoperative year after the Cox Maze III procedure. This corresponded to functional recovery of the autonomic nervous system and reinervation of parasympathetic and sympathetic systems. The stroke rate after the Maze surgery was 0.7 % in the peri-

operative period and 0.4 % during a follow-up period of 11.5 years. The decrease in stroke rate after Maze surgery is due to restoring SR and atrial function, and surgical removal of atrial appendages [108]. The Maze III procedure, together with mitral valve surgery (MVS) compared with MVS alone in patients with preoperative AF, abolished AF in 92 % versus 20 % of patients [109]. The levels of ANP are decreased for at least six months after the Maze III procedure probably because of atrial scarring and exclusion of atrial appendages [110].

Due to a temporary lack of response of the atrial baroreceptors postoperatively, the levels of plasma arginine vasopressin and aldosterone levels are increased [111]. The hormonal changes seem to be responsible for the fluid retention seen after the Maze III procedure. During the first three postoperative months, spironolactone is given to prevent fluid retention and is thereafter withdrawn [106]. Postoperatively, anticoagulation with warfarin is given only to patients with preoperative stroke for a period of three months and lifelong to patients with other reasons for anticoagulation, such as mechanical valve replacements [108].

After the Maze procedure patients may have AF, atrial flutter and atrial tachycardias due to atrial edema, elevated levels of catecholamines and surgical trauma. Recovery from the surgical trauma usually takes two to three months, and there will be a gradual reduction of arrhythmias during this time [112]. Patients with postoperative arrhythmias are often given beta-blockers or sotalol to promote SR and reversal of atrial remodeling.

Variations of the Maze III procedure

Due to the high success rates of the Maze III procedure and its complexity, alternative simplified methods have been tried under other but similar names. None of these have reached the success rates of the original cut-and-sew Cox Maze III procedure and should in all reference to data and results be kept apart from the Maze III results [113, 114].

Intraoperative ablation

For clarity, the term intraoperative ablation should be reserved for patients accepted for open-heart surgery because of coronary artery disease, valvular disease or some other reason. Per definition, this means that these patients largely belong to another patient population than those primarily treated for AF. Patients may or may not have been treated earlier for symptomatic AF, but a good portion of the patients have not had

enough symptoms to seek medical care. When documenting AF in a candidate for open-heart surgery, the decision to offer intraoperative ablation rests on a rationale of the combination of the previously discussed aspects, i.e.

a) reducing symptoms associated with tachyarrhythmia

b) improving cardiac output

c) reducing risk of stroke and other systemic embolism

In addition, this should be weighed against the added risk of an ablation procedure.

Patient population

The prevalence of AF varies in patients scheduled for cardiac surgery depending on the underlying cardiac disorder. The preoperative prevalence of AF in patients undergoing coronary artery bypass grafting (CABG) varies between 0.96 % and 8.7 %. Patients with AF preoperatively are older and have more pronounced left ventricular dysfunction and hypertension [115, 116]. In patients with planned aortic valve replacement, there is a prevalence of about 3.5 % -10 % [117, 118], and AF is present in about 30 % - 54 % of those with a significant mitral valve disease [117, 119]. Patients undergoing CABG with uncorrected preoperative AF have a significantly increased risk of late mortality by 40 % (all causes) and a late cardiac death rate of about 2.8 times that of patients in SR [115].

Lesion set

A variety of intraoperative ablation lesion sets in either the left or both atria has been suggested *(Fig 3)* and tried with variable success.

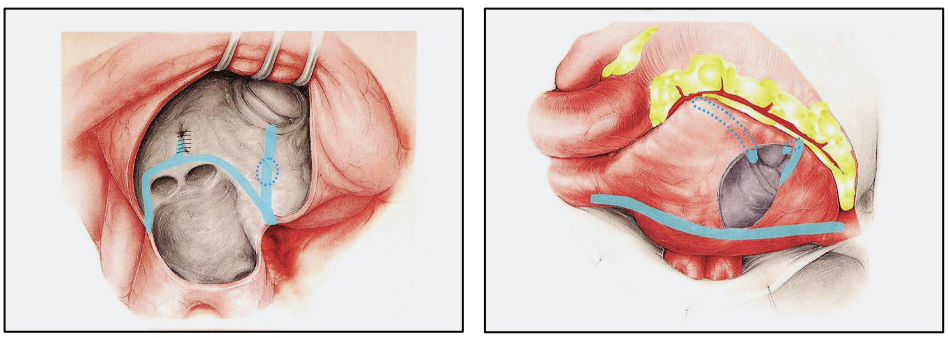

Figure 3. Biatrial lesions in the Cox CryoMaze Procedure. Left and right atrial lesions. (With permission from ATS Medical, Inc., Minneapolis, USA.)

Our left atrial lesion set consists of two ipsilateral rings encircling the pulmonary veins with a connecting lesion between the rings, one lesion to the LAA and one lesion to the mitral valve. The LAA is excluded. In a pilot study, endocardial intraoperative ablation was performed during mitral valve procedures, which offered access to the LA. This technique was later adapted to the epicardial approach, which can in part or entirely be performed on a beating heart and is also used concomitantly with other types of surgery where the LA is not opened, such as aortic valve surgery or CABG.

Later, biatrial ablation has been found to further improve rhythm outcome. The ablation lines are similar to the Cox Maze III incisions with only a few incisions to gain access to the atria. A meta-analysis of biatrial "cut-and-sew" or ablation lesion sets shows a better outcome with regard to rhythm than left atrial lesion sets only [120].

Energy sources

Different energy sources have been evaluated in recent years, such as hyperthermic sources (radiofrequency, microwave, laser, ultrasound) and hypothermic sources (cryoablation). We have used radiofrequency or cryo energy for intraoperative ablation.

Radiofrequency energy

RF energy uses alternating current to emit electromagnetic energy at the frequency of the radio band. The probe heats the tissue in contact directly through a resistive effect to a depth of about 1 mm [121]. Deeper layers are heated by conduction from the superficial layer and reach temperatures of about 50-60 ° C, high enough to create necrosis of myocardial cells and damage to collagen fibers [122, 123]. Histologic sections from the PV ostia have exhibited thermal injury of nerve fibers as well. Zones of intramural hematoma have been detected up to 22 days after intraoperative RF ablation due to thermal damage of small vessels. The initial lesion will grow further owing to in growth of granulation tissue in these zones and later replacement by fibrin and collagen during the process of tissue repair [124].

Transmurality and lesion size depend on electrode temperature and dimensions, duration of ablation, electrode contact, tissue convection and resistance [122]. Depending on whether the application is endocardial or epicardial, convection of air or blood

influences temperature [125]. Endocardial RF ablation may produce a disruption of the endocardial layer, leading to platelet adhesion, aggregation, activation, fibrin generation and subsequent thrombus formation [126].

RF energy can be delivered in a unipolar mode with a grounding pad serving as the return pole. A goal temperature is preset, and the device regulates power delivery. Irrigated unipolar ablation tools with a saline cooled electrode tip have been developed to further enhance the chances of transmurality [127].

Bipolar epicardial RF ablation is another modality. Atrial tissue is clamped between the jaws of the probe and, when conductance falls to a set level, transmurality is reached and energy application ceases. The time necessary for bipolar applications to reach acute transmurality is very short – about 10 s [128]. A unipolar RF probe was used in the studies of the present thesis, delivering a maximum of 150 W over a period of 120 seconds at a preset temperature of 70 º C at each lesion site.

Cryo energy

Cryosurgical ablation of arrhythmias has been used for many years [129]. The cooling agents used are nitrous oxide, liquid nitrogen, argon or helium gas, and low temperatures are reached through rapid expansion. The effects on cardiac tissue when freezing occur in three phases. In phase one (freeze/thaw), intra and extracellular ice crystals form. These ice crystals cause irreversible damage through compressing and distorting organelles [130]. In phase two (inflammation), hemorrhage appears with subsequent oedema and apoptosis and is visible within 48 hours. Within a week, there is an in growth of capillaries, infiltration of inflammatory cells and fibrin deposition, which is phase three (fibrosis) [131]. The advantages of cryo energy are preservation of tissue architecture, due to preservation of collagen tissue, minimal risk of thrombus formation and non-arrhythmogenic lesions [130].

In the studies of the present thesis, we used an argon-based linear surgical probe that could reach temperatures of – 160 º C. When freezing, the catheter adheres to underlying tissue with a good stability (*Fig 4).*

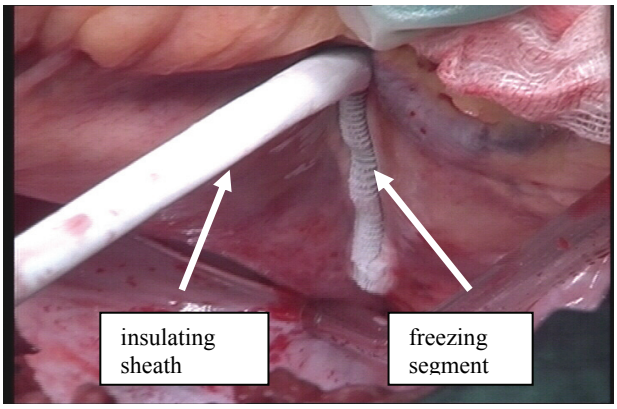

Figure 4. Cryosurgical probe, Surgifrost (ATS CryoMaze Ablation System, ATS Medical, Inc., Minneapolis, USA) during freezing. Observe the ice block around the tip and along the freezing segment of the probe.

The size of the lesion depends on tissue temperature, probe size, probe temperature, duration and number of freeze cycles, cooling agent and type of cardioplegia [121].
Argon-based cryo clamp devices have been developed that are able to temporarily occlude blood flow and facilitating transmurality [132] (*Fig 5).*

Figure 5. CryoMaze Surgical Ablation Clamp (with permission from ATS Medical, Inc., Minneapolis, USA).

HIFU and microwave energy

High-intensity focused ultrasound (HIFU) [133] and microwave energy are hyperthermic energy sources. Microwave energy uses high-frequency electromagnetic radiation which causes oscillation and rotation of dipoles like water molecules in tissue. [121]. Applications can be depicted endo-or epicardially, and microwave heating does not char the endocardial surface. The freedom from AF 12 months postoperatively after ablation with microwaves seems comparable with results after cryo -or RF ablation [134, 135].

Rhythm

Many reports have been published on intraoperative ablation for AF and its effect on rhythm. Few studies are randomized. Randomized, controlled and observational studies with a minimum of about 50 patients (except for two) are summarized in Tables 2 a-b on the following pages. In these studies intraoperative ablations were performed with RF or cryo energy and with varying lesion sets.

Tables 2a and 2b.

Randomized studies: Deneke 2002 [136], Akpinar 2003 [137], Doukas 2005 [138], Abreu Filho 2005 [139], Wang 2009 [140], von Oppell 2009 [141].

Controlled studies: Guang 2002 [142], Mantovan 2003 [143], Ghavidel 2008 [144].

Observational studies: Williams 2001 [145], Pasic 2001 [146], Benussi 2002 [147], Raman 2003 [148], Fayad 2005 [149], Halkos 2005 [150], Geidel 2005 [117], Beukema 2008 [151], Gaynor 2004 [152], Benussi 2005 [153], Gillinov 2005 [154], Geidel 2008 [155], Manasse 2003 [156], Tada 2005 [157], Sueda 2005 [158], Mack 2005 [159].

* cumulative rates of SR

Abbreviations: n = number, pers = persistent, perm = permanent, dur = duration, yrs = years, MVS = mitral valve surgery, biatr =biatrial, endo = endocardial, epi = epicardial, FU = follow-up, Rx = randomized, irr = irrigated, vs =versus, observ = observational, mort = mortality, CVA = cerebrovascular accident, PM = pacemaker

TABLE 2a.
Studies

Author	Year	Type of study	Comparison	n=	Pers/ Perm (%)	Dur (yrs)	MVS (%)	Biatr (%)	Endo/ epi RF	SR (%)	AF-free (%)	FU (months)
Deneke	2002	Rx	biatr irr RF vs no RF	30	100	3.6/3.7	100	100/0	endo	81.8 / 21.4		12
Akpinar	2003	Rx	biatr irr RF vs no RF	67	100	1.7/1.8	100	100/0	endo/epi	93.6 / 9.4		12
Doukas	2005	Rx	left RF vs no RF	97	100	4.8/3.9	100	0	endo	44.4 / 4.5		12
Abreu Filho	2005	Rx	biatr irr RF vs no RF	70	100	5.5/3.7	100	100/0	endo	79.4 / 26.9*		12
Wang	2009	Rx	biatr bipolarRF vs left bipolarRF	299	100	2.9/3.1	90/89	100/0	epi	84.1/ 85.2		28 ± 5
von Oppell	2009	Rx	bipolar biatr irr RF vs no RF	49	100	7.0/5.0	100	100/0	endo/epi	75 / 39		12
Guang	2002	controlled	biatr RF vs no RF	183	100	9.8/10.7	100	100/0	endo		77/25	36
Mantovan	2003	controlled	left RF vs no RF	130	80	3.5/3.3	86/92	0	endo	81 / 11		12.5±5
Ghavidel	2008	controlled	left cryo/biatr cryo	90	100	0.78/1.2	100	0/100	endo	67.7/60		10/8
Williams	2001	observ	biatr/left RF	48	100	4.8	81.3	17	endo	81		4.5
Pasic	2001	observ	left RF	48	100	7.0	79.2	0	endo	92		6
Benussi	2002	observ	left RF	132	91.7	3.5	97.7	0	25 / 107		77	36 (16.9±14.2)
Raman	2003	observ	biatr RF	132	75	3.0	59.8	100	92 / 40	100		12
Fayad	2005	observ	left RF	70	100		100	0	endo	91	62.5	24 (22±10)
Halkos	2005	observ	biatr/left RF	54	59.3	3.9	87.0	22.2	endo	77.3		8.7(3-22)
Geidel	2005	observ	mono/bipolar RF	106	100	5.8	62.3	0	86/20	75		12
Beukema	2008	observ	biatr irr RF	285	100	5.1	79.1	100	endo	53.4		60 (43.6±25.4)
Gaynor	2004	observ	biatr bipolar	40	37.5	6.6	30	100	epi/endo	91		6
Benussi	2005	observ	left bipolar	90	82	1.3	88.9	0	epi/endo	89		12
Gillinov	2005	observ	left/biatr bipolar	513	70	2	69	34	epi/endo		72	12
Geidel	2008	observ	left bipolar	85	100	6.3	0	0	epi/endo	78		32±15
Manasse	2003	observ	left cryo	95	100	5.4	87.4	-----	endo	81.4		36
Tada	2005	observ	left cryo	66	100	9.0	100	-----	endo	61		31±16
Sueda	2005	observ	left cryo/RF	49	100	6.8	83.7	-----	endo		70.2	28.6±15.1
Mack	2005	observ	left/biatr cryo	63	62	2.5	82.5	25	endo		88.5	12

TABLE 2 b. Author	Bleeding (%)	30-day mort (%)	CVA/ TIA (%)	PM	Survival	Predictors for AF postoperatively	Rhythm assessment
Deneke	-----	0	0	6.7 / 6.7	73 / 93		ECG/Holter
Akpinar	3 / 2.9	3 / 2.9	0 / 5.9	3 / 0	93.9 / 91.2		ECG
Doukas	-----	6.1/8.3	4 / 6.3	4.4 / 9.1	93.8 / 91.7	LA-diameter > 60 mm	ECG/(Holter)
Abreu Filho	-----	2.3 / 0	0	2.3 / 3.5	95.1 / 92.8		ECG/Holter
Wang	2.7/3.4	3.3/1.3	1.4 / 0	2.9 / 0.7	95.3 / 98.7	LA-diameter > 80 mm	ECG/Holter
von Oppell	-----	0	0	4.2 / 4	100 / 92		ECG
Guang	2.3 / 1	0	-----	-----	100		ECG
Mantovan	0 / 11	1/0	1/0	1/0	96.1 / 92.6		ECG/Holter
Ghavidel	3.3	0/1.2	-----	-----	98.5 / 92		ECG/(Holter)
Williams	-----	6.2	-----	0	87.5		ECG
Pasic	-----	4.2	2	11	95.8	coronary artery disease	ECG
Benussi	2.3	2.3	2	0	94	age, early postop arrhythmias	ECG/Holter
Raman	-----	6.8	-----	3.0	93.2		ECG
Fayad	-----	2.8	8.6	2.9	97.1	LVEF, mitral rheumatic lesion	ECG/Holter
Halkos	-----	12.9	3.7	12.7	87		ECG
Geidel	-----	1.9	1.9	1.9	-----		ECG
Beukema	-----	4.2	2.1	-----	68.4	LA-size, AF-duration	ECG
Gaynor	12.5	0	0	15	100		ECG/(Holter)
Benussi	4	0	0	1.1	98.9	LA-diameter	ECG/Holter
Gillinov	5	2	2.3	-----		LA-diameter, AF-dur, lesion set	ECG
Geidel	-----	0	-----	1.2	96		ECG/Holter
Manasse	2.1	3.2	4.2	6.3	90.5	lesion set, AF at discharge	ECG
Tada	-----	0	9	4.5	-----		ECG
Sueda	-----	-----	-----	8.1	-----		ECG/(Holter)
Mack	-----	0	0	19	95.2		ECG/Holter

The efficacy of concomitant ablation for AF was also evaluated in one major review by Chiappini et al. [160]. Six studies that used the RF ablative technique were summarized. Freedom from AF was 76.3 ± 5.1 %, and the survival rate was 97.1 % after a mean follow-up of 13.8 ± 1.9 months.

In a meta-analysis by Barnett et al. [120] surgical ("cut-and-sew") and ablative techniques for AF used intraoperatively were compared with controls undergoing cardiac surgery only without concomitant interventions for AF (Table 3).

Table 3. A meta-analysis of 69 studies by Barnett et al. 2006.

	Surgical / ablative subjects		**Control subjects**		
	No. of studies	Mean	No. of studies	Mean	*p- value*
1-yr freedom from AF (%)	37	84.5	10	30.8	0.001
2-yr freedom from AF (%)	21	84.3	5	39.7	0.001
3-yr freedom from AF (%)	18	85.4	6	60.9	0.013
	Biatrial lesion		**Left atrial lesion**		
	No. of studies	Mean	No.of studies	Mean	*p-value*
1-yr freedom from AF (%)	24	88.9	13	75.9	0.001
2-yr freedom from AF (%)	15	85.8	6	74.5	0.001
3-yr freedom from AF (%)	16	87.1	2	73.4	0.001

The results of studies on surgical interventions for AF are often difficult to compare. Patients may have paroxysmal, persistent or permanent AF and different underlying disorders such as ischemic heart disease or valve disorders. There is also a great variety of lesion sets with left or biatrial approaches, energy sources, devices or cut-and-sew techniques. Rhythm assessment differs postoperatively with resting ECGs, Holter monitoring, event recorders or continuous rhythm monitoring devices at varying follow-up time points. The definition of success has also been unclear. To overcome this and

report data in a more uniform way, there are now ”Guidelines for reporting data and outcomes for the surgical treatment of atrial fibrillation” [161]. In this thesis the classification of AF in the referred studies has been cited from the authors.

Postoperative medication

After intraoperative ablation due to atrial oedema, elevated levels of catecholamines, pericarditis and surgical trauma, patients may have AF, atrial flutter and atrial tachycardias. Recovery from surgical trauma usually takes two to three months, and there will be a gradual reduction of arrhythmias during this time [112]. After intraoperative ablation, many authors recommend amiodarone or other antiarrhythmic drugs for three months to promote SR and a reversal of atrial remodeling. Other authors recommend beta blocking therapy during the first six postoperative months and thereafter cardioversions and specific antiarrhythmic therapy as needed [162].

Predictors for sinus rhythm

In patients with permanent AF undergoing MVS with a concomitant left atrial ablation, preoperative AF duration of less than two years and an LA diameter less than 55 mm were predictors for SR [163]. Independent preoperative predictors for SR after biatrial RF ablation for persistent AF in patients undergoing MVS were left atrial diameter of < 56.8 mm or a preoperative AF duration < 66 months [164]. The relation between atrial size and preoperative AF duration versus postoperative rhythm was confirmed by Beukema et al. [151] in a similar patient group also with biatrial RF lesions. They also found a correlation between postoperative use of ACE inhibitors and SR. In patients with permanent AF undergoing biatrial cryo ablation combined with MVS, a left atrial diameter of > 65 mm and repair for rheumatic mitral valve disease were independent predictors of late recurrence of AF [165].

AIMS OF THE STUDY

1. To compare the long-term clinical effects on rhythm and QoL after epicardial left atrial RF ablation versus no ablation in patients undergoing CABG +/-valve surgery and with documented AF.

2. To compare whether epicardial left atrial cryoablation combined with MVS results in a better elimination of preoperative permanent AF than MVS alone.

3. To assess the long-term effects of intraoperative epicardial cryoablation on the atrial and ventricular function in relation to rhythm before and after CABG in patients with documented AF.

4. To explore preoperative echocardiographic and other predictors for maintenance of SR in patients undergoing intraoperative ablation for AF.

PATIENTS AND METHODS

Study population

All patients described in papers I, III and IV were studied at Sahlgrenska University Hospital, Gothenburg. The study population in paper II was recruited in a multicenter design from the University Hospitals of Uppsala, Gothenburg, Umeå and Stockholm. The study protocols were approved by the institutional ethics and review committees. Each patient signed a written informed consent.

Patients

Papers I, III and IV

Eligible patients were scheduled for CABG +/- valve surgery and had a history of AF with ECG documentation. AF was classified according to the ACC/AHA/ESC guidelines into either paroxysmal, persistent or permanent [166]. Patients with unstable angina pectoris, permanent pacemaker treatment, hypertrophic cardiomyopathy and previous cardiac surgery were excluded. In papers III and IV patients with a need of concomitant valve surgery were excluded. All patients were identified on the waiting list for CABG and were consecutively asked to participate regardless of whether or not their AF was perceived to be symptomatic. All patients were included between September 2001 and November 2004.

Paper II

Patients aged 18-80 years with permanent AF and mitral valve disease requiring MVS +/- concomitant CABG were included. Permanent AF was defined as ECG-verified AF that had been present for at least three months with failed or not attempted cardioversion. Exclusion criteria were heart failure NYHA function class IV, previous cardiac surgery, planned MVS combined with surgical procedures other than CABG and tricuspid valvuloplasty, and permanent pacemaker. All patients were included between November 2003 and May 2005.

Study design and protocol

Paper I - Epicardial left atrial RF ablation and CABG +/- valve surgery versus CABG+/- valve surgery alone

Patients were consecutively asked to participate in the study. One patient group underwent CABG +/- valve surgery with epicardial left atrial RF ablation, and an age and gender matched control group underwent CABG +/- valve surgery alone. A Holter recording and a two-dimensional and Doppler echocardiography were made preoperatively. All patients were postoperatively monitored with telemetry until hospital discharge. Amiodarone and/or sotalol were given to all patients in the ablation group for at least three months. This concept was adopted because of an increased susceptibility to supraventricular arrhythmias due to the ablation procedure, *per se*, with oedema, surgical trauma and elevated levels of catecholamines with subsequent delayed reversal of shortened refractory periods [112]. Control patients were treated with antiarrhythmic drugs as needed. All patients with an indication for anticoagulation according to ACC/AHA/ESC guidelines received warfarin [166]. DC cardioversion was attempted both in ablated and control patients during the hospital stay and after discharge in the case of AF recurrence.

A 12-lead ECG was obtained at three, six and 12 months postoperatively, and patients were asked about their current medication, arrhythmic events, DC cardioversions, hospital admissions and NYHA class.

A long-term follow-up was made using a 12-lead ECG, a Holter recording and a two-dimensional and Doppler echocardiography. An assessment of QoL and symptoms was also made with the SF-36 Questionnaire and the Symptom Checklist for Frequency and Severity.

Paper II – Epicardial left atrial cryo ablation and mitral valve surgery versus mitral valve surgery alone

Patients were randomly assigned to MVS combined with epicardial left atrial cryoablation or to MVS alone (controls). All patients were postoperatively monitored with telemetry. Beta-blocking agents were administered from the day of surgery to prevent postoperative AF.

In the case of AF recurrences, treatment with amiodarone-/sotalol infusion or DC cardioversion was given. Prophylactic antiarrhythmic drugs were administered to

patients with postoperative AF that required cardioversion and were continued for the first three months postoperatively and then withdrawn in the absence of AF recurrence. Warfarin was advised from the day of surgery and for at least three months or longer if patients had mechanical valve prosthesis or a recurrence of AF.

After hospital discharge, the patients were evaluated at one, two, three, six and 12 months after surgery with a 12-lead ECG and clinical examination and asked about current medications, medical history, previous cardioversions, NYHA class and adverse events. Rhythm and type of AF were defined as paroxysmal, persistent or permanent based on subjective symptoms, ECG recordings and cardioversions performed between visits or at follow-up visits. Continuous rhythm monitoring was not performed.

Prior to and six months postoperatively, a two-dimensional and Doppler echocardiography was made to assess atrial and ventricular function.

Paper III – Epicardial left atrial cryo ablation and CABG versus CABG alone

Patients were consecutively asked to participate in the study. One patient group underwent CABG with epicardial left atrial cryoablation, and an age and gender matched control group underwent CABG alone. The preoperative and follow-up protocol up to 12 months postoperatively was identical to that in paper I.

A long-term follow-up was made using a 12-lead ECG and a two-dimensional and Doppler echocardiography.

Paper IV - Predictors for SR in patients undergoing intraoperative ablation

Patients undergoing CABG and epicardial left atrial RF or cryo ablation described in papers I and III were included in the study. A 12-lead ECG and a complete pre- and postoperative two-dimensional and Doppler echocardiography at long-term follow-up were necessary for the assessments.

Anaesthesia and extracorporeal circulation (ECC) *(papers I-IV)*

The anaesthetic procedure followed the routine protocol for cardiac patients and consisted of induction with fentanyl (4-6µg/kg bw), thiopenthal (2-5 mg/kg bw) and pancuronium bromide (0.1 mg/kg bw). After intubation, anaesthesia was maintained with isoflurane and intermittent doses of fentanyl. During ECC, a continuous infusion of

propofol (3–6 mg/kg bw/h) was administered (papers I, III, IV). In study II, anaesthesia was given according to current routines for cardiac patients at each center.

Surveillance during surgery included monitoring of continuous central venous/pulmonary and arterial pressures, ECG, blood gases, urinary output and nasopharyngeal or bladder temperature.

The standard approach was sternotomy. Before cannulation, all patients were fully heparinized to reach an activated clotting time of 480 seconds, which was then kept at that level with intermittent doses of heparin. A cannula was inserted in the ascending aorta and the right atrium was cannulated for venous drainage with a double lumen cannula in studies I, III and IV while bicaval cannulation was used in study II and in one patient in study I, where the right atrium was opened to allow for a tricuspid valve procedure.

The dissection needed for the ablation was performed after cannulation but before going on bypass to save ECC time. In the case of unstable circulation or ECG changes during manipulation of the heart, ECC could be instantaneously started, thus reducing the working load of the heart and minimizing the risk for the patient. After dissection of the pulmonary veins and the dome of the LA, ECC was started and the heart was vacuum emptied to allow only minimal amounts of circulating blood in the heart, thereby avoiding its cooling (during RF ablation) or re-warming effect (during cryo ablation). All ablation lines were made with the heart beating and empty. The LAA was closed with a purse string suture in all ablated patients, either from the inside if the left atrium was opened (paper II) or from the outside if it was not opened (papers I, III and IV).

When ablation was completed, the aorta was clamped and 800 – 1000 ml cold blood cardioplegia was infused in the aortic root (antegrade fashion). Cardioplegia (300 ml) was thereafter repeated every 20 minutes during aortic cross clamping: in CABG cases in antegrade fashion and in aortic valve cases in retrograde fashion via a catheter in the coronary sinus. No active or mild hypothermia (34 ^{o} C) was applied. CABG +/- valve surgery were/was thereafter performed as planned. No measures were taken to assess conduction block. After weaning off cardiopulmonary bypass, the heparin effect was reversed with protamin sulfate. Before closing the sternotomy, two temporary pacing wires were attached to the left ventricle and two to the right atrium. Chest drainage was applied as customary, and left atrial pressure monitoring was used when needed.

All patients were extubated in the intensive care unit (ICU) as soon as the hemodynamic situation was stable, no excess bleeding occurred and body temperature and blood gases were normal.

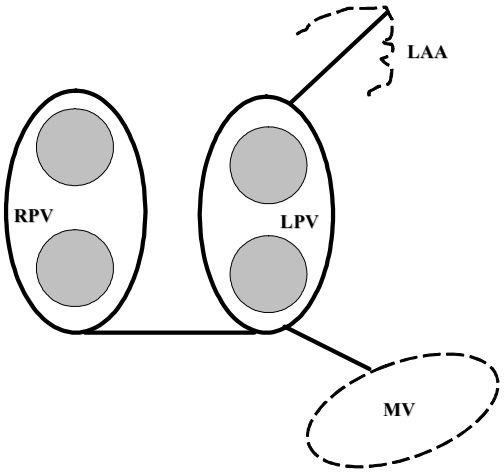

Figure 6. Schematic representation of left atrial lesion set. LAA, left atrial appendage; LPV, left pulmonary veins; MV, mitral valve; RPV, right pulmonary veins.

Epicardial RF ablation *(papers I and IV)*

All RF ablation lines were applied epicardially on pump and on beating, but emptied, heart. A thorough dissection was made to expose the LA to optimize the contact with the ablation probe. A monopolar RF probe (Cobra, Boston Scientific Corporation, San José, CA, USA) was used, delivering a maximum of 150 W over a period of 120 seconds at a preset temperature of 70º C at each lesion site. 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 LAA and from the inferior part of the left circle to the fat pad of the AV groove were added *(Fig 6)*. No tests were made to confirm that the ablation lines were continuous or transmural. The ablation procedure was performed before valve surgery and CABG. The LAA was closed from the outside with a purse string suture in all

ablated patients and checked for residual flow after declamping the aorta. Following the CABG routines at the time, the LAA was not closed in the control group.

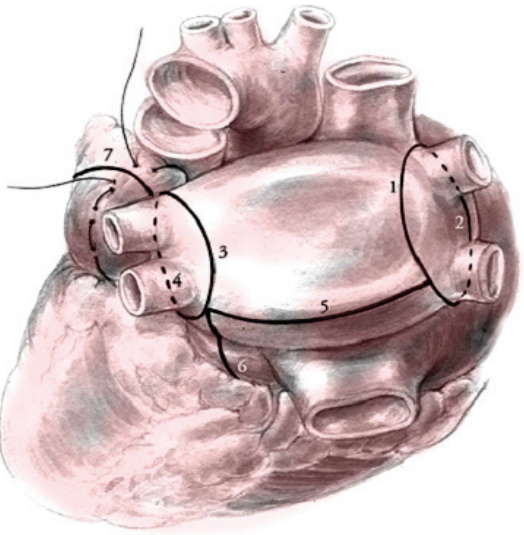

Figure 7. Dorsolateral aspect of left atrium

Epicardial cryo ablation *(papers II-IV)*

All cryo ablation lines were applied epicardially during cardiopulmonary bypass on the beating and emptied heart before the aortic cross-clamp and cardioplegic arrest. A cryosurgical probe, Surgifrost 60 mm (ATS CryoMaze Ablation System, ATS Medical, Inc., Minneapolis, USA), was used for the ablation procedure. The handheld probe has a variable freezing segment (4-60 mm long) and an integrated thermocouple for temperature monitoring and is capable of reaching a temperature of -160°C using an argon based cooling system. Cryo ablation lesions were applied in an overlapping fashion for a period of 90 seconds at each site as recommended by the company at that time. The ablation lesion set was similar to that described for RF ablation except for the mitral line, which was allowed to cross over the AV groove fat pad, covering the coronary sinus *(Fig 7)*. No tests were made to confirm that the ablation lines were continuous or transmural. After the ablation procedure, MVS and/or CABG were/was

performed. The LAA was closed with a purse string suture endocardially in all patients in paper II and epicardially in all ablated patients in papers III and IV.

Holter recording *(paper I)*

A Holter recording was performed at long-term follow-up. Any AF period exceeding 30 seconds was noted.

Echocardiographic assessment

Pre- and postoperative two-dimensional and Doppler echocardiography (papers I-IV)

An Acuson Sequoia echocardiograph (Siemens, Mountain View, Ca, USA) with a 3 MHz transducer was used. The patients were studied in the left lateral recumbent position. Echocardiographic techniques and calculations were in accordance with the recommendations of the American Society of Echocardiography´s guidelines and standards committee [167]. The maximal antero-posterior diameter of the left atrium was assessed during systole. The maximal areas of the atria were identified in the apical four-chamber view by scrolling frame by frame and were measured by planimetry, excluding pulmonary veins and the left atrial appendage [168]. The amplitude of the MAM was recorded by M-mode at four sites of the mitral ring, situated about 90 degrees apart. Recordings from the septal and lateral part of the mitral annulus were obtained from the apical four-chamber view and recordings from the posterior and anterior sites from the apical two-chamber view. The leading edge technique was used [57]. Left atrial function was assessed during SR by M-mode recording of mitral ring motion [56, 58]. The annular motion amplitude and velocity during the atrial contraction were then calculated as the average of the four sites. The maximal LV long axis contraction velocity was measured as the steepest part of the curve during systole [68, 70], and the maximal LV long axis relaxation velocity (MLVLARV) was measured as the steepest part of the curve in early diastole [69, 71, 169] *(Fig 8)*.

In addition, the maximal flow velocity during atrial contraction was recorded by pulsed Doppler technique from the apical four-chamber view, with the sample volume located at the tip of the mitral leaflets [54]. The LVEF was determined by the biplane modified Simpson´s rule, except for a few patients in whom clear imaging of the LV was obtained only in the four-chamber view. In these cases LVEF was visually assessed independently

by two experienced echocardiographists. A consensus was reached in the case of disagreement.

All echocardiographic data were obtained during quiet respiration and averaged over at least five consecutive beats during AF and three beats during SR. All Doppler data were averaged over at least five consecutive beats regardless of rhythm. The registrations were required to be free from extrasystoles prior to and immediately after the registration. All investigations were stored on optical discs and later analysed in an EchoPAC Workstation (Echo PAC PC Dimension, GE Medical Systems, Milwaukee, USA). All measurements were made and checked for quality by one experienced echocardiographist, who was blinded to the identity of the patients.

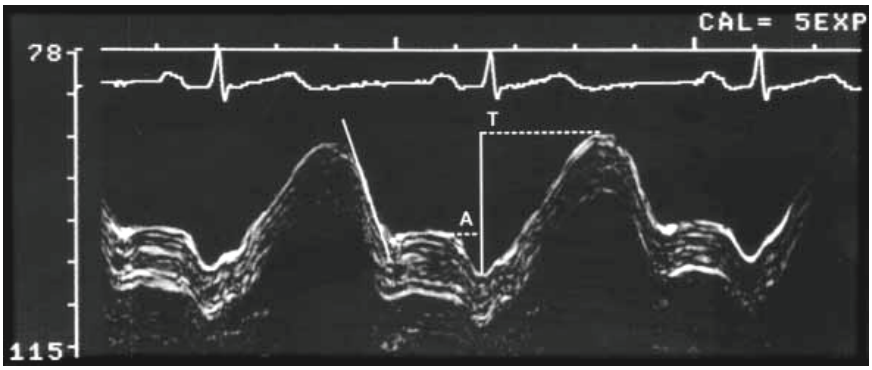

Figure 8. M-mode recording of mitral annulus motion. Maximal long-axis relaxation velocity is measured as maximal slope on the early diastolic part of the curve. Atrial contribution (A) and total (T) amplitude of motion are marked.
Reprinted from Nilsson et al. [69] with permission from Elsevier.

SF-36 Questionnaire *(paper I)*

The SF-36 (Short Form 36 questions) Health Survey Questionnaire is a generic health-related quality-of-life instrument that has been validated across seven general populations in Sweden. A published Swedish normative database is available. The questionnaire uses 35 items grouped into eight multi-item scales of QoL: physical functioning, role limitations due to physical problems, bodily pain, general health

perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. A further single item concerns reported health transition over the past year. Scores are transformed into a scale ranging from 0 (worst possible health state measured) to 100 (best possible health state). Scale scores can be computed if one-half or more of the items within a scale is answered [41].

The questionnaire was initially developed in the US and has shown clinical validity in reflecting changes in health-related quality of life associated with changes in disease severity and also discriminating levels of severity within a medical diagnosis [170].

Symptom Checklist for Frequency and Severity *(paper I)*

The Symptom Checklist is a disease specific instrument. It measures the patient´s perception of the frequency and severity of 16 symptoms related to atrial tachyarrhythmias over the past month. The possible scores range from 0 to 48 for symptom severity and from 0 to 64 for symptom frequency, with higher scores representing greater symptom burden and worse QoL [43].

Statistical analysis *(papers I-IV)*

Data are presented as mean ± standard deviation or percentages unless otherwise stated.

Fisher's exact test was used in the univariate analyses for comparisons of dichotomous variables, and the Mann-Whitney U test or Student's t test was used for continuous/ordered variables. Wilcoxon's signed rank test was used in paper III to test for changes between different time points. Multiple logistic regression analysis was used in all papers to identify predictors of rhythm at follow-up. In papers I and III, freedom from AF/flutter during follow-up was estimated using the Kaplan-Meier method and the log-rank test was used to test for the corresponding differences between groups. Receiver operating characteristic (ROC) curves were used in paper IV to describe sensitivity and specificity and to identify optimal cut-off values. All p-values are two-sided and considered significant if below 0.05. Data were analysed using SAS program version 9.1.

RESULTS PAPERS I-IV. For patient characteristics, operative data, in-hospital and late complications see Tables 4 a-c.

Table 4 a. Patient characteristics

	PAPER I		PAPER II		PAPER III	
Variable	**RF** (n = 39)	**Control** (n= 39)	**Cryo** (n=30)	**Control** (n=35)	**Cryo** (n=35)	**Control** (n=35)
Age, years	73 ± 5	72 ± 6	70 ± 8	66 ± 9	72 ± 5	70 ± 7
Sex, (male / female)	31 / 8	31 / 8	25 / 5	26 / 9	32 / 3	32 / 3
BMI	26.5 ± 2.9	28.6 ± 4.7			27.2 ± 3.3	28.3 ± 3.2
Type of AF, n (%)						
Paroxysmal/persistent	19 (49)	19 (49)	-----	-----	20 (57)	21(60)
AF duration, years	3.0 ± 4.9 (<0.5-21)	4.2 ± 5.5 (<0.5-22)	-----	-----	9.5 ± 9.3 (0.9-29)	4.9 ± 6.3 (<0.5-22)
Permanent	20 (51)	20 (51)	30 (100)	35 (100)	15 (43)	14 (40)
AF duration, years	6.9 ± 4.8 (< 0.5-15)	8.6 ± 5.9 (< 0.5-20)	4.1 ± 4.8 (<0.5-20)	5.8 ± 6.2 (<0.5-22)	8.6 ± 4.4 (1.4-17)	11.6 ± 7.6 (1.3-25)
DC cardioversions	15 (38)	19 (53)	15 (50)	17 (48.6)	17 (49)	19 (58)
Comorbidity, n (%)						
Hypertension	20 (51)	21 (54)	9 (30)	11 (31.4)	21 (60)	23 (66)
Diabetes mellitus	8 (21)	8 (21)	2 (6.7)	6 (17.1)	10 (29)	11 (31)
History of embolic stroke/ TIA	10 (26)	5 (13)	1 (3.3)	3 (8.6)	8 (23)	1 (3)
Myocardial infarction/ coronary artery disease	20 (51)	17 (44)	6 (20)	9 (25.7)	24 (69)	16 (46)
Hyperlipidemia	22 (56)	23 (59)	-----	-----	26 (74)	26 (74)
Chronic obstructive pulmonary disease	2 (5)	0 (0)	2 (6.7)	6 (17.1)	2 (6)	1 (3)
Higgins score	2.2±1.3	1.8±1.7	------	------	2.1±1.6	1.8±1.5
LVEF %	54 ± 10	53 ± 10	54 ± 9	57 ± 12	54 ± 11	53 ± 8
LA area (cm²)	26 ± 7	29 ± 6	44 ± 12	40 ± 8	25 ± 6	28 ± 6
RA area (cm²)	22 ± 7	24 ± 8	27 ± 8	26 ± 5	20 ± 6	23 ± 6

n indicates number of patients, % within brackets

Figures are mean ± 1SD with min-max values in brackets

Table 4 b

Operative data,

n (%)	PAPER I		PAPER II		PAPER III	
	RF	**Control**	**Cryo**	**Control**	**Cryo**	**Control**
CABG	38 (97)	39 (100)	6 (20)	5 (14.3)	35 (100)	35 (100)
Aortic valve replacement	12 (30)	9 (23)	0	0	0	0
Mechanical	2 (5)	6 (15)	0	0	0	0
Biological	10 (26)	3 (8)	0	0	0	0
Tricuspid valve repair	0 (0)	1 (3)	1 (3.3)	3 (8.6)	0	0
Mitral valve repair	1 (3)	1 (3)	21 (70)	28 (80)	0	0
Mitral valve replacement	0	0	9 (30)	7 (20)	0	0
Closure of ASD	0	0	1 (3.3)	1 (2.9)	0	0
Ablation procedure, min	24 ± 6	na	22 ± 6	na	21 ± 5	na
(range)	(11-35)		(14-37)		(13-33)	
ECC time, min	114 ± 33	89 ± 39	147 ± 28	119 ± 33	92 ± 17	76 ± 25
(range)	(52 -178)	(28-190)	(95-215)	(73-193)	(58-132)	(41-172)
Aortic clamp time, min	56 ± 28	58 ± 34	87 ± 95	84 ± 23	42 ± 15	44 ± 21
(range)	(10-108)	(13-156)	(53-181)	(52-142)	(17-76)	(17-140)

n indicates number of patients, % within brackets

Figures are mean ± 1SD with min-max values in brackets

ASD=atrial septal defect, na=not applicable

Table 4 c

In-hospital and late complications

	PAPER I		PAPER II		PAPER III	
	RF	Control	Cryo	Control	Cryo	Control
	(n=39)	(n=39)	(n=34)	(n=35)	(n=35)	(n=35)
In-hospital, n						
Reoperation (bleeding)	1	2	2	2	1	3
Low cardiac output syndrome #	0	1	3	0	0	0
Myocardial infarction	0	1	1	0	2	3
TIA	1	0	1	0	0	0
Stroke	0	2	0	0	0	2
Renal failure	1	0	0	0	0	0
Sepsis	0	0	1	1	0	0
Postoperative ICD	0	0	0	0	0	1
Postoperative permanent pacemaker	0	1	7	4	0	1
Operative mortality	1	1	1	0	0	0
Late complications, n						
Mitral valve prosthesis thrombosis	0	0	1	0	0	0
Myocardial infarction	1	0	0	1	0	0
Angina pectoris	4	0	0	0	1	0
Congestive heart failure	0	2	1	3	2	4
Pericardial effusion ##	1	1	0	1	1	0
TIA	1	0	4	0	1	0
Stroke	2	3	0	2	1	2
Arterial embolus (leg)	0	1	0	0	0	0
Renal failure	1	1	0	0	0	1
Bleeding - ocular	0	0	0	1	0	0
ICD	0	1	0	0	0	2
Permanent pacemaker	2	0	0	0	1	0
Atrial tachycardia	0	0	0	1	0	0
His-ablation	1	0	0	0	0	0
Death	3	4	1	0	4	2

ICD=Implantable Cardioverter Defibrillator

Treatment with intra-aortic balloon pump #

Treatment with drainage ##

PAPER I

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

For patient characteristics, operative data and complications see Tables 4 a-c. Thirty-nine patients underwent concomitant RF ablation and 39 patients served as controls. A full lesion pattern was performed in all ablation patients. In one patient in the ablation group, the intended CABG was not performed due to a coronary artery unsuitable for grafting. The prevalence of risk factors for AF was similar in both groups with the exception of a higher BMI in the control group (p=0.02). The additional extracorporeal circulation time in the RF ablation group was 24 ± 6 minutes. In hospital, one patient had a TIA in the ablation group. Two patients in the control group suffered a stroke and one patient had a permanent pacemaker. There was one in-hospital death in each group.

Morbidity and mortality

The long-term follow-up period was 32 ± 11 months. Follow-up was attempted in the 69 survivors and complete data were retrieved for 61 patients.

In the ablation group, two permanent pacemakers were implanted two years post-operatively, one because of AV block II on exertion and one before the planned His-ablation. In the control group, the same patient who received a permanent pacemaker post-operatively, due to slow AF alternating with nodal rhythm, later received an ICD. In the ablation group, two patients with $CHADS_2$ score 1 and 2, respectively, developed embolic stroke two and three years post-operatively, respectively. In the control group, three patients with $CHADS_2$ score of 1, 2 and 3 respectively developed embolic stroke at three months, one year, and one month postoperatively. Four of them were in SR at all rhythm follow-ups and had been given aspirin, and the fifth patient had a contraindication for warfarin. One patient with atherosclerotic plaque in the carotid artery in the ablation group had a TIA three years post-operatively, and one patient on warfarin in the control group had a peripheral arterial embolus in a leg three months post-operatively. During the follow-up period, there were three deaths in the ablation group and four deaths in the control group.

Rhythm and prediction of rhythm

The cumulative freedom from documented AF or atrial flutter was significantly higher in the ablated patients, p=0.002 (*Fig 9*).

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 long-term follow-up as 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 first rhythm follow-up, at three months, was highly predictive of the rhythm at subsequent controls. In the ablation group, all but three patients with SR at three months had SR at 32 months (sensitivity 95 %, positive predictive value (PPV) 86 %) (*Fig 10 a)*. All but two of the 24 patients in the control group with AF at three months also had AF at long-term follow-up (sensitivity 91 %, PPV 91 %) (*Fig 10 b).*

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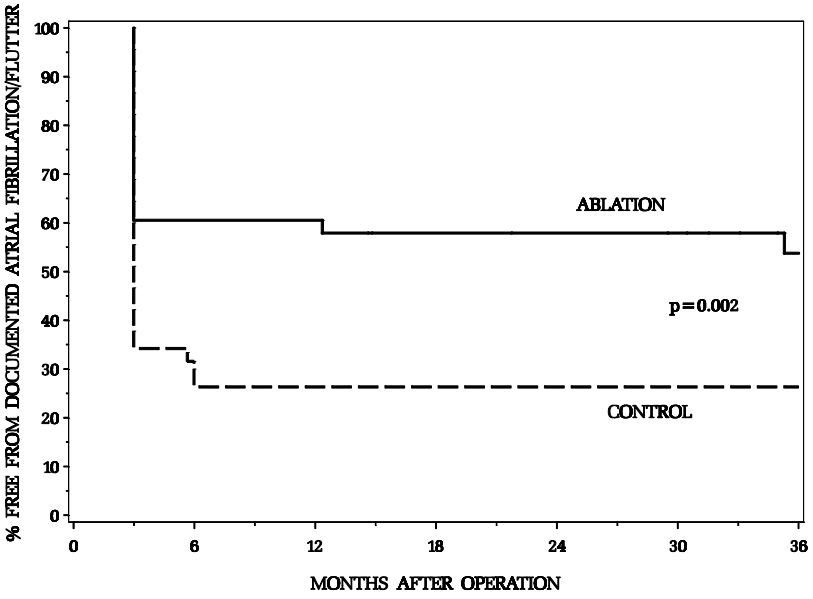

Figure 9. Cumulative freedom from documented atrial fibrillation and atrial flutter in the ablation group (n=39) and the control group (n=39). There was a significant difference between the two groups (p=0.002).

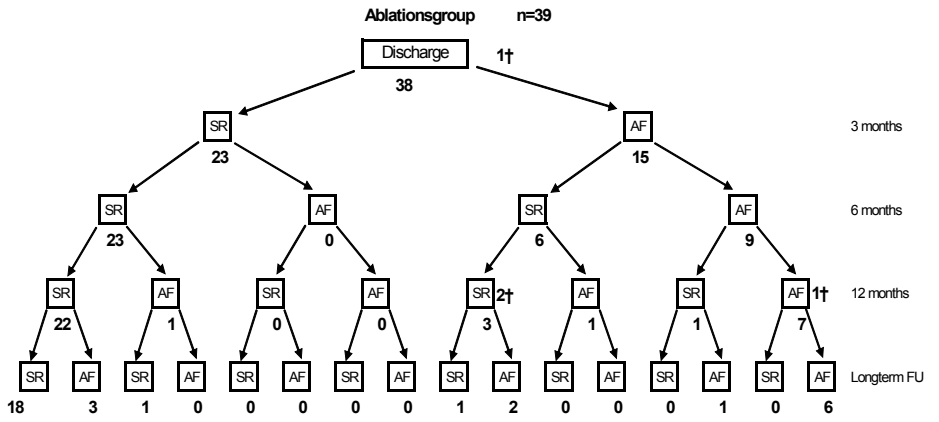

Figure10 a. Flow chart of rhythm development during follow-up in the ablation group.

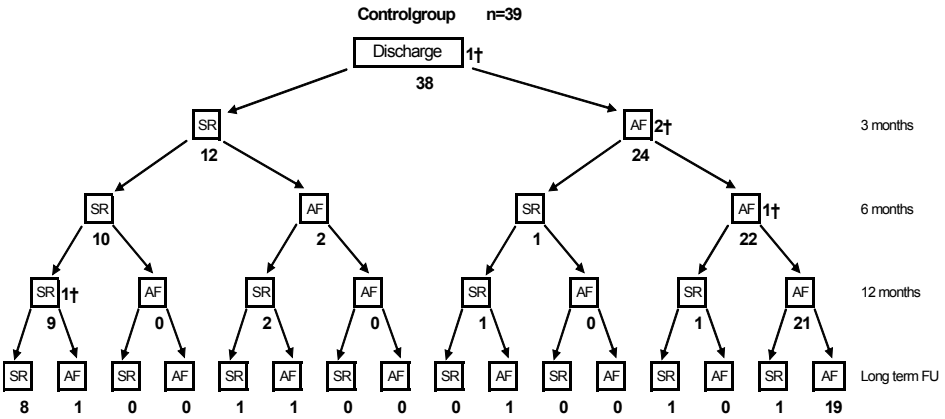

Figure 10 b. Flow chart of rhythm development during follow-up in the control group.

The following drugs were used for rhythm or rate control: 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

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.

There were no significant differences in SF-36 scores between the ablation and the control group at 32 months. When all patients in SR were compared with all patients in AF, irrespective of their original groups, those in SR scored better with respect to bodily pain (p=0.002) and general health (p=0.005) (*Fig 11).*

Symptom check list scores for severity of symptoms were better in the ablation group than in the control group (p=0.03), but not for frequency of symptoms (p=0.08) *(Fig 12 a).* A comparison between patients in SR versus AF showed significant differences in both scores, for severity (p=0.0004) and for frequency (p=0.0009) (*Fig 12b).*

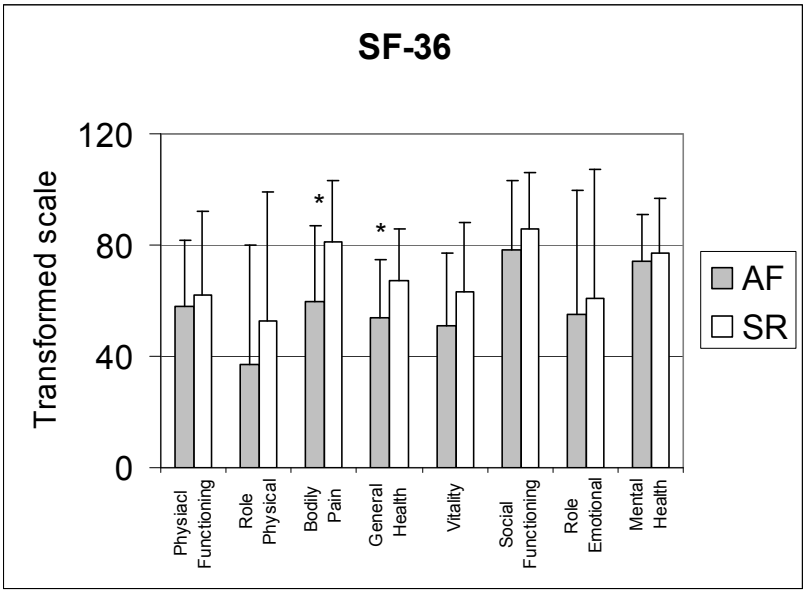

*Figure 11. Comparison of quality of life scores (SF-36) between patients in sinus rhythm and patients in atrial fibrillation at long-term follow-up. The scale is 0-100; a higher score is better. *p<0.05.*

Figure 12 a.

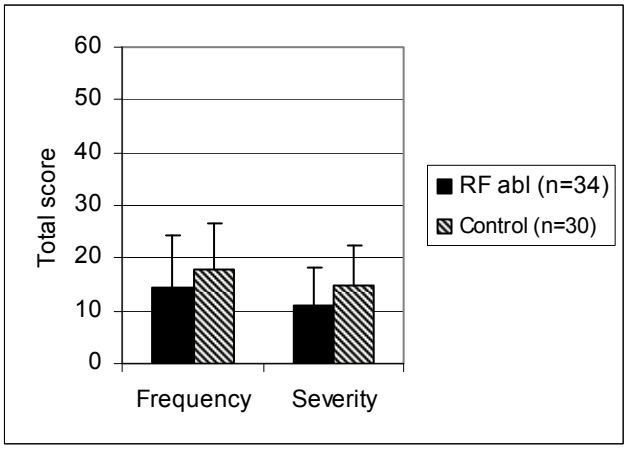

Figure 12 b.

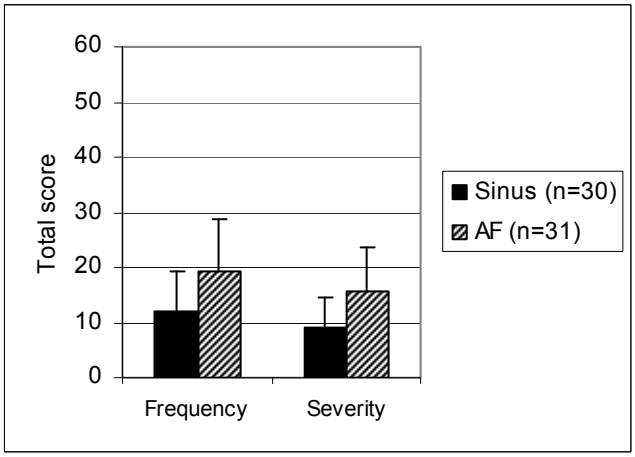

*Figure 12 a-b. Symptom checklist for frequency and severity. (a) Comparison between the ablation and the control groups. (b) Comparison between patients in sinus rhythm and patients in atrial fibrillation. The scale is 0-64 for frequency and 0-48 for severity;a lower score is better for both.*p<0.05*

PAPER II

A randomized double-blind study of epicardial left atrial cryo ablation for permanent atrial fibrillation in patients undergoing mitral valve surgery: the SWEDish Multicentre Atrial Fibrillation study (SWEDMAF)

For patient characteristics, operative data and complications see Tables 4 a-c. A total of 71 patients were randomized. The number of patients included at each centre was: Uppsala 28 patients, Gothenburg 26 patients, Umeå 12 patients and Stockholm three patients. There were no significant differences in the two patient groups with regard to baseline characteristics or peroperative data. All patients had mitral valve regurgitation except for one in the ablation group who had mitral valve stenosis. The additional extracorporeal circulation time in the cryo ablation group was 21.6 ± 5.6 minutes.

In hospital, seven patients in the ablation group had permanent pacemakers, two because of AV block and five because of bradycardia. In the control group, four permanent pacemakers were implantated, three because of AV block and one because of bradycardia. One patient in the cryo ablation group had a TIA and one patient died.

Morbidity and mortality

Sixty-five patients reached the primary endpoint and were analysed for primary and secondary events during the 12-month follow-up.

Four cryo ablated patients had TIA attacks, of whom two were off warfarin at discharge, one was on warfarin and one occurred during thrombolysis of mitral valve prosthesis thrombosis. In the control group, one patient on warfarin had an embolic stroke during myocardial infarction and another suffered a small pons bleeding.

One patient died in the cryo ablation group during follow-up. Two patients could not be evaluated because of a senile psychosis and patient refusal, respectively.

Rhythm and prediction of rhythm

At the six-month follow-up 73.3 % of patients in the cryo ablation group were in SR versus 45.7 % in the control group ($p=0.024$). At 12 months 73.3 % in the ablation group versus 42.9 % in the control group were still in SR ($p=0.013$). Of the patients in SR at 12 months, 72.7 % in the ablation group and 53.3 % in the control group were without antiarrhythmic drugs.

Multiple logistic regression analysis identified the presence of coronary artery disease (CAD) (p=0.047) and longer duration of ECG-verified pre-operative permanent AF (p=0.012) as independent risk factors for failed cryo ablation in eliminating AF at the 12-month follow-up (*Fig 13 and 14*).

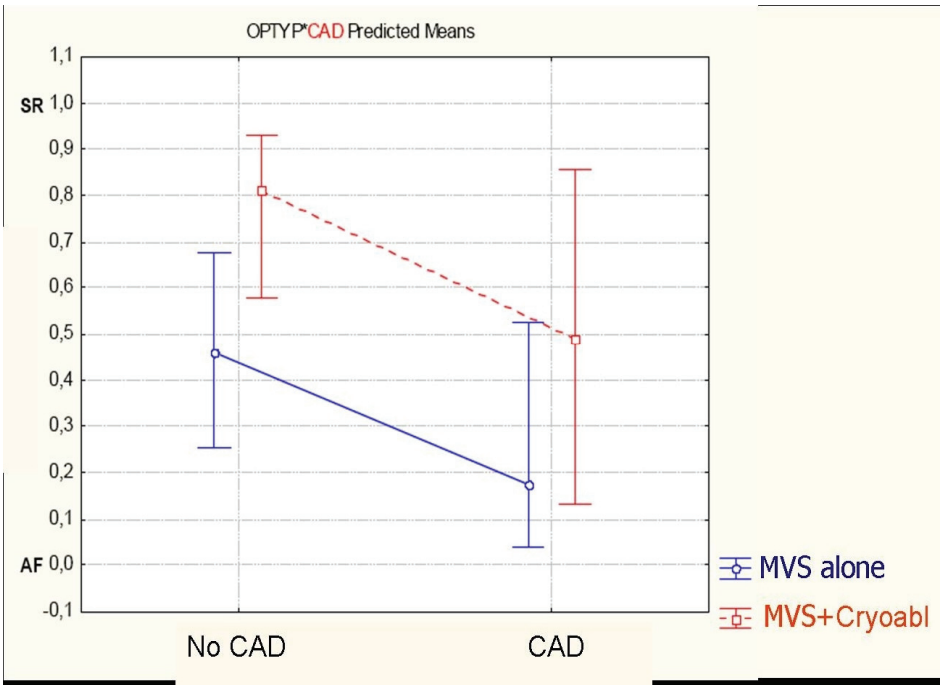

Figure 13. Plot of predicted means from a multiple logistic regression analysis showing that sinus rhythm could only be achieved in 50 % of patients with CAD compared with 80 % of patients without CAD after concomitant MVS and cryo ablation. The efficacy of cryo ablation was, however, of the same magnitude in both patient groups. The vertical bars indicate 95% confidence intervals, and the scaling on the y-axis is the probability of sinus rhythm. (Printed with permission from C Blomström-Lundqvist).

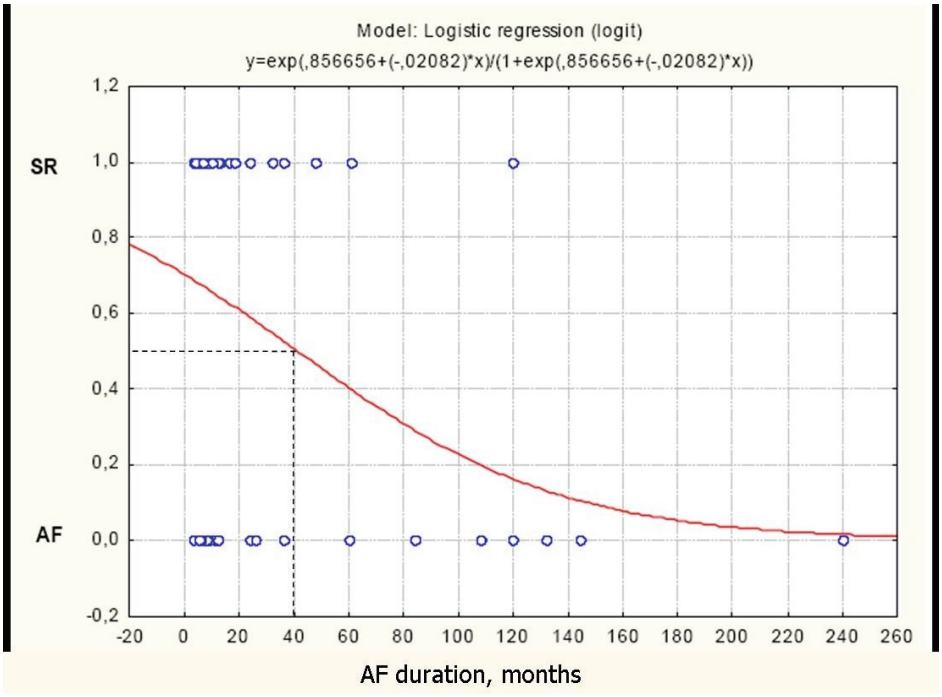

Figure 14. Scatterplot of a simple logistic regression analysis showing that ECG verified atrial fibrillation duration was an independent predictor of outcome at 12 months (p=0.012). For patients with a permanent AF duration equal to or exceeding 40 months, the probability of maintaining sinus rhythm at 12 months after combined surgery with cryo ablation was less than 50 %. (Printed with permission from C Blomström-Lundqvist).

PAPER III

Effects on echocardiographic measures in relation to rhythm before and after intraoperative epicardial cryo ablation for atrial fibrillation

For patient characteristics, operative data and complications see Tables 4 a-c. Thirty-five patients underwent concomitant cryo ablation and 35 patients served as controls. A complete left atrial lesion set was performed in all cryo ablated patients. The BMI was slightly higher in the control group (p=0.04), while the history of paroxysmal/persistent AF was longer in the ablation group (p=0.04) and eight versus one patient had a history of stroke/TIA (p=0.03). Echocardiographically, there were no significant differences in the LVEF, left or right atrial areas. The additional extracorporeal circulation time in the cryo ablation group was 21 ± 5 minutes. One patient in the control group received an ICD because of peroperative infarction and repeated ventricular fibrillation. Another patient in the control group received a VVI-R pacemaker postoperatively because of AF with slow ventricular rhythm. There was no early (30-day) mortality.

Morbidity and mortality

The long-term follow-up period was 22 ± 6 months. Follow-up was attempted in the 64 survivors and complete data were retrieved for 59 patients.

One patient in the ablation group had a DDD-R pacemaker implanted 11 months after surgery because of sick sinus syndrome. In the control group, two patients received an ICD six and 13 months postoperatively because of recurrent, rapid, monomorphic ventricular tachycardia.

In the ablation group, one patient with $CHADS_2$ score 2 developed a TIA after a successful DC cardioversion 29 months postoperatively even though he was on warfarin. One patient with $CHADS_2$ score 0 with SR during follow-up and on aspirin had a stroke 18 months postoperatively. In the control group, two patients with $CHADS_2$ scores 1 and 3, respectively, developed embolic stroke three months and one month after surgery. Both had been given aspirin due to contraindications for warfarin.

During the follow-up period, there were four deaths in the ablation group and two in the control group.

Rhythm follow-up

The cumulative freedom from documented AF or atrial flutter was significantly higher in the ablated patients, p=0.0001 *(Fig 15).* The proportion of patients in SR in the ablation group versus the control group at three months was 91 % versus 34 % (p=<0.0001) and at long-term follow-up 63 % versus 34 % (p=0.04) *(Fig 16 a-b).* The following drugs were used for rhythm or rate control: sotalol (n=3), amiodarone (n=2), beta-blockers (n=22) and digoxin (n=4) in the ablation group and sotalol (n=4), amiodarone (n=1), beta-blockers (n=25) and digoxin (n=5) in the control group. Multiple logistic regression analysis identified two variables that were independently predictive of SR at long-term follow-up. These were SR before surgery (OR 22.5; 95% CI 3.8,131.4; p=0.0006), and left atrial area at baseline (OR 0.85 per cm²; 95% CI 0.73,0.99; p=0.04).

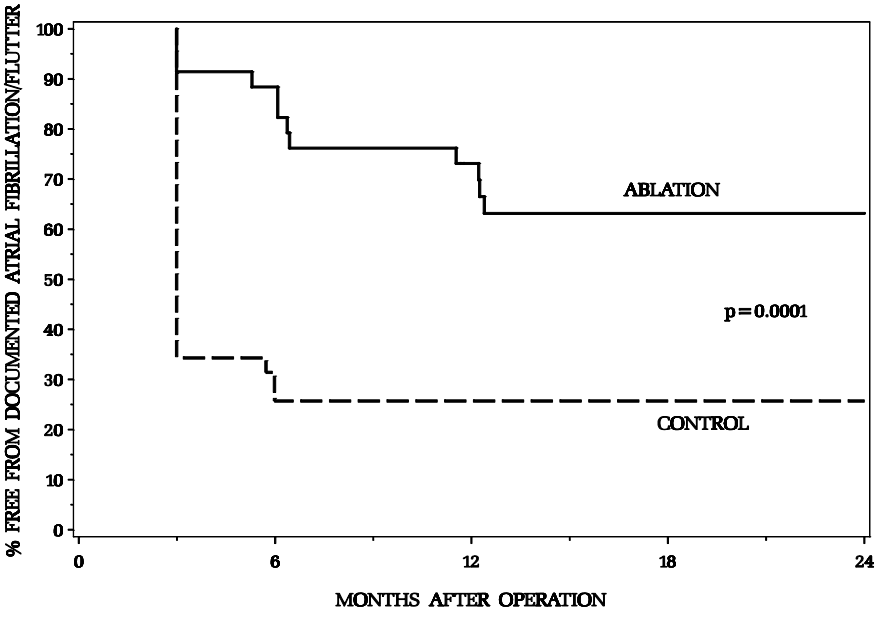

Figure 15. Cumulative freedom from documented atrial fibrillation and atrial flutter in the cryo ablation (n=35) and the control group (n=35). There was a significant difference between the two groups (p=0.0001).

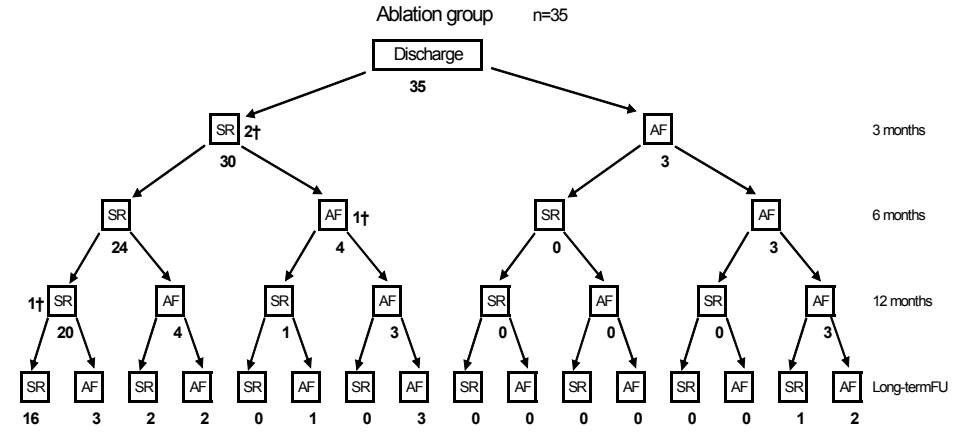

Figure 16 a. Flow chart of rhythm development during follow-up in the cryo ablation group.

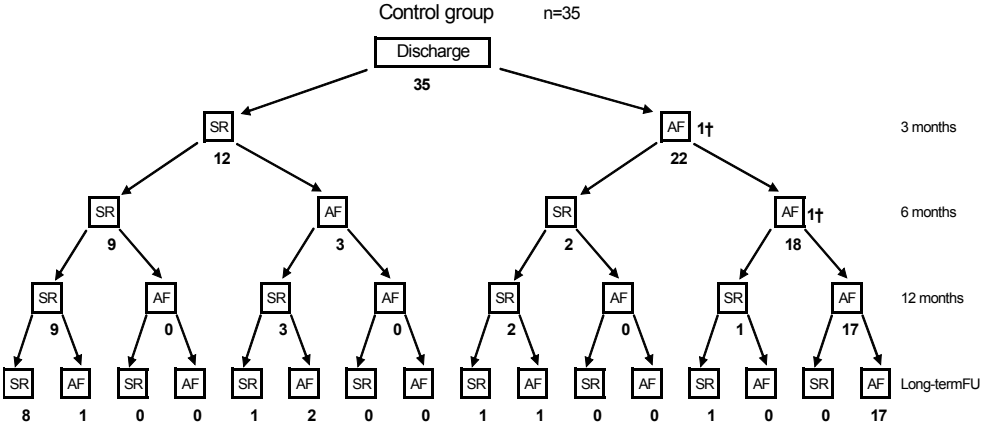

Figure 16 b. Flow chart of rhythm development during follow-up in the control group.

Echocardiographic effects of cryo ablation

Patients in the cryo ablation group with SR before and after surgery had a decreased mitral flow velocity during atrial contraction (p=0.002) and a decreased left atrial systolic contraction amplitude (p=0.01) at long-term follow-up. An increase in the left (p=0.002) and the right (p=0.01) atrial areas and an increased LV diameter (p=0.03) was also seen, whereas the LVEF was decreased (p=0.03). In the control group the right atrial area had increased at follow-up (p=0.02). There were statistically significant differences in the magnitude of changes between the ablation and the control groups regarding the LV diameter (p=0.04) and the A-wave velocity (p=0.009). The atrial and ventricular function was slightly decreased at long-term follow-up, but still within or close to reference limits in patients with SR before and after surgery (Table 5a).

Patients with AF before surgery and at follow-up in both groups showed a significant continued deterioration of echocardiographic measures (Table 5b).

Table 5 a. Patients with sinus rhythm both before surgery and at follow-up 22±6 months postoperatively (only patients with echo both before surgery and at follow-up included)

	CRYO PATIENTS			CONTROL PATIENTS			
	Before surgery	At follow-up	p#	Before surgery	At follow-up	p#	p##
Males/Females; n	11 / 1			8 / 1			
Age (years); mean±sd	72 ± 6			70 ± 8			
AF paroxysmal/permanent/persistant; n	12 / 0 / 0			9 / 0 / 0			
AF duration (years); mean±sd median (min-max)	9 ± 8 6 (1-24)			7 ± 9 3 (<1-22)			
Heart rate (bpm); mean±sd (1/0)*	60 ± 8	63 ± 10	0.43	65 ± 13	59 ± 9	0.07	0.04
PQ (ms); mean±sd (2/0)	172 ± 19	172 ± 12	0.94	170 ± 18	185 ± 37	0.20	0.10
LV diameter (mm); mean±sd (1/1)	45 ± 5	49 ± 5	0.03	51 ± 7	50 ± 5	0.78	0.04
LVEF (%); mean±sd (2/0)	59 ± 6	56 ± 8	0.03	55 ± 9	53 ± 8	0.50	0.61
Left atrial area (cm^2); mean±sd	21 ± 4	26 ± 5	0.002	24 ± 4	26 ± 5	0.06	0.28
Right atrial area (cm^2); mean±sd	18 ± 4	21 ± 4	0.01	19 ± 3	23 ± 4	0.02	0.99
A-wave velocity (m/s); mean±sd (1/0)	0.76 ± 0.14	0.51 ± 0.20	0.002	0.70 ± 0.21	0.64 ± 0.26	0.27	0.009
Atrial systolic $velocity_m$ (cm/s); mean±sd (2/0)	9.8 ± 2.4	8.2 ± 2.9	0.07	8.5 ± 2.1	7.1 ± 3.1	0.055	0.76
Atrial systolic $amplitude_m$ (cm); mean±sd (2/0)	0.60 ± 0.18	0.46 ± 0.15	0.01	0.50 ± 0.14	0.49 ± 0.18	0.65	0.11

for change within group; ## for difference in change between cryo and control groups
* number of patients where information was missing in the cryo and control groups, respectively

Table 5 b. Patients with atrial fibrillation/flutter both before surgery and at follow-up 22±6 months postoperatively (only patients with echo both before surgery and at follow-up included)

	CRYO PATIENTS			CONTROL PATIENTS			
	Before surgery	At follow-up	p#	Before surgery	At follow-up	p#	p##
Males/Females; n	8 / 1			15 / 2			
Age (years); mean±sd	70 ± 7			70 ± 6			
AF paroxysmal/permanent/persistant; n	0 / 9 / 0			3 / 11 / 3			
AF duration (years); mean±sd (0/3)* median (min-max)	8 ± 5 8 (1-17)			9 ± 8 6 (<1-25)			
Heart rate (bpm); mean±sd	76 ± 8	83 ± 18	0.34	72 ± 13	74 ± 16	0.81	0.45
LV diameter (mm); mean±sd (1/2)	51 ± 4	49 ± 6	0.19	51 ± 6	51 ± 6	0.81	0.28
LVEF (%); mean±sd	47 ± 15	45 ± 11	0.47	53 ± 8	44 ± 9	0.002	0.21
Left atrial area (cm^2); mean±sd (1/0)	30 ± 7	33 ± 8	0.047	30 ± 7	33 ± 5	0.03	0.94
Right atrial area (cm^2); mean±sd (2/0)	24 ± 4	28 ± 7	0.09	26 ± 6	29 ± 6	0.0006	0.96

for change within group; ## for difference in change between cryo and control groups
* number of patients where information was missing in the cryo and control groups, respectively

PAPER IV

Left ventricular diastolic function and right atrial size are important rhythm outcome predictors after intraoperative ablation for atrial fibrillation

Thirty-five consecutive patients scheduled for CABG and with a history of ECG-verified AF were enrolled. The cryo technique was used in 27 patients and RF in eight. The multiple logistic regression analysis only included patients in which all echocardiographic variables were obtained (n=29) (Table 6).

Baseline characteristics and medication

Paroxysmal AF and SR preoperatively were significantly (p=0.0006 and p=0.003, respectively) associated with SR at long-term follow-up (2.3 ± 0.4 years after surgery). Medication preoperatively with sotalol also correlated with SR at follow-up (p=0.03).

Atrial area

Both the RA and LA areas were significantly associated with the rhythm outcome at follow-up (p= 0.004 and p= 0.03, respectively). In a multivariate analysis, only the RA area remained significantly associated with outcome. The optimal cut-off value for the RA area from the ROC curve was found at 24 cm^2, corresponding to the third quartile *(Fig 17).*

Diastolic LV function

Decreased LV diastolic function preoperatively, measured as the maximal left ventricular long-axis relaxation velocity (MLVLARV), was significantly associated with SR at follow-up (p=0.02). The optimal cut-off value for the MLVLARV was 6.8 cm s^{-1}, which equalled the third quartile of this variable (*Fig 18).*

Multivariate analysis

When simultaneously considering RA area and the MLVLARV, both these variables remained significantly associated with the rhythm at follow-up, and the c-statistic was 0.94 for the corresponding logistic regression model in which, due to non-linearity, the squared value of right atrial area was also included. The prediction of SR after intraoperative ablation was given by the following equation:

Logit(p) = RAA*3.2275 – RAA*RAA*0.0853 –MLVLARV *1.5662 – 16.9122. The likelihood for SR after ablation can then be calculated from the following formula: $p = e^{-logit} / (1 + e^{-logit})$.

Table 6. Echocardiographic variables before surgery in relation to sinus rhythm (SR) or atrial fibrillation (AF) at follow-up (n=35)

	Rhythm at follow-up			
	SR (n=24)	**AF** (n=11)	***p***	**AUC on ROC graph**
Left atrial area (cm^2)	24±5 (23)	29±6 (10)	0.03	0.73
Right atrial area (cm^2)	19±4 (23)	25±7 (10)	0.004	0.81
(LAA+RAA)/2 (cm^2)	21±4 (23)	27±6 (10)	0.02	0.76
Left ventricular end diastolic diameter (mm)	48±7 (23)	50±5 (10)	0.14	0.63
Left ventricular wall thickness (mm)	12.2±1.4 (24)	11.3±1.5 (11)	0.20	0.64
Left ventricular ejection fraction	0.56±0.09 (23)	0.49±0.15 (11)	0.32	0.61
Left ventricular maximal longitudinal contraction velocity ($cm\ s^{-1}$)	5.7±1.8 (24)	4.7±1.5 (7)	0.24	0.65
Mitral annulus motion amplitude (mm)	9.7±2.9 (22)	8.1±1.8 (8)	0.13	0.68
Maximal left ventricular long axis relaxation velocity ($cm\ s^{-1}$)	5.6±1.5 (22)	7.1±1.3 (7)	0.02	0.79

Abbreviations: AUC=area under the curve; LAA=left atrial area; (n) = number of observations; RAA=right atrial area; ROC= Receiver Operating Characteristic Curves

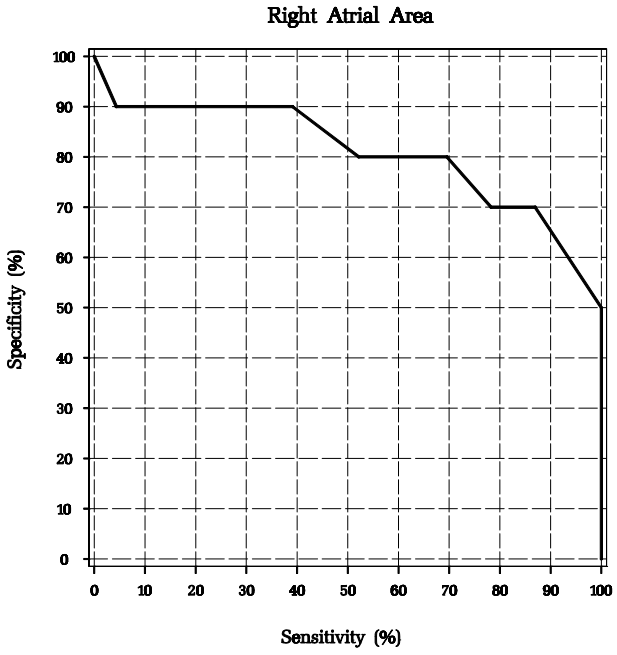

Figure 17. ROC curve of the right atrial area in predicting SR after ablation.

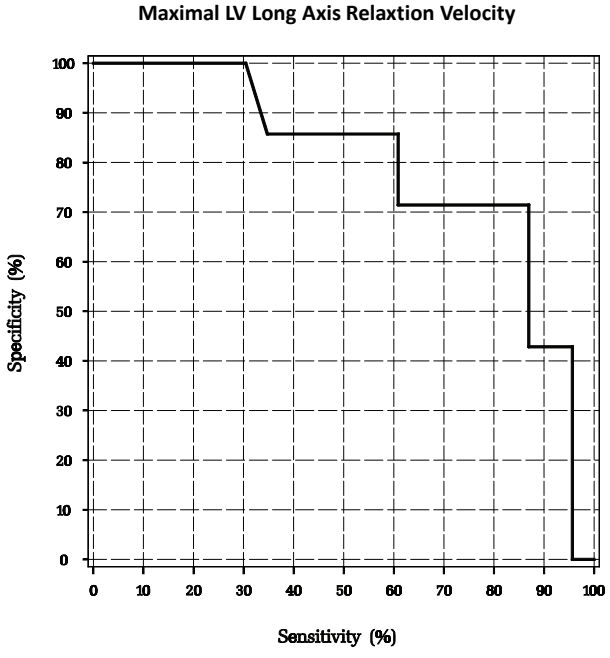

Figure 18. ROC curve of the maximal LV long axis relaxation velocity in predicting SR after ablation.

DISCUSSION

Intraoperative AF ablation was made feasible when an RF probe capable of creating linear lesions (as opposed to point-by-point lesions) became available in 1998. It was soon tried as a tool to endocardially ablate AF in patients undergoing MVS, i.e. in procedures that offered access to the LA [171]. After gaining experience in a pilot study (1999-2000) using the endocardial technique with RF (Thermaline/Cobra, Boston Scientific Cooperation, San José, CA, USA) in consecutive patients undergoing MVS, we adapted the endocardial lesion set to an epicardial application (2001-2002), which also made AF ablation possible in patients undergoing surgery during which the LA was not opened, such as in CABG and aortic valve replacement. When a linear cryo probe was developed (Surgifrost^{TM} Cryoablation system, CryoCath Technologies Inc., Quebec, Canada) in collaboration with and tested at Sahlgrenska University Hospital (2001), it was soon found that it could be used similarly, with the same lesion set, and with the advantages of a) sticking to the surface during freezing, creating a very distinct lesion line, b) being applicable directly on the coronary sinus as well, which is an important part of the left atrial lesion pattern in the Cox Maze III procedure and c) being less damaging to adjacent tissues than heat-producing energy sources. We decided to apply an unbiased approach, offering intraoperative ablation to any patient undergoing CABG with or without valve surgery and with documented AF, whether paroxysmal or persistent/permanent (papers I, III and IV). In the SWEDMAF study (paper II), only patients with permanent AF were randomized.

Papers I, III and IV reflect our early experience of intraoperative AF ablation, starting patient enrolment in 2001. Patients were enrolled sequentially and consecutively into the single-center studies, I and III, during 2001 to 2004. Paper II followed after development of the cryo probe and was a multicenter study in mitral valve patients, thus running in parallel with the other two. Paper IV specifically addresses the capabilities of echocardiographic variables at baseline to predict rhythm outcome after intervention.

The effect on rhythm outcome *(papers I, II and III)*

The cumulative freedom from documented AF/atrial flutter at long-term follow-up was significantly higher in the ablated patients (papers I and III). Patients with paroxysmal/persistent AF had a higher chance of regaining and maintaining SR than

those with permanent AF (I) reflecting that it is possible to stop or delay the progression of AF. Recognizing that this patient population is different in important aspects from those undergoing primary treatment for AF, this is a satisfactory outcome. Furthermore, defining success or failure simply by the occurrence of at least one documented recurrence of AF may not give full credit to the benefits for the patient. Thus, a substantial reduction of AF, rather than complete elimination, would most likely confer symptom relief and be an acceptable endpoint for treatment. The proportion of patients in SR at 12 months reported in paper III was 69 % in the cryo ablation group versus 47 % in the control group. SR before surgery and a small left atrial area were independent predictors for SR at long-term follow-up (paper III). Long-term follow-up was shorter in the study reported in paper III (22 ± 6 months) compared with long-term follow-up in paper I (32 ± 11 months). All patients studied in papers I and III had ischemic heart disease, and the study protocol was identical up to 12 months postoperatively. The prevalence of valve surgery did not influence rhythm outcome in a univariate analysis reported in paper I. In our studies, the rhythm follow-up at three months was predictive of the rhythm status at subsequent controls and at long-term follow-up (papers I and III).

The postoperative period after primary Cox Maze III procedure and intraoperative ablation is often characterized by electrical instability with a stabilization of rhythm over time. We therefore decided to give all patients in the ablation group amiodarone as this is the most effective prophylactic antiarrhythmic drug, starting immediately after surgery, and to reevaluate the treatment at three months when it would normally be stopped. As an alternative, patients would receive sotalol in the case that amiodarone was contraindicated or unsuitable. At the time that these studies were designed, an emerging concept was that antiarrhythmic drugs would be beneficial by maintaining SR and facilitating reverse remodeling of the atria. This policy also included DC cardioversions when necessary. The first three postoperative months served as a “treatment stabilization period”, during which the rhythm outcome of surgery was not to be evaluated. This was supported by the first HRS/EHRA/ECAS guidelines in this field, which were published in 2007 and suggested that there should be a “blanking period” of three months after ablation before assessing efficacy endpoints [172]. The HRS/EHRA/ECAS guidelines further suggest a minimum of one 24-hour Holter monitoring at three to six month

intervals for one to two years after ablation. If an AF/atrial flutter or tachycardia is present for > 30 seconds, it should be considered a relapse [172].

In the SWEDMAF study (paper II), the results at 12 months with 73.3 % of ablated versus 42.9 % of control patients in SR show quite a high SR rate in both ablated and control patients, as compared to another randomized study in patients with left atrial RF ablation during MVS with a SR maintenance rate of 44.4 % versus 4.5 % [138]. This might be explained by an earlier intervention in relation to progression of the mitral valve disease and a more active postoperative treatment in our study. Von Oppell-et al [141] used an active postoperative treatment policy with DC cardioversions and amiodarone in both treatment groups after MVS and biatrial RF ablation versus MVS alone and had SR rates at one year of 75 % versus 39 %. In another randomized study, however, where amiodarone was also given to the control patients undergoing MVS alone, the SR maintenance rate was only 9.4 % one year postoperatively while 93.6 % were in SR after MVS and biatrial irrigated RF ablation [137]. In the SWEDMAF study (paper II), coronary artery disease was a risk factor for failed cryoablation in patients with mitral valve disease. The rhythm results at 12 months after intraoperative epicardial cryoablation in paper II were supported by the rhythm results of two other studies after endocardial left atrial cryoablation in patients with mainly MVS [144, 159] (Table 2a).

Lesion set *(papers I-III)*

Our left atrial lesion set was created to imitate as far as possible the left atrial part of the Cox Maze III procedure. Gillinov et al. [173] used the similar approach in patients with longstanding persistent AF with underlying mitral valve disease undergoing intraoperative ablation comparing different lesion sets or the Cox Maze III procedure. Lesion sets with wide encircling rings of the pulmonary veins with a connecting lesion in between, one lesion to the mitral valve and another to the LAA, yielded results at 12 months comparable with the traditional Cox Maze III procedure.

In a meta-analysis by Barnett et al. [120] there was a significantly better rhythm outcome defined as freedom from AF with biatrial lesions compared to left atrial lesions. The reported success rates were 88.9 % at one year and 87.1 % at three years, i.e. in the lower range of what has been demonstrated after the Cox Maze III procedure. However, this was a meta-analysis including a variety of techniques and lesion sets without

comparisons between specific techniques, but focusing on differences in outcome after biatrial versus left atrial lesions (Table 3).

In a review, the Cox Maze III procedure or cryo applications in a similar biatrial lesion set for AF concomitantly with mitral valve repair seemed to significantly improve survival rates and cardiac function and to increase freedom from late stroke eight years postoperatively as compared with valve surgery alone [174].

Aspects of operative technique, energy source and epicardial ablation *(papers I-III)*

The linear probes (RF and cryo) used in our studies were "first generation" and have later been modified. Ablations were made on an empty beating heart, which made it somewhat difficult for the RF probe to produce defined linear lesions rather than "areas". The cryo probe created well defined lesions in that the freezing segment immediately adhered to the tissue when freezing was started.

Our ablation technique included a very thorough dissection of epicardial fat before RF or cryo applications on the LA in order to minimize the insulating effect of fat tissue and to optimize atrial tissue contact with the probe [175]. The reason for applying the lesions on a vacuum-"emptied" beating heart on pump was to minimize the cooling/ re-warming effect of intracardiac blood flow. Intraoperative tests for electrical isolation were not made because no techniques were available for that purpose at the time. There were no dissection or ablation related complications, such as damage to the esophagus [176], coronary arteries [177], phrenic nerve or bronchial tree [178], that has been described with unipolar energy devices.

The epicardial approach with RF energy has the challenge of the convective cooling effect by endocardial blood flow, by which thermal energy is dissipated. Epicardial fat also insulates cardiac tissue because of the lower water content and limits energy penetration [121]. Temperatures have been measured in human atrial myocardium sub-epicardially and sub-endocardially during epicardial RF ablation in mitral valve patients. The application temperature and intra-tissue temperature *per se* do not seem to be the only factors that determine lesion depth. The thickness and composition of the epicardium and the myocardium are important factors with different properties that will affect the conduction of RF energy in the tissue. Transmurality is not achieved more effectively by prolonging the application duration or by increasing the application temperature or energy delivered [123, 179].

There have been doubts as to whether epicardial cryoablation can achieve transmural lesions, especially on a beating heart, and also concerning the relation of transmurality to electrical isolation. In an experimental study carried out by Doll et al. [180] , epicardial cryoablation of the pulmonary veins with a linear cryoprobe in sheep resulted in electrical isolation in 25 % in the acute phase and in 62.5 % after two hours. They referred to the effect of the endocardial blood flow, re-warming the atrial tissue. In another study on dogs with epicardial cryoclamp lesions on the beating heart, Milla et al. [132] demonstrated conduction block in the PVs and LAAs with full transmurality in 93 % of applications. In the same study, epicardial cryoablation using a linear cryoprobe demonstrated transmurality in 84 % of the applications. In a recent study by Masroor in pigs, endocardial temperatures in the LA were assessed in relation to electrical isolation during epicardial cryoablation using an argon-based cryoprobe. Adequate endocardial hypothermia was produced in myocardial tissue at a thickness of 5-7 mm. Transmurality was seen in 89 % of histologic sections and chronic electric isolation (>30 days) was maintained in 88 % of the animals [181]. The use of cooler cryoprobes with temperatures consistently less than – 130 º C [181], longer ablation times (five minutes) [182], repeat ablations and a slower thaw [130] seem to create larger and deeper lesions. In the study of Masroor [181], regional endocardial temperature differences of the left atrium were also seen as a result of varying wall thickness and epicardial fat.

The issue of transmurality and electrical isolation has been addressed by many authors. Immediate transmurality during intraoperative ablation may not be necessary. The size of the lesion may become larger during the process of tissue repair, and transmurality will come later. This may explain the progressive SR recovery up to three to six months after surgery. Reverse electrical and structural remodeling may also be involved in this process [124]. The wall thickness varies between 3 and 10 mm in the LA. The wall is thinnest in the region of the PVs and in the posterior region and thickest between the left inferior PV ostium and mitral valve annulus, the left isthmus region [124]. A line between the left ablation circle and the mitral valve annulus including the circumference of the coronary sinus seems to be important, and it is essential to require a continuous line of block in this region. Incomplete lesions in this area may create prerequisites for macroreentrant tachycardias.

Autonomic GP containing efferent parasympathetic, efferent sympathetic and afferent neurons have the ability to induce changes in cardiac rhythm, including induction of AF.

Intraoperative epicardial mapping has revealed a clustering of GP in the fat pads around the interatrial groove in the right side of the heart and along the ligament of Marshall on the left [183]. The thorough dissection in our technique [175] made to optimize contact between the ablation probe and atrial surface, may help in eliminating GP in the epicardial fat and thus add to the restoration of SR.

Evaluating success after intraoperative ablation

Assessment of rhythm outcome (papers I-III)

While "freedom of AF" would be the optimal outcome, it is not possible to claim complete elimination of AF on the basis of intermittent ECG and Holter recordings. A series of recordings showing SR during follow-up is very reassuring but does not exclude the existence of asymptomatic, undetected episodes. However, we could show, both after radiofrequency (I) and cryo ablation (III), that SR on the ECG recorded three months postoperatively was highly predictive of subsequent SR, implying that our follow-up routine was adequate, especially since postoperative SR was associated with symptom relief and improvement in QoL.

This also raises the question of how to define a treatment failure based on rhythm outcome. Recent guidelines advocate that a documented recurrence of AF of >30 seconds would be sufficient to decide that a treatment, pharmacological or non-pharmacological, has failed. While this may be technically correct, there may be better outcome variables than time to first symptomatic AF recurrence. Recurrences may also be asymptomatic, and continuing undetected AF carries a risk, especially if the patient is considered "cured" and anticoagulation is stopped. Thus, the frequency and type of ECG monitoring during follow-up is crucial in the evaluation of success based on rhythm outcome. Martinek et al. [184] followed patients with permanent pacemakers before and after percutaneous catheter ablation and found that the proportion of patients "free of AF" decreased from 71% to 57% when Holter monitoring was extended from 24 h to 48 h and seven days and to 21% during continuous monitoring by means of the pacemaker memory. Recently, implantable loop recorders have been equipped with algorithms to detect episodes of AF and to add these to provide the AF burden, e.g. hours in AF per day. It is likely that this technology will become increasingly important and that AF burden will become an important efficacy variable when assessing rhythm outcome.

Patient reported outcomes (paper I)

Since symptoms most often bring the patient to the doctor, symptom relief and improvement in QoL are valuable indicators of success. However, in candidates for intraoperative ablation, AF symptoms were not a requirement or a selection criterion for surgery (paper I). We therefore decided to evaluate the effects on symptoms and the impact on QoL, not only as conventional group-wise comparisons on an intention-to-treat basis, but also based on rhythm outcome, so that any differences would most probably be due to the change in rhythm. We thus found less symptoms and better QoL in patients, who at long-term follow-up were in SR as opposed to AF, while we do not know how much symptoms and QoL might have changed from before surgery (paper I). Since all patients underwent similar open heart surgery, the beneficial effects would most likely be explained by the maintenance of SR.

The Symptom Check List for Frequency and Severity is frequently used and has been validated for several languages. This instrument includes scales for assessment of the frequency and severity of symptoms. In our patients, at long-term follow-up, symptoms were less severe when compared between ablated and non-ablated patients, both less frequent and severe when compared in patients in SR and in AF (I). The lack of baseline data is a limitation, but the important point is that, if maintenance of SR can be achieved, it is associated with symptom relief in this population as well.

Symptoms have an impact on the quality of life. However, there is as yet no commonly used, disease-specific instrument to assess QoL in patients with AF. We used the generic SF-36 questionnaire that has been used in patients with AF with varying results. Again, our way of using it differed from others in that we, in addition to a comparison between ablated and non-ablated patients, wanted to show the link between maintenance of SR and better QoL (I). There were similar results in a study of 91 consecutive patients with permanent AF undergoing MVS, the last 53 patients of whom also had an intraoperative left atrial RF ablation. SR was obtained in 68 % of patients with ablation and in 10 % of patients with MVS only, and a stepwise logistic regression analysis showed the presence of SR to be associated with a significantly better QoL as assessed by SF-36 [185].

In a recently published randomized study by von Oppell et al. [141] of patients undergoing MVS and biatrial RF ablation and control patients undergoing MVS only, the SF-36 was used pre- and postoperatively to assess QoL. The success rate in restoring

SR was 75 % versus 39 %, respectively, at 12 months. The scores for physical functioning, role-physical, general health, vitality and social functioning increased significantly in both treatment groups, but there was no statistically significant difference in any of the QoL parameters between patients in SR or AF in the ablation group or when ablation and control patients were combined. One reason for this could be that symptoms from the valve disease *per se* dominated and, when corrected, patients experienced significantly better QoL irrespective of AF. It also implies that the symptoms of AF may be variable and that a certain level of symptoms must be present for the SF-36 instrument to be useful.

In 48 patients with drug-refractory AF undergoing the Cox Maze III procedure, QoL significantly improved at six and 12 months postoperatively compared to the preoperative QoL. QoL was assessed with the SF-36 and reached the levels of the general Swedish population [44]. After percutaneous catheter ablation, QoL was assessed using the SF-36 in four non-randomized studies. Patients with highly symptomatic paroxysmal/persistent AF undergoing successful ablation showed a significant improvement of QoL and reached the levels of healthy control subjects from one month and onwards after the procedures [42, 43, 186, 187]. The SF-36 was also used in the AFFIRM study, which compared the rhythm and rate control strategies in patients with risk factors for morbidity and mortality and more or less AF on top, but excluded highly symptomatic patients. No difference was seen between the treatment arms. QoL was also similar in patients with SR and AF when assessed in a subsequent sub-study [45].

Cardiac dimensions and function *(paper III)*

The role of cardiac function and its potential for recovery after SR has been restored and maintained has gained increasing interest. Traditionally, the left atrial diameter and possibly the area have been reported together with the LVEF, but less often other data.

Our data are consistent with the ablation procedure, *per se*, causing some trauma to the atria. Patients in the cryo ablation group with SR before and after surgery had a decreased mitral flow velocity during atrial contraction and a decreased left atrial systolic contraction amplitude at long-term follow-up. There was also an increase in the left and right atrial areas. Compared to the control group, the mitral flow velocity was significantly reduced. The magnitude of changes was small and atrial function and areas

were still within or close to reference limits. Other authors report similar results after interventions for AF. In a recent study by Boyd et al. six months after intraoperative RF ablation for chronic AF, a global and regional left atrial dysfunction was seen, especially in the inferior and lateral segments, suggestive of injury caused by the ablation process *per se.* A control group with chronic AF patients who had undergone cardioversion six months previously did not show the same magnitude of dysfunction [188]. In two other studies, a significant decrease in left atrial diameters was seen 22-30 months after intraoperative left atrial endocardial RF ablation in patients with persistent/permanent AF undergoing MVS [149, 189]. In the study of Fayad [149], right and left atrial filling fractions were improved during follow-up, even though right atrial filling fraction was higher at all times. This might have been an effect of the RF ablation *per se*, but could also have been an effect of the MVS with increased early left ventricular filling.

An initial decrease in maximal left and right atrial areas was seen after Cox Maze III surgery for paroxysmal AF, followed by an increase of the areas 56 months after surgery, with no difference as compared to the preoperative values. The left and right atrial contractility was also significantly reduced after six and 56 months versus baseline. The initial reduction in the atrial areas was proposed to depend on atrial scarring due to surgery, but the later deterioration of atrial dimensions and function was unexpected in patients with SR [51]. Still, QoL in these patients was significantly improved after restoration and maintenance of SR [44].

There are several possible interpretations of our results and those of others. AF is a progressive condition and, at the time AF is diagnosed, there may already be some impairment of atrial contractility. After interventions for AF, as mentioned above, scar formation may influence dimensions and function. However, since some stabilization seems to take place over time, although not full recovery, one possibility is that long-term SR facilitates reverse remodeling and prevents or delays further progression.

The aims of surgical AF ablation procedures are not only to restore SR but also to restore biatrial contractions to an optimal level or inhibit further deterioration of atrial function caused by AF. This is essential in the prevention of thromboembolism after AF interventions [112] and necessary if withdrawal of anticoagulant therapy is considered. In patients undergoing intraoperative ablation with preoperative persistent/permanent AF, recovery of atrial transport function has been described in about 63 - 100 % of patients [139, 141, 147]. There is however no defined cut-off limit for what is acceptable

as atrial transport function to prevent embolic stroke after AF interventions. Factors that negatively influence the postoperative return of atrial function are rheumatic and ischemic heart disease [141].

In our study, the left ventricular diameter increased and the LVEF decreased in patients with SR before and after cryo ablation. However, left ventricular function and dimensions were still within reference values. Patients with AF before and after surgery in both the ablation and the control groups showed a continued deterioration of echocardiographic measures during follow-up.

Patients undergoing surgery and concomitant intraoperative ablation in our studies all had structural heart disease, and few had clinically important systolic dysfunction preoperatively. Because of this, there may not be margins for recovery but only a possible deterioration.

Predictors for long-term sinus rhythm after intraoperative ablation *(papers I-IV)*

In studies on intraoperative ablation, the left atrial diameter, the AF duration and the lesion set are often described as predictive factors for rhythm outcome. See table 2 b. We tested a number of baseline variables (I, II, III, IV), including specific echocardiographic variables (IV). One interesting finding was that SR at three months, i.e. at the first assessment after the therapy stabilization period, was a strong predictor of long-term SR (I, III). Geidel et al. [155] also found that cardiac rhythm at three months after intraoperative bipolar RF ablation for permanent AF was a predictive factor for long-term SR at 32 months. It is impossible to say whether our policy to give amiodarone/sotalol during this period may have helped to shorten the time needed to full rhythm stabilization. Independent predictors for long-term SR were paroxysmal/persistent AF (I), a low BMI (I), short preoperative AF duration (II), no CAD (II), SR before surgery (III) and a small left atrial area (III). Patients with less structural changes of the atria due to a shorter duration of a paroxysmal/persistent AF seemed to have better chances of regaining and maintaining SR postoperatively. Moreover, specific echocardiographic variables were tested in the work reported in paper IV. A decreased diastolic function, measured as a decreased MLVLARV, was a

predictor for SR at long-term FU. It is known that very early changes in ventricular systolic and diastolic function in patients with hypertension, myocardial ischemia or aortic stenosis may affect the longitudinal fibers located in the sub-endocardial layers earlier than the radial fibers located more epicardially [190]. Paroxysms of AF may also lead to impaired ventricular function [191], and early longitudinal and circumferential left ventricular systolic function abnormalities in patients with isolated paroxysmal AF but with normal ejection fraction have been seen [192]. After successful percutaneous catheter ablation, a reverse remodeling of these abnormalities together with a significant improvement of a previous diastolic dysfunction has taken place [192]. Our patients had both ischemic heart disease and AF, factors known to cause impaired diastolic function. Revascularisation and intraoperative ablation may have improved the diastolic function and, as a consequence of this, also the chances of regaining and maintaining SR.

The results reported in paper IV indicated that a small right atrial area was a predictor for SR, implying that not only left atrial dimensions but also the right atrial area should be taken into account in rhythm outcome prediction of ablation treatment.

Patients undergoing the Cox Maze III procedure with a left atrial diameter of 6 cm or more and/or a preoperative duration of AF of five years or longer do not have the otherwise expected SR regain of 90 % or more [193, 194]. This is consistent with the notion that the duration of AF and remodeling plays an important role. Another explanation would be that Maze incisions in much enlarged atrial walls may leave areas large enough to allow macroreentrant circuits to form, thus giving substrate for AF. Therefore, in patients with pronounced atrial enlargement, atrial wall reduction has been suggested in combination with the Cox Maze III procedure or modifications of this procedure [195].

Complications

Early mortality (papers I-III)

In the work reported in paper I, one patient in the ablation group died 18 days postoperatively. In paper II, one patient in the ablation group died on the third post-operative day. There were no early deaths in the work reported in paper III. None of the deaths were related to the ablation procedure.

Stroke/TIA (papers I-III)

See Table 7. The study protocol did not require long-term postoperative warfarin treatment, and it was thus allowed to discontinue warfarin after at least three months provided the patient was considered to be in stable SR. Since the patients were operated with CABG, they were routinely on low dose aspirin (I, III). Our data support that this routine was insufficient and that long-term warfarin treatment should be mandatory. The most likely explanation is that this particular patient population with documented AF represents a subgroup of patients undergoing open heart surgery at a higher than average risk of AF related complications. The only reasonable conclusion is thus that patients, once they have been documented with AF, are assessed according to their risk of stroke by means of e.g. $CHADS_2$ score and that treatment is started and continued accordingly.

In papers I and III the calculation of the $CHADS_2$ score at baseline was made retrospectively with scores in the ablated patients with events ranging between 0-2. This means that, even with the $CHADS_2$ score, three of these five patients would not have had an absolute indication of warfarin. Interestingly, the events occurred 18 months to three years postoperatively, and we do not know whether the $CHADS_2$ score would have been the same at the time of the event. The current policy at this hospital is to maintain anticoagulation and recommend the treating physician not to stop warfarin without a thorough reevaluation.

Table 7. Stroke/TIA/peripheral embolism after discharge in the total patient material

							Echo at long-term FU			
	Postop	$CHADS_2$	SR	AF	warfarin	aspirin	A-wave	E/A-ratio	LVEF	Other reason
Paper I										
RF										
1.Embolic stroke	2 yrs	1	X			X	0.43	1.93	65%	
2.Embolic stroke	3 yrs	2	X			X	0.87	1.20	35%	
3.TIA	3 yrs	1	X			X	0.57	1.02	45%	carotid plaque
Paper III										
Cryo										
1.Embolic stroke	18 mo	0	X			X	0.32	2.13	45%	
2.TIA	29 mo	2	X		X		0.45	1.6	55%	
Paper I and III										
Control										
1.Embolic stroke	1 mo	3	X			X	dead			warfarin contraind
2.Embolic stroke	3 mo	1		X		X	------			ethylism
3.Peripheral embolus	3 mo			X	X		dead			
4.Embolic stroke	1 yrs	2	X			X	dead			
Paper II										
Cryo										
1.TIA	<3mo	>1	X	X						
2.TIA	<3mo	>1	X	X						
3.TIA	<3mo	>/=2			X					
4.TIA	<3mo				X					prosthesis thrombosis
Control										
1.Embolic stroke					X					myocardial infarction
2. Pons bleeding					X					

Abbreviations: Postop = postoperatively, echo = echocardiography, A-wave =atrial filling wave, E/A-ratio = early filling / atrial filling wave ratio, mo = months, yrs = years, contraind = contraindicated

CONCLUSIONS

1. Epicardial left atrial RF ablation of AF in patients undergoing CABG +/- valve surgery is effective in restoring and maintaining SR. Long-term SR is associated with better QoL and fewer symptoms as compared to AF (I).

2. Epicardial left atrial cryo ablation combined with MVS results in a larger proportion of patients in SR at 12 months than after MVS alone (II).

3. Atrial and ventricular function is decreased at long-term FU after epicardial left atrial cryo ablation of AF in patients undergoing CABG. The echocardiographic values in patients with SR before and after surgery are slightly decreased but still within or close to reference limits, while there is a continued deterioration in patients with AF before and after surgery (III).

4. Right atrial size and left ventricular diastolic function are important variables in the prediction of long-term rhythm outcome in patients undergoing intraoperative ablation (IV). SR at three months is a strong predictor of long-term SR (I and III). Independent preoperative predictors for SR at follow-up are paroxysmal/persistent AF (I), low BMI (I), short duration of AF (II), no CAD (II), SR before surgery (III) and a small left atrial area (III).

5. Anticoagulation should be used according to current guidelines and should not be discontinued unless because of insufficient tolerability and safety, even when SR has been restored and maintained.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Based on our experience, it seems justified to routinely offer patients scheduled for open heart surgery and with AF an additional ablation procedure, regardless of whether the documented AF is paroxysmal or persistent/permanent.

On the basis of our findings and the literature we have adopted an individualized approach with regard to the patient´s heart disease, type of AF and general condition. Thus, patients with paroxysmal AF who are to undergo a concomitant procedure where the left atrium does not need to be opened are offered epicardial left atrial ablation. Patients with any type of AF and a concomitant procedure that necessitates opening of left atrium are offered a biatrial ablation, in appropriate cases.

The success rates may have been appropriate for these patient populations but were not at the level of those after the Cox Maze III procedure in patients with AF and little or no underlying heart disease. Thus, a further improvement in success rates is desirable, and new surgical and technical approaches are continuously being tested.

New technologies allowing continuous monitoring of rhythm may change the view of how to determine success following intervention for AF, e.g. intraoperative ablation. Rhythm outcome in combination with some other meaningful clinical improvement may become more appropriate than assessing rhythm control alone.

Patients should be followed with careful surveillance after intraoperative ablation. As many patients with AF are elderly and have risk factors for stroke, anticoagulation should be continued in most patients. Adherence to guidelines and consensus documents and use of risk scores can be improved.

Intraoperative ablation through a minimally invasive approach is an interesting but challenging concept [196]. While it has mainly been used in patients with AF and little or no underlying heart disease [197], some centers have performed combined procedures involving mitral valve surgery and intraoperative ablation [198]. To further enhance the

results of AF ablation, specific targeting of GP has been tried [199]. Closure of the left atrial appendage has now become accepted as part of the procedure. Results of these approaches need to be tested in sufficiently large, randomized, controlled studies.

The results of the Cox Maze III procedure in patients with no or little underlying heart disease have not yet been reliably replicated with any intraoperative ablation technique. The complexity of the Cox Maze III, but also the excellent long-term results, will stimulate the development and testing of new technologies that are simple enough to be used more frequently but with similar success rates.

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