Atrial Fibrillation in Cardiac Surgery

To Ester and Hilding
Elin and Gotte

Ridéntem dícere verum quid vetat?
(Vad är det som hindrar att den som skrattar talar sanning?)
HORATIUS

Örebro Studies in Medicine 18

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Atrial Fibrillation in Cardiac Surgery

Title: Atrial Fibrillation in Cardiac Surgery

Publisher: Örebro University 2008
www.publications.oru.se

Editor: Heinz Merten
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Printer: Intellecta DocuSys, V Frölunda 08/2008

ISSN 1652-4063
ISBN 978-91-7668-615-7

Abstract

Atrial fibrillation (AF) is the most common arrhythmia seen in clinical practice. In cardiac surgery, one-third of the patients experience episodes of AF during the first postoperative days (postoperative AF), and patients with preoperative AF (concomitant AF) can be offered ablation procedures in conjunction with surgery, in order to restore ordinary sinus rhythm (SR). The aim of this work was to study the relation between postoperative AF and inflammation; the long-term consequences of postoperative AF on mortality and late arrhythmia; and atrial function after concomitant surgical ablation for AF.

In 524 open-heart surgery patients, C-reactive protein (CRP) serum concentrations were measured before and on the third day after surgery. There was no correlation between levels of CRP and the development of postoperative AF.

All 1,419 patients with no history of AF, undergoing primary aortocoronary bypass surgery (CABG) in the years 1997–2000 were followed up after 8.0 years. The mortality rate was 191 deaths/1,000 patients (19.1%) in patients with no AF and 140 deaths/419 patients (33.4%) in patients with postoperative AF. Postoperative AF was an age-independent risk factor for late mortality, with a hazard ratio (HR) of 1.56 (95% CI 1.23–1.98). Postoperative AF patients had a more than doubled risk of death due to cerebral ischaemia, myocardial infarction, sudden death, and heart failure compared with patients without AF.

All 571 consecutive patients undergoing primary CABG during the years 1999–2000 were followed-up after 6 years. Questionnaires were obtained from 91.6% of surviving patients and an electrocardiogram (ECG) from 88.3% of all patients. In postoperative AF patients, 14.1% had AF at follow-up, compared with 2.8% of patients with no AF at surgery ($p<.001$). An episode of postoperative AF was found to be an independent risk factor for development of late AF, with an adjusted risk ratio (RR) of 3.11 (95% CI 1.41–6.87).

Epicardial microwave ablation was performed in 20 open-heart surgery patients with concomitant AF. Transthoracic echocardiography was performed preoperatively and at 6 months postoperatively. At 12 months postoperatively 14/19 patients (74%) were in SR with no anti-arrhythmic drugs. All patients in SR had preserved left and right atrial filling waves (A-waves) and Tissue velocity echocardiography (TVE) showed preserved atrial wall velocities and atrial strain.

In conclusion, postoperative AF is an independent risk factor for late mortality and later development of AF. There is no correlation between the inflammatory marker CRP and postoperative AF. Epicardial microwave ablation of concomitant AF results in SR in the majority of patients and seems to preserve atrial mechanical function.

Keywords: Atrial fibrillation, Inflammation, CABG surgery, Survival analysis, Follow-up studies, Ablation, Microwave, Transmurality, Atrial function, Tissue velocity echocardioqraphy.

Swedish summary

Förmaksflimmer är den vanligaste behandlingskrävande hjärtarytmin. Förmaksflimmer är ett elektriskt och mekaniskt kaos i hjärtats förmak som leder till en oregelbunden och snabb puls. Patienter med förmaksflimmer har en ökad risk för hjärtsvikt och slaganfall och många patienter besväras också av andfåddhet och trötthet. Omkring 0.4–1% av befolkningen har förmaksflimmer i någon form. Förekomsten ökar med stigande ålder; således har cirka 8% av personer över 80 år förmaksflimmer.

Förmaksflimmer är en kliniskt utmaning inom hjärtkirurgi av flera skäl. En tredjedel av alla hjärtopererade patienter drabbas av en episod av förmaksflimmer de närmaste dagarna efter genomgången kirurgi (*postoperativt förmaksflimmer*), vilket leder till förlängd vårdtid och ökad risk för komplikationer. Under senare år har också tekniker utvecklats med vilka man kan behandla patienter som har förmaksflimmer innan operationen, s.k. ablation. Med denna behandling vill man återställa hjärtats normala sinusrytm.

Syftet med detta avhandlingsarbete var att undersöka om postoperativt förmaksflimmer påverkar långtidsöverlevnad och utvecklingen av sena rytmrubbningar; om inflammation efter hjärtkirurgi mätt med inflammationsmarkören C-reaktivt protein (CRP) påverkar förekomsten av förmaksflimmer; samt att undersöka förmaksfunktion hos patienter som genomgått kirurgisk ablation mot förmaksflimmer.

CRP-koncentrationen i blodet analyserades före och tredje dagen efter operationen hos 524 patienter som genomgått hjärtkirurgi i någon form. 34.7 % av patienterna fick postoperativt förmaksflimmer. Det fanns inget samband mellan CRP-koncentration och utvecklingen av förmaksflimmer i denna studie.

Långtidsöverlevnaden hos patienter med postoperativt förmaksflimmer studerades genom att inkludera alla 1 419 kranskärlsopererade patienter opererade mellan 1997–2000. 29.5% av patienterna hade minst en episod av postoperativt förmaksflimmer. Efter en medianuppföljningstid på 8 år kontrollerades alla patienter mot Folkbokföringen och Svenska Dödsorsaksregistret. I gruppen patienter utan postoperativt förmaksflimmer hade 191/1000 (19.1%) av patienterna avlidit, och i gruppen med postoperativt förmaksflimmer hade 140/419 (33.4%) av patienterna avlidit. Postoperativt förmaksflimmer var en åldersoberoende riskfaktor för sen död med en hasard rat på 1.56 (95% konfidensintervall 1.23–1.98). Risken för död orsakad av hjärnischemi, hjärtinfarkt, plötslig död och hjärtsvikt var mer än fördubblad i gruppen av patienter som haft en episod av postoperativt förmaksflimmer.

I nästa studie inkluderades alla 571 patienter som kranskärlsopererades åren 1999–2000. Efter en medianuppföljningstid på 6 år insamlades enkätsvar från 91.6% av alla överlevande patienter och EKG registreringar från 88.3% av alla patienter. 14.1% av patienterna med postoperativt förmaksflimmer hade förmaksflimmer vid uppföljningen jämfört med 2.8% av patienterna som inte hade förmaksflimmer. En episod av postoperativt förmaksflimmer var en oberoende riskfaktor för sent förmaksflimmer med en relativ risk på 3.11 (95% konfidensintervall 1.41–6.87).

Förmaksfunktion efter kirurgisk ablation studerades genom att inkludera 20 patienter som hade förmaksflimmer och skulle genomgå hjärtkirurgi i någon form. Mikrovågsablation från hjärtats utsida genomfördes i samband med operationen och ultraljudsmätningar av hjärtats förmaksfunktion gjordes innan operation och sex månader efter kirurgi. 14 av 19 patienter (74%) hade normal sinusrytm efter ett år. Alla patienter i sinusrytm hade bevarade förmakskontraktionsvågor på både höger och vänster sida och förmakets väggar rörde sig i samma hastigheter som innan operationen.

Sammanfattningsvis är postoperativt förmaksflimmer en oberoende riskfaktor för sen död och senare utveckling av förmaksflimmer. Den högre dödligheten hos patienter med postoperativt förmaksflimmer orsakas framför allt av hjärnischemi, hjärtinfarkt, plötslig död och hjärtsvikt. Det finns ingen korrelation mellan inflammationsmarkören CRP och postoperativt förmaksflimmer. Mikrovågsablation av förmaksflimmer leder till sinusrytm hos majoriteten av patienterna och bevarar förmaksfunktionen.

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I. Ahlsson A, Bodin L, Lundblad O, Englund A: Postoperative atrial fibrillation is not correlated to C-reactive protein. *Ann Thorac Surg* 2007; 83:1332-7.

II. Ahlsson A, Bodin L, Fengsrud E, Englund A: Patients with postoperative atrial fibrillation have a doubled cardiovascular mortality. Submitted.

III. Ahlsson A, Fengsrud E, Bodin L, Englund A: Postoperative atrial fibrillation as risk factor for late arrhythmia and cardiovascular death – a six-year follow-up study after coronary artery bypass surgery. Submitted.

IV. Ahlsson A, Linde P, Rask P, Englund A: Atrial function after epicardial microwave ablation in patients with atrial fibrillation. *Scand Cardiovasc J* 2008; 42:192-201.

List of abbreviations

ACC	American College of Cardiology
AF	atrial fibrillation
AHA	American Heart Association
AMI	acute myocardial infarction
ANP	atrial natriuretic peptide
ASD	atrial septal defect
AV	atrioventricular
A-wave	atrial-filling wave
BMI	body mass index
BNP	brain natriuretic peptide
CABG	coronary artery bypass graft/coronary artery bypass surgery
CCS	Canadian Cardiovascular Society
$CHADS_2$	cardiac failure, hypertension, age >75 years, diabetes, stroke (doubled)
CI	confidence interval
CK-MB	creatine kinase-muscular band
COPD	chronic obstructive pulmonary disease
CPB	cardiopulmonary bypass
CRP	C-reactive protein
CV	coefficient of variation
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EF	ejection fraction
ESC	European Society of Cardiology
HR	hazard ratio
HRS	Heart Rhythm Society
LA	left atrium
LVEF	left ventricular ejection fraction
MI	myocardial infarction
MRI	magnetic resonance imaging
NT-proBNP	amino terminal precursor of brain natriuretic peptide
OR	odds ratio
PM	pacemaker
RR	risk ratio
SD	standard deviation
SR	sinus rhythm
TIA	transitory ischaemic attack
TVE	tissue velocity echocardiography
VSD	ventricular septal defect

Errata

Paper I

p. 1334, Table 2 "Type of surgery in study cohort", right column "Hospital mortality":

value for OPCABG was given as 2, should be 1
value for ASC was given as 1, should be 3

p. 1334, last sentence, "… had more often preoperative ß-blockade ..." should say, "…had less often preoperative ß-blockade …"

Paper IV

p. 196, Table I "Preoperative patient characteristics", explanation below table:

"…[l]number paroxysmal/persistent/permanent…" should say
"…[l]number paroxysmal/persistent/longstanding persistent…"

p. 197, Table II "Per –and postoperative data", explanation below table:

"…[j]Success defined as no atrial fibrillation on 72 hour ECG registration and no antiarrhythmics drugs…" – should be deleted

1 Background

1.1 History

Until the early 20th century, atrial fibrillation (AF) as a pathophysiological entity was unknown. In previous centuries, diagnoses such as "ataxia of the pulse", "delirium cordis" or "pulsus irregularis perpetuus" were used to describe clinical conditions with irregular pulse and heart failure [11]. The diagnosis of AF, or "auricular fibrillation" as first described, required the invention of the electrocardiograph by William Einthoven in 1902 (*Figure 1*). In 1906, Einthoven published a review article called "Le télécardiogramme" [47], which included single-lead electrocardiogram strips illustrating what Einthoven described as "pulsus inaequalis et irregularis". In the same year, Cushny and Edmunds coined the term "auricular fibrillation" [40], but it was not until 1909 that AF was recognized as a common clinical condition [56].

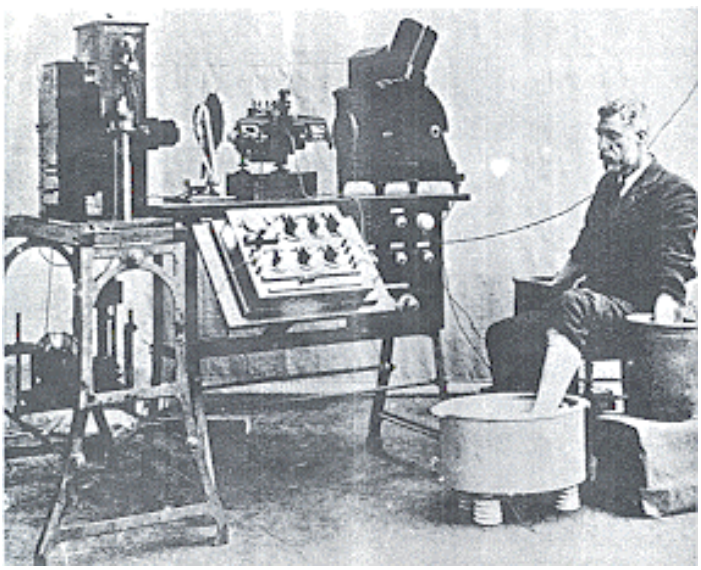


Figure 1. The first electrocardiograph (Einthoven 1902).

The concept of *postoperative* AF was first described in 1943 in a series of patients undergoing pneumonectomy [15]. With the development of open-heart surgery after World War II, it became evident that postoperative episodes of AF were frequent and as such a common clinical problem [8, 45, 109]. The introduction of electrical countershock and more effective drugs reduced arrhythmia-related mortality [122, 128], but did not affect the incidence of postoperative arrhythmias. In fact, despite continuous development of surgical

procedures, methods of myocardial protection, new pharmacological agents, improved anaesthesiological methods and improvement in postoperative care, the incidence of postoperative AF has not decreased – it has, on the contrary, tended to increase in recent years, probably because of increased age of cardiac surgery patients [65, 91, 94].

1.2 Heart rhythm definitions

Sinus rhythm – the normal heart rhythm

In the human myocardium, the conduction system consists of specialized cells capable of electrical impulse formation and conduction. The electrical impulses are created by alterations of ion channels in the cellular membrane, causing regular de- and repolarizations with different frequencies. The starting point in the conduction system, the sinus node, is located in the ventral part of the junction between the superior caval vein and the right atrium (*Figure 2 A*). The specialized cells in the sinus node, "pacemaker (PM) cells", normally depolarize with the highest frequency in the conduction system and thus determine the heart rate. The depolarizations are conducted through the walls of the right and left atrium to the atrioventricular (AV) node. The AV node is situated in the inferomedial aspect of the right atrium and is the only normal electrical connection between the atria and ventricles. In the AV node the conduction is slowed down, allowing atrial systole to occur at the end of ventricular diastole, and thus optimizing ventricular filling. The conduction is then transmitted through the bundle of His, which divides into the left and right bundle branch of the Purkinje system. The left branch is further divided into the anterior and posterior fascicles. The Purkinje cells are located subendocardially, thus transmitting impulses rapidly into the ventricles and creating ventricular contraction. In the normal heart, the heart rhythm is determined by the sinus node and is therefore called sinus rhythm (SR). The sinus node is influenced by the autonomic nervous system as well as hormones, to adapt the heart rate to physiological conditions.

Atrial fibrillation

Atrial fibrillation is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of mechanical function (*Figure 2 B*). The chaotic mechanical activity of the atria leads to loss of atrial contraction and AV dyssynchrony. If the AV node is intact, the irregular atrial activity leads to loss of SR and irregular ventricular contractions, typically showing as an irregular tachycardia.

Atrial fibrillation can present itself in a variety of ways, the most important feature being whether it is of short duration and stops spontaneously, or of longer duration requiring pharmacological treatment or cardioversion to terminate. Traditionally, self-terminating AF is called "paroxysmal AF" while non-terminating AF is called "continuous" or "chronic AF". In an attempt to more clearly classify AF, the American College of Cardiology (ACC), the American Heart Association (AHA) and the European Society

of Cardiology (ESC) in conjunction with the Heart Rhythm Society (HRS) have defined the different forms of AF as follows [22, 55]:

Paroxysmal AF is defined as recurrent AF (two or more episodes) that terminates spontaneously within 7 days.

Persistent AF is defined as AF which is sustained beyond 7 days, or lasts <7 days but necessitates pharmacological or electrical cardioversion.

Long-standing persistent AF is defined as continuous AF of >1 year's duration.

Permanent AF is defined as continuous AF in which cardioversion has failed or has been abandoned.

Importantly, the ACC, AHA and ESC guidelines also introduce the term "secondary AF", designating AF in the setting of acute myocardial infarction (AMI), cardiac surgery, pericarditis, myocarditis, hyperthyroidism or acute pulmonary disease. "In these situations, AF is not the primary problem, and concurrent treatment of the underlying disorder usually terminates the arrhythmia," according to the guidelines [55]. Following this definition, postoperative AF is a secondary AF and is as such not further defined in this thesis work.

The term "lone AF" applies to AF in individuals younger than 60 years without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension [55]. The term "non-valvular AF" refers to AF in the absence of valvular heart disease, and is often used in epidemiological studies of stroke risk and AF.

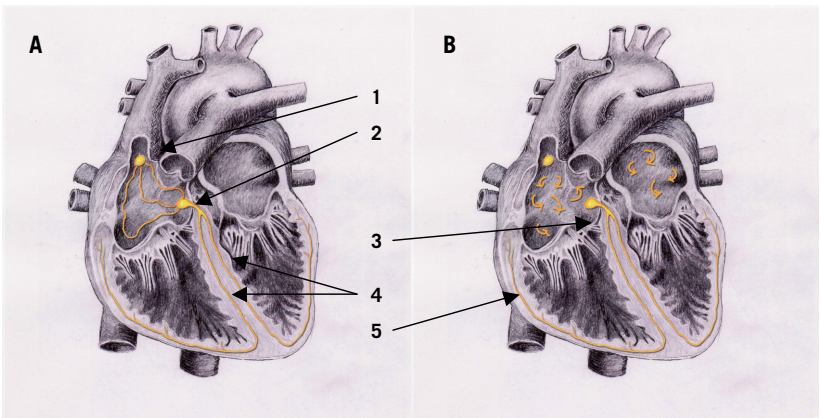


Figure 2. The conduction system in normal sinus rhythm (A) and atrial fibrillation (B). 1 = sinus node; 2 = AV node, 3 = bundle of His; 4 = left and right bundle branch, 5 = Purkinje fibers.

Atrial flutter

Atrial fibrillation can be associated with other arrhythmias, such as atrial flutter or atrial tachycardia. The most common form of atrial flutter, right-sided, counter-clockwise flutter, has a typical saw-toothed pattern of regular atrial activation called "flutter (f) waves" on the electrocardiogram (ECG). The atrial rate typically ranges from 240 to 320 beats per minute. Two-to-one AV block is common, producing a ventricular rate of 120–160 beats per minute. Atrial flutter can degenerate into AF, and AF may convert to atrial flutter, and the ECG pattern can alternate between atrial flutter and AF, reflecting changing atrial activation [55]. In the context of *postoperative AF*, episodes of atrial flutter are sometimes observed, but the treatment and clinical consequences are the same as for AF. Therefore, in the present thesis, postoperative atrial flutter episodes are not distinguished from postoperative AF.

1.3 Atrial fibrillation – an overview

Epidemiology

The estimated prevalence of AF is 0.5–1% in the general population, increasing with age to 8% in those older than 80 years [25, 55]. In Sweden, the number of persons with a diagnosis of AF is estimated to be 120,000, which leads to a prevalence of AF in Sweden of 1.3%. The lifetime risk for development of AF is about 25% for men and women aged ≥40 years [83, 84]. An increasing overall prevalence of AF in the Western world during the last three decades has been attributed to an ageing population, but the age-adjusted prevalence in men has more than doubled over a generation, while in women it has remained constant [25, 127] (*Figure 3*). The greater susceptibility to AF in men is unexplained. Because of the increasing prevalence of AF in the population and also because of the socioeconomic consequences of this disease, AF has been referred to as a "growing epidemic" [25].

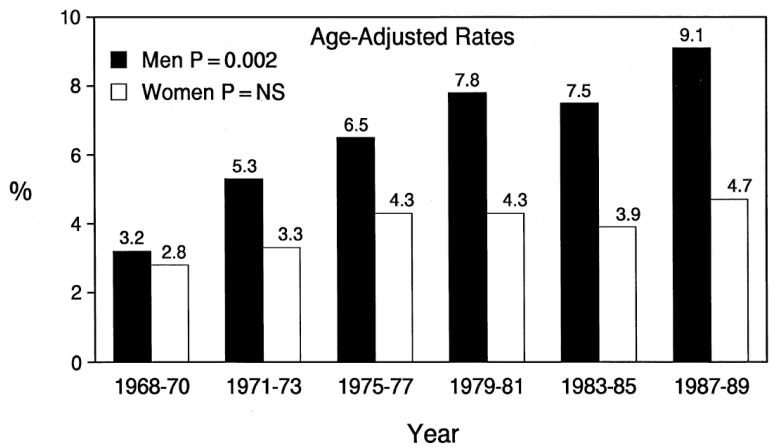


Figure 3. Secular trends in the prevalence (percentage) of atrial fibrillation in subjects 65 to 84 years old in the Framingham study. Reprinted from 25 with permission from Elsevier.

Atrial fibrillation is associated with an increased long-term risk of *stroke*, *heart failure* and all-cause *mortality* [116, 126].

The risk of ischaemic *stroke* among patients with non-valvular AF averages 5% per year, which is twice to seven times that of individuals without AF [55]. In the Framingham Heart Study, the stroke risk was found to increase with age; the percentage of strokes attributable to AF was 1.5% in participants aged 50–59 years and 23.5% in those aged 80–89 years [126]. The stroke risk in AF patients is generally attributed to embolism of thrombus formation in the left atrium due to reduced flow velocities in the atrial appendage [59]

but the pathogenesis of thromboembolism in AF patients is probably more complex. Up to 25% of strokes in patients with AF may be due to intrinsic cardiovascular diseases, other cardiac sources of embolism, or atheromatous pathology of the ascending aorta [18, 96]. Closure or resection of the left atrial appendage is often performed in surgical treatment of AF to reduce the risk of thromboembolism. While this measure seems reasonable, its protective efficacy has not been proven and reports of incomplete closure exist [63, 71].

The definition of "*heart failure*" is problematic, and a wide range of definitions have been used in clinical trials and epidemiological studies [130]. In the Framingham Heart Study, heart failure has been defined as the presence of two major or one major and two minor criteria: the major criteria including paroxysmal nocturnal dyspnea or orthopnea, distended neck veins, rales, radiographic cardiomegaly, pulmonary oedema, third heart sound, increased venous pressure, and weight loss on diuretic therapy. Minor criteria were, among others, ankle oedema, night cough, dyspnea on exertion, hepatomegaly, pleural effusion, and tachycardia [119]. More modern definitions have been proposed that include a left ventricular ejection fraction (LVEF) <40% and a serum concentration of amino terminal precursor of brain natriuretic peptide (NT-proBNP) >400 pg/mL [130].

The relation between AF and heart failure is bidirectional. Atrial fibrillation aggravates heart failure and heart failure promotes AF; individuals with either condition who develop the alternate condition share a poor prognosis [119]. The proposed mechanism whereby AF leads to heart failure is by tachycardia-induced dilated cardiomyopathy and the loss of atrial transport function, causing a reduction in cardiac output. Heart failure may lead to AF by atrial dilatation and sympathetic activation [119]. In the Framingham Heart Study, AF preceded heart failure about as often as heart failure preceded AF [119].

Atrial fibrillation is associated with a doubled long-term *mortality* risk after adjustment for pre-existing cardiovascular conditions associated with AF [17, 116]. The increased mortality in AF patients is mainly due to cardiovascular death causes such as myocardial infarction (MI), heart failure and cerebrovascular accidents [52, 82, 97]. Interestingly, paroxysmal AF seems to carry a higher long-term mortality than persistent AF [52].

Aetiology

In the last decade, considerable progress has been made in defining the mechanisms of AF. The predominating theory of AF aetiology until the late 1980s was the "multiple-wavelet hypothesis" suggested by Moe [98]. According to this hypothesis, AF results from the presence of multiple re-entrant wavelets occurring simultaneously in the left and right atria. The

development of the surgical Maze procedure was intimately connected to this theory, which proposes that a critical mass of atrial tissue is necessary for the maintenance of multiple wavelets, and that by reducing the mass by surgical incisions in the atria, AF is no longer possible [33–35].

In 1998, Haissaguerre and colleagues published the landmark observation that AF can be triggered from a focal source, often located in the pulmonary veins, and that ablation of that focal trigger can eliminate AF [61]. This discovery led to the concept of catheter ablation of AF, and subsequently to various surgical devices for isolating the pulmonary veins in conjunction with other open-heart surgery procedures.

Our understanding of AF mechanisms is now more complex than it was 10 years ago. Today, several mechanisms are proposed for the structure and mechanism of AF [22] (*Figure 4*). Focal triggers, local wavelets ("rotors") and autonomic ganglionic plexa all play a role in the initiation and sustaining of AF [22]. In addition to this, several studies support the role of inflammation in the genesis of AF. The inflammatory marker C-reactive protein (CRP) has been linked to AF if several ways; serum levels of CRP are raised in patients with AF [26], and CRP concentration has also been found to be predictive of later development of AF [13, 93].

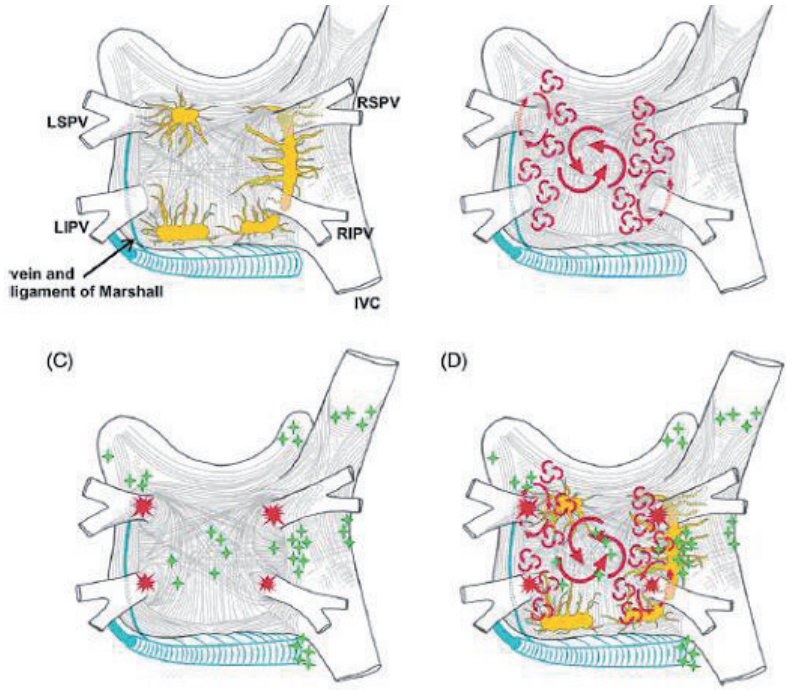


Figure 4. Structure and mechanisms of atrial fibrillation. A: Schematic drawing of the left and right atria as viewed from the posterior. The extension of muscular fibers onto the pulmonary veins can be appreciated. Shown in *yellow* are the four major LA autonomic ganglionic plexi and axons (superior left, inferior left, anterior right, and inferior right). Shown in *blue* is the coronary sinus which is enveloped by muscular fibers which have connections to the atria. Also shown in blue is the vein and ligament of Marshall which travels from the coronary sinus to the region between the left superior PV and the LA appendage. B: Large and small re-entrant wavelets that play a role in initiating and sustaining AF. C: Common locations of PV (*red*) and also the common sites of origin of non PV triggers (shown in *green*). D: Composite of the anatomic and arrhythmic mechanisms of AF. Reprinted from [22] with permission from Elsevier.

1.4 Management of atrial fibrillation

Pharmacological treatment

The treatment of AF has two objectives – control of rhythm or rate and the prevention of thromboembolism. In the *rhythm* control management, restoration and maintenance of SR is the key issue. Vaughan Williams class IA (disopyramide), IC (flecainide, propafenone) and III (amiodarone, sotalol) drugs are effective in maintaining SR, but all have important adverse effects including ventricular arrhythmias, heart failure and different kinds of toxicity (*Table 1*). In the *rate control* strategy, the main purpose is to control ventricular rhythm with no intention to restore SR. For rate control, Vaughan Williams class II (beta blockers) or class IV (calcium channel antagonists) drugs are the recommended therapy choice [55, 113].

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 (atenolol, metoprolol)
Class III	Amiodarone Sotalol Ibutilid
Class IV	Calcium channel antagonists (verapamil, diltiazem)

Several studies have been conducted to address the issue of rate v. rhythm control, the most important being the AFFIRM, RACE, PIAF, and STAF trials. In these, there was no difference in stroke rates, mortality or quality of life between rhythm and rate control strategy [23, 60, 118, 129]. From this perspective, there seems to be no advantage of restoring SR in AF patients. The issue is, however, more complex. These studies focused on the differences between rhythm and rate control *strategies*, not on the difference between having SR and not having it. In the AFFIRM study, the percentage of patients in SR at 5 years was 34.6% in the rate control group and 62.6% in the rhythm control group [129]. Consequently, one-third of the patients in the rhythm control group did not achieve SR but were exposed to anti-

arrhythmic pharmacological treatment with potentially dangerous adverse effects. When analysed from the perspective of whether SR is achieved or not, the data from the AFFIRM study show that patients in SR have better survival [28]. This is an important finding; if an effective drug or method was available for maintaining SR, it could be beneficial for survival [28]. Another important aspect is the presence of symptoms. Some patients with AF are asymptomatic, while others have severe symptoms such as palpitations, dyspnea and fatigue [83]. Consequently, in the ACC, AHA and ESC guidelines for management of AF, it is stated that the treatment with regard to the choice between rhythm and rate management must be tailored to each individual patient [55].

For the *prevention of thromboembolism* in AF patients, anticoagulation with vitamin K antagonist agents (warfarin) or aspirin reduces the risk of stroke compared with placebo treatment, by 62% and 22%, respectively [62]. Vitamin K antagonists are therefore more effective than aspirin, but they also increase the absolute risk of bleeding by 0.3% per year [62]. The key question is therefore which patients with AF should be treated, and which drug to use. The $CHADS_2$ (cardiac failure, hypertension, age >75 years, diabetes, stroke [doubled]) index is a tool for estimating the risk of stroke in AF patients, each condition giving one point, apart from prior stroke/transitory ischaemic attack (TIA) giving two points. In patients with zero (0) points, the stroke risk is estimated to be 1.9% per year, while in patients with 5 points, the risk is estimated to be 12.5% per year [55]. The present recommendation is to use aspirin or no drug at all in patients with no risk factors, aspirin or warfarin in patients with 1 point and warfarin in patients with ≥2 points [55, 113]. While these recommendations are plain and explicit, in clinical practice there is an evident underuse of warfarin in AF patients [53, 54].

Percutaneous catheter ablation

In patients with symptomatic drug-refractory AF, or with intolerance to at least one Class I or III anti-arrhythmic medication, percutaneous catheter ablation is today an accepted method for restoring SR [22, 113]. In randomized trials, 56–86% of patients were free from symptomatic AF after 1 year [103, 105, 114, 121]. The ablation strategy included pulmonary vein with or without additional lines, and the results were better in patients with paroxysmal AF than in persistent AF [22]. Reported complications to percutaneous catheter ablation are rare and include pulmonary vein stenosis, stroke and vascular access complications [22]. In clinical practice, an increasing demand for catheter ablation and too few ablation centers constitutes a problem.

Surgical ablation

The original Maze surgery is the gold standard for AF surgery. It was developed in the early 1980s by James Cox and consists of multiple incisions in the right and left atria ("cut and sew"), thereby prohibiting multiple wavelets and also directing the sinus impulse towards the AV node [34] (*Figure 5*). One important feature of the Maze procedure is the isolation of the pulmonary veins; it should be noted that the procedure was designed before the discovery of pulmonary veins as focal triggers in AF genesis. The Maze procedure has two primary goals, viz. to restore SR and to diminish the risk of stroke. There are no randomized studies published, but in several studies between 68% and 100% of patients were reported free from AF after 1 year [3, 73, 88]. In his thesis, Albåge found that 75–92% of Maze patients were free from AF at 1 year, and the author reports a lower incidence of thromboembolic events in Maze surgery patients compared with matched controls [4]. The Maze operation is technically challenging and is therefore performed in a limited number of centres.

After the discovery of focal triggers in the pulmonary veins by Haissaguerre in 1998 [61], new ablation catheters designed for surgical ablation procedures were introduced. These use different types of energy (radiofrequency, microwave, ultrasound, cryothermy or laser) to produce lesions in the atria, leading to electric isolation [58]. Based on the experiences from Maze surgery and percutaneous catheter ablation, different lesion sets have been developed, all of which include pulmonary vein isolation of some form. The advantage in surgery is the direct visualization of the left atrium and pulmonary veins, and the ability to produce lesions both from the inside (endocardially) and from the outside (epicardially). Randomized trials and meta-analyses have shown absence of AF after 1 year in 60–80% of patients, depending on type of AF [16, 73, 108]. In a systematic review, the classical Maze procedure and the modern energy forms yielded the same rate of SR conversion [73]. The modern methods have gained wide acceptance because of the less complex surgical procedure involved, and today the recommendation is to surgically ablate all patients with symptomatic AF, and to also consider ablation in asymptomatic AF patients undergoing open-heart surgery [22, 113].

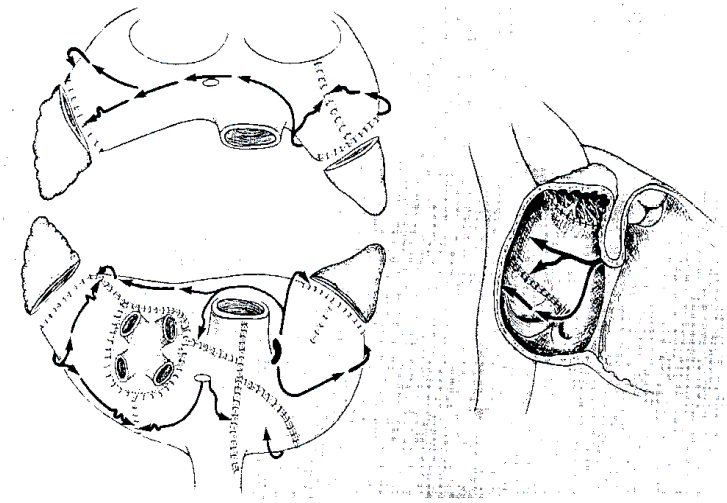


Figure 5. Two dimensional representation of the Maze III procedure for atrial fibrillation. In the *left* panels, the atria are depicted as if viewed from the posterior direction with the back of both atria in the *lower* panel. The atria are then divided in a sagittal plane and the anterior half of the atria are "flipped" up in the upper panel. The *right panel* shows the surface of the right atrial septum. Both atrial appendages are excised and the pulmonary veins are isolated. Atrial incisions interrupt the conduction routes of the most common re-entrant circuits, and direct the sinus impulse from the sinus node to the atrioventricular node along a specified route. Reprinted from [34] with permission from Elsevier.

With the introduction of the new technology, less invasive procedures for stand-alone AF as an alternative to percutaneous catheter ablation have been developed. These include endoscopic techniques and pulmonary vein isolation by epicardially administered energy. The methods are new and a limited number of anecdotal and small studies have been published [74, 77, 107]. The methods need to be evaluated in controlled trials, and guidelines for reporting data and outcomes for the surgical treatment of AF have been developed [112].

Atrial function after ablation

In a normal heart in SR, the right and left atrial contraction in late ventricular diastole causes an increased flow through the respective atrioventricular valve, the atrial-filling wave (A-wave). Atrial mechanical function in SR has traditionally been evaluated by measuring transmitral and transtricuspid A-waves with the use of pulsed Doppler signals to establish whether they are present or absent and measure their velocities [95, 117]. New methods for estimating atrial mechanical function include tissue velocity echocardiography (TVE), also called "colour Doppler tissue imaging", in which the velocities and the strains in the atrial walls can be measured [117], and magnetic resonance imaging (MRI) measuring atrial stroke volumes and ejection fractions (EFs) [50].

One objective in AF surgery is to reduce the risk of thromboembolic complications. Since thrombus formation as a result of stasis in the left atrium is thought to be the main source of embolic strokes in AF, restoration of atrial contraction is probably required in order to reduce stroke risk. While some data support a decreased risk of stroke in Maze surgery patients at follow-up [4, 32], other investigators have found a loss of atrial contraction in patients with SR after the Maze procedure [24, 86, 95]. In a recently published study the decrease in left atrial contractility was sustained several years after the Maze procedure [87], and it has been speculated that loss of atrial contraction leads to maintained risk of stroke [95]. Little is, however, known regarding the new ablation techniques and their influence on atrial contractile function.

1.5 Postoperative atrial fibrillation

Epidemiology

Postoperative AF affects 10–65% of cardiac surgery patients, depending on patient profile, type of surgery and method of arrhythmia surveillance [92]. In a meta-analysis of 24 trials, the incidence of postoperative AF was estimated to be 29.5% [7]. The highest incidence of AF is in postoperative days 2–3, and the total median duration of one or more episodes of AF is 2 days [2, 92]. After 6 weeks, >95% of postoperative AF patients have regained SR [76].

A number of risk factors for the development of postoperative AF have been identified. The most consistent and important risk factor is age, showing a non-linear relationship [2, 5, 36, 66, 92, 94], with increasing risk at >75 years of age. Other risk factors vary across different studies and include male gender, hypertension, congestive heart failure, aortic cross-clamp time and renal or respiratory insufficiency [5, 10, 12, 69, 92]. In her thesis, Jideus found that patients who subsequently developed postoperative AF were preoperatively characterized by premature supraventricular beats and decreased heart rate variability [69]. While further attempts have been made to preoperatively identify patients at risk by constructing risk indexes and algorithms, both the sensitivity and the specificity have been too low to be of clinical value [91, 94].

Aetiology

Postoperative AF is a constant finding after surgery and the aetiology may potentially shed light on AF aetiology per se. Two main perspectives predominate, which are not mutually exclusive: from an *electrophysiological* view, postoperative AF is caused by multiple wavelets of re-entry made possible through dispersion of atrial refractoriness [66, 98]. When adjacent atrial areas have dissimilar refractoriness, a depolarizing wave front becomes fragmented as it encounters both refractory and excitable myocardium. This allows the wave front to return and stimulate previous refractory, but now repolarized, myocardium, leading to re-entry [66]. This inhomogenous dispersion of refractoriness has been reproduced in animal models using extracorporeal circulation [31]. Although this is a conceivable model for re-entry mechanisms, it is based mainly on animal research and does not explain why some patients develop AF postoperatively and others do not [30].

From a *biochemical* view, postoperative AF is caused by a postsurgical inflammatory response causing alterations in atrial or serum concentrations of acute-phase proteins and membrane proteins, and thereby inducing membrane ion channel dysfunction. The inflammatory response to cardiac surgery is pronounced and complex and involves the complement system, pro-inflammatory cytokines, production of nitric oxide from endothelial

cells, and oxygen-free radicals [104, 123]. C-reactive protein (named for its capacity to precipitate C-polysaccharide of *Streptococcus pneumoniae*) is an acute-phase protein and one of the most sensitive systemic markers of inflammation. In the clinical setting, the serum concentration of CRP is used as a marker of inflammatory activity. Its precise role in the inflammation process is unclear; it binds to phosphocholine and is potentially able to recognize damaged cell membranes [49]. C-reactive protein has been linked to AF in several ways. Serum levels of CRP are raised in patients with primary AF [26], and CRP concentration has also been found to be predictive of later development of AF [13, 93]. The levels of CRP usually peak at days 2–3 postoperatively [20, 29], coinciding with the median onset of postoperative AF. The incidence of postoperative AF has been shown to correlate with white blood cell counts, postoperative levels of CRP-complement complexes, and preoperative CRP levels [1, 20, 85]. However, no study so far has been able to demonstrate whether there is a true relation between postoperative AF and CRP.

Treatment

For the *prevention* of postoperative AF, different drugs and regimens have been studied. While they have proven to significantly reduce the incidence of postoperative AF, the effects have been moderate; the incidence of postoperative AF has been measured to 31–40% in the control groups and 18–23% in the treatment groups [39]. Specifically, pretreatment with amiodarone has proved to be effective in many studies [14, 21, 39, 42, 110, 124] and is recommended as an "appropriate prophylactic therapy for patients at high risk for postoperative AF" [55]. While practical considerations and potential adverse effects have limited the prophylactic use of amiodarone, in one meta-analysis it has been shown to have reduced the risk of postoperative stroke [21]. Pretreatment with ordinary beta blockers or sotalol also significantly reduces the risk of postoperative AF [21, 38, 39], and is the recommended prophylaxis in the ACC, AHA and ESC guidelines [55]. In practice, >80% of coronary surgery patients are treated with beta blocker medication preoperatively (see Study III). Finally, overdrive atrial pacing has been studied and proven to be effective in preventing postoperative AF [39, 41], but the method is of limited use because of practical considerations.

When postoperative AF occurs, the treatment principles are the same as for ordinary AF. Rate control is typically achieved with beta blockers, and in order to restore SR, amiodarone or sotalol is recommended [55]. Antithrombotic treatment adheres to the same guidelines as for ordinary AF [55].

Short-term consequences of postoperative atrial fibrillation

Postoperative AF is associated with an increased 30-day mortality compared with patients who do not experience postoperative AF [5, 92]. Cerebrovascular accidents during hospital stay are more common among postoperative AF patients [37, 46, 92] and the length of stay is prolonged [46, 92]. The extra cost per patient with postoperative AF has been estimated to US$10 000–$11 000, leading to a total cost of postoperative AF in the USA of US$2 billion/year [46].

Long-term consequences of postoperative atrial fibrillation

"Secondary AF in the setting of … cardiac surgery…is considered separately. In these situations, AF is not the primary problem, and concurrent treatment of the underlying disorder usually terminates the arrhythmia" [55]. According to the ACC, AHA and ESC guidelines, postoperative AF is a short-lived arrhythmia induced by cardiac surgery with no important long-term consequences. However, the long-term implications of an episode of postoperative AF are not well known.

In a large registry study comprising 6,475 coronary artery bypass surgery (CABG) patients, Villareal et al found that patients with postoperative AF had a higher mortality after 5 years compared with patients in stable SR [125]. This finding was perhaps not so surprising since the postoperative AF patients were older, but even after adjusting for age and other potential confounders, postoperative AF was an independent predictor of late mortality with an adjusted odds ratio (OR) of 1.5. The reasons for this new observation were not clear from the study. The incidence of postoperative AF in this retrospective cohort study was 16%, which is fairly low. Causes of death were not available, and late arrhythmias were not reported. The findings from this study have so far not been confirmed or contradicted by any other study.

One study with a follow-up period of >1 year has been performed that addresses the issue of postoperative AF and late arrhythmias. In 305 non-consecutive CABG patients seen in an outpatient clinic and followed for a median time of 2 years, symptomatic episodes of AF requiring medical care were more common during follow-up in postoperative AF patients (20.4%) than in non-AF patients (3.2%) [9]. In four studies with shorter follow-up times involving a total of 1,286 CABG patients, postoperative AF was found to be self-limiting, with a total prevalence of AF of 1–4% at 1 year [27, 48, 76, 79]. One exception is the study of Loubani et al comprising 375 CABG patients operated at a single institution, in which 39% of postoperative AF patients had AF after 6 months [89]. In this study, age was not a risk factor for postoperative AF and the medication and postoperative follow-up regimen were not well described.

To summarize, there are indications that patients with an episode of postoperative AF carry a higher long-term mortality risk, and that this increased risk persists after adjustment for potential confounders. The impact of postoperative AF on development of late arrhythmias is uncertain; beyond 2 years of follow-up it is unknown.

2 Aims of the thesis

The general aim of this work was to study the relation between postoperative AF and inflammation; the long-term consequences of postoperative AF on mortality and late arrhythmia; and atrial function after surgical ablation for concomitant AF.

The specific aims of this thesis were to investigate

- pre- and postoperative CRP levels and predictors of postoperative AF in a large cohort of heart surgery patients (Paper I)

- the impact of postoperative AF on late mortality and cause of death 8 years after CABG surgery (Paper II)

- the relationships of mortality, heart rhythm, and arrhythmia-related symptoms 5 years after CABG surgery (Paper III)

- epicardial microwave ablation of concomitant AF and its effects on AF after 1 year and on postablation atrial function after 6 months, measured by echocardiography and TVE as well as by levels of cardiac natriuretic peptides (Paper IV)

3 Patients and methods

3.1 Patients

The patients included in the studies of this thesis work were all operated at the Department of Cardiothoracic Surgery and Anaesthesiology, Örebro University Hospital, during different time periods, as follows:

- All 575 patients who underwent open-heart surgery between 1 July 2004 and 30 June 2005 were eligible for inclusion in Study I. This was a prospective cohort study in which 51 of the 575 patients were excluded: three patients died before postoperative day 3, ten patients were excluded due to having undergone miscellaneous surgery which was hard to classify (rewarming, atrial myxoma, postinfarction ventricular septal defect (VSD), acute pulmonary embolism, and so on), and 38 patients were excluded because they had had preoperative AF. The remaining 524 patients formed the study cohort (*Figure 6*).
- All 1,559 patients who underwent primary CABG between 1 January 1997 and 30 June 2000 were eligible for inclusion in Study II. This was a retrospective cohort study in which 140 of the 1,559 patients were excluded: 104 patients had preoperative AF, 19 had a preoperative PM, and 17 died before postoperative day 6. The remaining 1,419 patients formed the study cohort (*Figure 7*).
- All 648 patients who underwent primary CABG between 1 January 1999 and 30 June 2000 were eligible for inclusion in Study III. This was a retrospective cohort study, consisting of a subcohort of the patients in Study II. For the same reasons as in Study II, patients with a preoperative history of AF (46 patients), patients with preoperative PM implants (seven patients) and patients not surviving postoperative day 5 (three patients) were excluded. In addition, 21 patients declined participation in the study. Of the screened 648 patients, the remaining 571 patients were included and formed the study cohort (*Figure 8*).

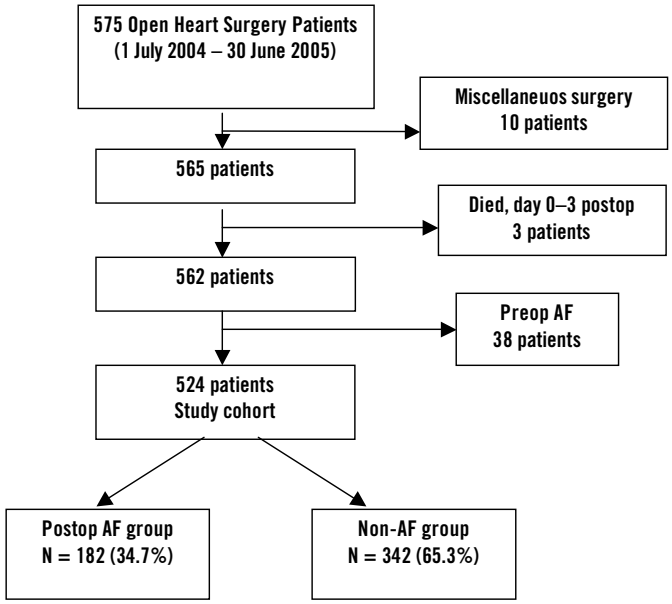


Figure 6. Study design in Study I.

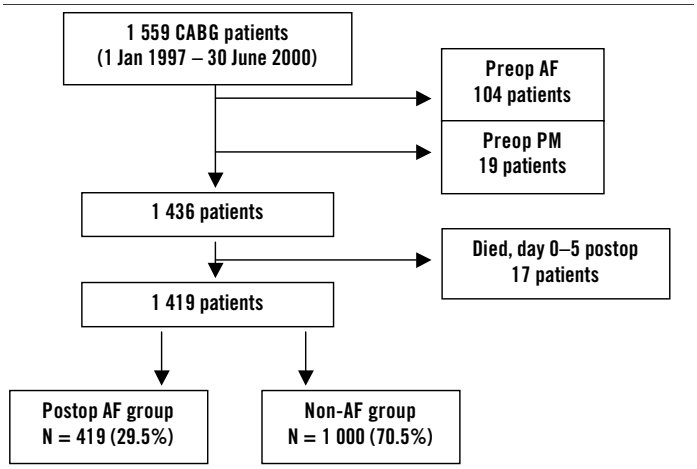
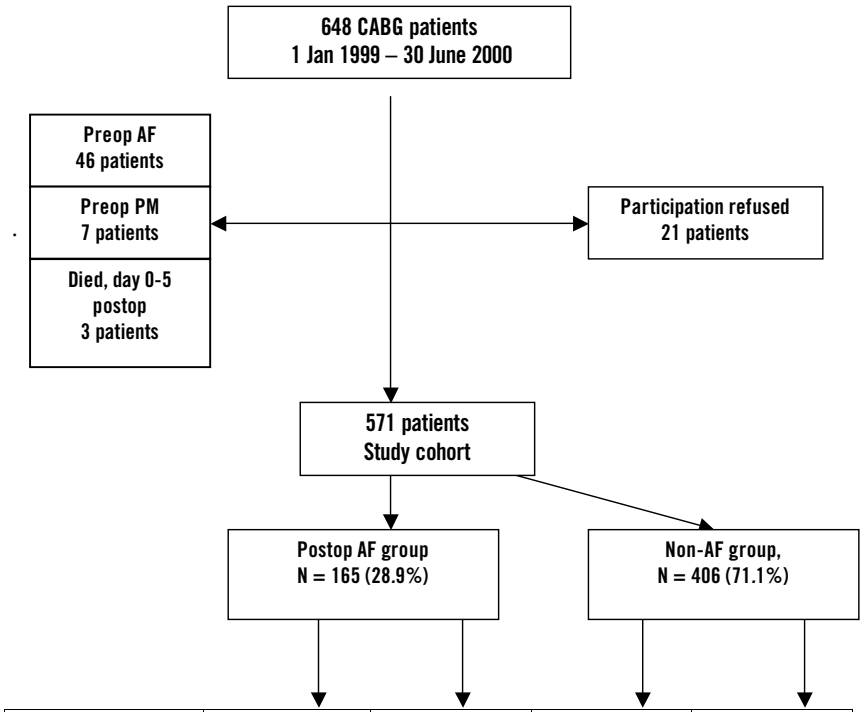


Figure 7. Study design in Study II.



	Alive* N =132	Dead* N =33	Alive* N =359	Dead* N =47
Questionnaire answers (N/%)	120 (90.9%)	–	330 (91.9%)	–
ECG available (N/%)	118 (89.4%)	24 (72.7%)	325 (90.5%)	37 (78.7%)

Figure 8. Study design in Study III.
* at time of questionnaire and ECG collection

- Twenty open-heart surgery patients with symptomatic concomitant AF included from September 2003 and the follow-up completed in November 2006 were included in Study IV. The study had a prospective and non-randomized design, and the inclusion criteria were symptomatic long-standing persistent AF (defined as continuous AF of >1 year's duration), persistent AF (defined as requiring pharmacological or electric cardioversion, or as being sustained beyond 7 days) or paroxysmal AF (defined as at least six episodes/year) in patients undergoing open-heart surgery of any form. The exclusion criteria were previous open-heart surgery and contraindication to anti-coagulants. During the study period, altogether 32 patients with concomitant AF were not included: seven patients with long-standing persistent AF of >6 months were included in the Microwave Ablation in Mitral valve surgery for Atrial fibrillation (MAMA) study (a randomized, placebo-controlled multi-centre study of endocardial microwave ablation in conjunction with mitral valve surgery), and 25 patients were not included because of asymptomatic concomitant AF.

3.2 Ethics

Studies I–III were approved by the Regional Ethical Committee of Uppsala. Signed informed consent was obtained in Study III and waived in Studies I and II. Study IV was approved by the Regional Ethical Committee of Örebro and individual signed informed consent was obtained.

3.3 General procedures

Anaesthetic management and extracorporeal circulation (Studies I–IV)

The anaesthetic management was similar in all patients and typically consisted of induction with thiopental 2–5 mg · kg^{-1}, fentanyl 4–6 µg · kg^{-1} and pancuronium bromide 0.1 mg · kg^{-1}. After intubation the patients were ventilated with isoflurane or sevoflurane, oxygen and air. After sternotomy closure, patients were sedated with propofol 1–2 mg · kg^{-1}· $hour^{-1}$ until extubation. Standard monitoring techniques (central venous/pulmonary artery and arterial pressure monitoring, urinary output, nasopharyngeal or urinary bladder temperature monitoring, and electrocardiography depending on access of equipment) were used in all patients.

The extracorporeal circuit consisted of an open venous reservoir (Sorin, Mirandola, Italy) primed with 2,000 mL Ringer's acetate, a roller pump, a hollow-fibre oxygenator with integrated heat exchanger (Sorin, Mirandola, Italy), and a polyvinyl tubing system. A non-pulsatile roller pump was used and the flow was kept at 2.4 L · min^{-1} · m^{-2}. Nasopharyngeal temperature was routinely allowed to drift to 34°C during the procedures. In Studies II and III, active body cooling to 30–32°C was sometimes used. Systemic heparinization (300 U/kg) was used to keep the activated clotting time >480 seconds.

For myocardial protection, patients received a bolus dose of 1,000 mL high potassium cold blood cardioplegia (8–10°C), followed by intermittent infusions of 300 mL every 20 minutes of aortic clamping. In Studies II and III, continuous cold blood cardioplegia was sometimes used, and also topical cooling with ice slush. Cardioplegia was administered in the aortic root or, in valve procedures, by retrograde administration through cannulation of the coronary sinus.

Surgical procedures (Studies I–III)

The CABG was routinely performed with cardiopulmonary bypass (CPB) using the left internal mammary artery to bypass the left anterior descending artery, and using the great saphenous vein to revascularize the circumflex and right coronary artery areas. After surgery, the patients were transferred to an intensive care unit, extubated after a few hours, and transferred to the patient ward the morning after surgery.

Surgical procedure (Study IV)

Using peroperative transoesophageal echocardiography, the left atrial appendage was checked for thrombus formation, which was not present in any patient. Epicardial microwave ablation was performed using a micro-

wave energy ablation catheter (Flex IV, Guidant; Boston Scientific, Natick, MA, USA) delivering 65 Watts over 90 seconds per ablation, with the patient on-pump as routine, if possible. The ablation line set was adopted from Maessen et al [90]; it consisted of lines surrounding the pulmonary vein pairs with a connecting line in the left atrial roof (*Figure 9*). Where a typical atrial flutter had been registered in the patient history, an isthmus ablation line between the tricuspid annulus and the orifice of the inferior caval vein was produced endocardially, using 65 Watts over 60 seconds. Testing for conduction block was not performed routinely. At the beginning of the series, the left atrial appendage was ligated at the base with a 4–0 prolene suture, but this procedure was later abandoned following reports of incomplete closure [71].

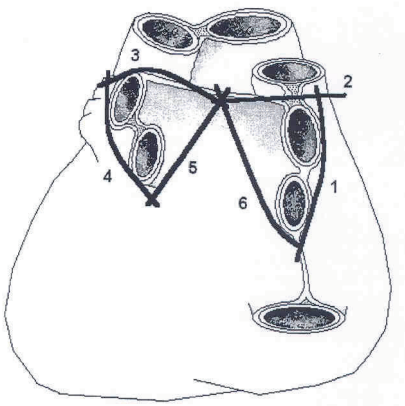


Figure 9. Dorsal view of the heart showing ablation line set. Numbers indicate the following: (1) lateral lesion to upper and lower right pulmonary veins, (2) lesion from upper right pulmonary vein to transverse sinus, (3) lesion from transverse sinus to upper left pulmonary vein, (4) lateral lesion to upper and lower left pulmonary vein, (5) lesion from lower left pulmonary vein through the oblique sinus into the transverse sinus, and (6) lesion from lower right pulmonary vein through the oblique sinus into the transverse sinus. Reprinted from 90 with permission from Elsevier.

Management of postoperative atrial fibrillation (Study I–IV)

Preoperative medication, including beta blockers and aspirin, was continued up to the day of surgery, with the exception of warfarin, which was discontinued 3 days before surgery. No specific AF prophylaxis was used during the study period, but all patients with preoperative beta blocker medication continued this medication postoperatively. Following the diagnosis of AF, patients received one or more of the following therapies at the physician's discretion: a beta blocker (sotalol was preferred, if tolerated by the patient), amiodarone, digoxin, or verapamil, which typically were maintained for at least 4 weeks. Cardioversion was considered if the AF was difficult to rate-control. Patients in AF were given heparin or low-molecular-weight heparin for anti-coagulation; warfarin was considered if AF persisted.

3.4 Data collection

Study database (Studies I–III)

In Studies I–III, a study database was constructed for each study. Patient background data as well as per- and postoperative parameters were prospectively entered into a clinical database. The study database comprised parameters from this database together with retrospectively collected data from patient records and laboratory data. Among the parameters registered were patient characteristics (age, sex, body mass index (BMI)), concomitant diseases, LVEF obtained from preoperative echocardiography or angiography, and Canadian Cardiovascular Society (CCS) angina class. Per- and postoperative data included CPB time, aortic cross-clamp time, postoperative neurological deficit of any kind (defined as "neurological event"), and medication at discharge.

All the baseline data in the study database for each patient were individually checked against the patient records, and corrections were made. Also, in case of missing data, efforts were made to retrieve the data in order to minimize data loss.

The study database was then completed with relevant follow-up data, laboratory analyses, and other variables as specified below. The study database was constructed using SPSS software, version 14 (SPSS, Inc., Chicago, IL, USA).

Registration and definition of postoperative atrial fibrillation (Studies I–III)

Postoperative AF was defined as an ECG-verified episode lasting >1 minute during the first 7 postoperative days.

In Studies II and III, all patients were monitored by continuous five-lead telemetry (Sirecust 960; Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA) until postoperative day 2. From day 2 until discharge, the pulse was checked at least twice daily; if arrhythmia was detected, telemetry was performed again. A standard twelve-lead ECG was routinely performed on postoperative days 1, 2 and 5, and was performed more often if an arrhythmia was detected. Episodes of arrhythmia were noted on patient surveillance charts, and assessed three times daily and at discharge by the heart surgeon responsible for the case. The onset and duration of AF were recorded in the patient's records as well as in the clinical database at the time of discharge. Two independent observers each looked twice through all patients' records to collect AF episode data.

In Study I all patients were monitored by continuous five-lead telemetry (Teleguard, GE Healthcare, WI, USA) until postoperative day 4. From day

5 until discharge, pulse was checked at least twice daily and telemetry was reinstituted if arrhythmia was clinically detected. A standard twelve-lead ECG was routinely obtained on days 1 and 5. Episodes of arrhythmia were captured by an automatic alarm function and were printed out and recorded. The telemetry recordings were also routinely assessed three times daily and at discharge by the heart surgeon responsible for the case. The onset and duration of AF were recorded as well as presence of AF at discharge.

Mortality and cause of death (Study II)

The Swedish Cause of Death Register, which is run by the Swedish National Board of Health and Welfare, includes all deaths of Swedish residents. In this register, the underlying cause of death is recorded from the death certificate issued by the doctor responsible for determining the cause of death. The cause of death is classified according to the International Statistical Classification of Diseases and Related Health Problems (ICD), revision 10 (ICD-10). Causes of death are obtained in 99.75% of all deaths (2005) and the coding error is estimated as being 0.3% [101]. Various methods, such as clinical examination before death, and autopsy, are used to establish the cause of death of individual patients. The quality of the Cause of Death Register has been repeatedly examined [70].

In Studies II and III all patients in the study who were deceased as of October 2006 were identified in the Swedish National Cause of Death Register. From these data, cause of death was classified as belonging to one of the following three *main groups* and eleven subgroups: (1) *cardiac*: AMI, heart failure, and sudden death; (2) *cerebral*: cerebral infarction, cerebral haemorrhage, and cerebrovascular insult (specific cause unknown); and (3) *other*: malignancy, infection, ruptured aortic aneurysm, miscellaneous cause, and unknown cause. In this classification scheme, no information was available regarding the patients' heart rhythm or previous postoperative AF.

Electrocardiogram collection at follow-up (Study III)

During the period from October 2005 to May 2006, all patients in the study cohort were located using the Swedish Population Registry. Deceased patients in the cohort were identified, and surviving patients were sent a questionnaire. The hospitals in the counties were contacted, and each patient's most recent ECG was obtained. If the ECG was older than 1 year, a new ECG was recorded at the local care centre. In deceased patients, the latest ECG recording prior to death was obtained from the electrocardiographic database at the local hospital.

All ECGs were evaluated by one observer, who was blinded to postoperative AF data. The heart rhythm was classified into one of four categories:

(1) *SR*; (2) *AF*, including some instances of atrial flutter; (3) *PM rhythm*; and (4) *other.*

Questionnaire (Study III)

The questionnaire contained questions about symptoms of irregular heart rhythm, hospital care due to heart rhythm problems or stroke, and current medication. Up to three telephone reminders were used to encourage questionnaire completion and return, and in some instances patients answered questions by phone.

Follow-up after epicardial microwave ablation (Study IV)

Follow-up time points were at 1, 3, 6 and 12 months postoperatively and follow-up consisted of ECGs, interviews and a physical examination. At 6 months post-operatively, a transthoracic echocardiography was performed. At 12 months' follow-up, 72-hour Holter monitoring was performed (R-test; Novacor, Cedex, France). Blood samples were collected by venipuncture on the day before surgery, on the morning after surgery, and at 12 months postoperatively for analysis of natriuretic peptides.

3.5 Analyses

C-reactive protein (Study I)

C-reactive protein concentration in serum, expressed as mg/L, was measured twice: on the morning of the day before surgery and on the morning of the third postoperative day. C-reactive protein was determined using dry chemistry methods on a Vitros 250 or Vitros 950 instrument (Ortho-Clinical Diagnostics, Rochester, NY, USA). The CRP method was an enzyme immunoassay, and the total coefficients of variation (CVs) were 8.4% and 7.5% at 24 and 70 mg/L, respectively.

Creatinine in serum (Studies I–III)

Creatinine in serum, expressed as µmol/L, was routinely obtained on the day before surgery, on the morning after surgery and on the third postoperative day. Creatinine was determined using dry chemistry methods on a Vitros 250 or Vitros 950 instrument (Ortho-Clinical Diagnostics, Rochester, NY, USA). The creatinine method was based on the enzyme creatinine amidohydrolase, and the total CVs were 1.4% and 1.2% at 83 and 510 µmol/L, respectively.

Creatine kinase (CK-MB) in serum (Studies I–III)

Creatine kinase (CK-MB) in serum, expressed as µg/L, was measured on the morning after the surgery (typically 18 hours after wound closure). Creatine kinase-MB was determined by an electrochemiluminescence immunoassay on an Elecsys 2010 instrument (Roche Diagnostics, Mannheim, Germany). Total CVs were 7.7% and 3.4 % at 2.6 and 48.7 µg/L, respectively.

Natriuretic peptides (Study IV)

Blood samples were collected by venipuncture on the day before surgery, on the morning after surgery, and at 12 months postoperatively.

Atrial natriuretic peptide

Blood samples were transferred to chilled blood collecting tubes containing aprotinin and ethylenediaminetetraacetic acid (EDTA), and centrifuged within 5 minutes at 2,000 g, 4°C, for 5 minutes. Plasma was then separated and aliquots were stored at –60°C. Atrial natriuretic peptide serum concentration was determined using an immunoradiometric assay (Shionora ANP; Schering SA, Gif-sur-Yvette Cedex, France) with a CV of 4.1% (ANP concentration 92.0 pg/mL).

Brain natriuretic peptide

Blood samples were transferred to blood collecting tubes containing EDTA, centrifuged, and stored at –60°C. Brain natriuretic peptide (BNP) concentration was determined using an immuno-chemiluminescence assay (Architect system; Abbot, Wiesbaden, Germany) with a CV of 5.6% (BNP concentration 961.6 pg/mL).

Amino terminal precursor of brain natriuretic peptide

Blood samples were transferred to standard sampling tubes with gel, centrifuged and stored at –60°C. The concentration of NT-proBNP was determined using an immunochemiluminescence assay (Cobas; Roche, Mannheim, Germany) with a CV of 2.9% (NT-proBNP concentration of 355 pg/mL).

Echocardiographic measurements

Transthoracic echocardiographies with Doppler studies were performed the day before surgery and at 6 months postoperatively (Vivid 7, Vingmed; General Electric, Horten, Norway). The left ventricular dimensions were measured by two-dimension-guided M-mode method, and the LVEF was visually assessed. Left atrial anteroposterior diameter was measured in the parasternal long axis view, and the left atrial area was calculated using

planimetry in the apical four-chamber view. Atrial mechanical function was assessed by pulsed Doppler examination of the tricuspid and mitral inflow, using the apical four-chamber view. The Doppler sample volume was positioned between the tips of the leaflets. All measurements were made during quiet respirations with the patient in the left lateral position. The presence of an A-wave, detected in late diastole after the ECG P-wave, was recorded and the A-wave peak velocity was measured.

Tissue velocity echocardiography was performed using the apical four-chamber view with a superimposed TVE image on the left atrium. The registrations were analysed offline using Echopac 4.1.1 computer software (Vingmed; General Electric, Horten, Norway). All measurements were made by two different observers (P.R. and A.A.). For each measurement, the interobserver mean was calculated and used in the analysis. Tissue velocity echocardiography was analysed in all patients with SR at registration, but only registrations with patients in SR at both preoperative and postoperative control were compared (six patients). The following measurements were made:

1. Atrial wall velocity. A sample volume was placed midway between the atrial roof and the atrioventricular plane in the left lateral and septal wall, and peak velocity (in cm/s) during atrial contraction was registered (*Figure 10*).

2. Atrial wall strain. Two sample volumes were placed at a distance of 10–20 mm from each other in the left lateral and septal wall. Displacement, in mm, during the time from the P-wave to the beginning of the Q-wave was measured in both sample volumes. Atrial wall strain, a measure of the atrial wall contraction, was defined as the difference in the displacements divided by the distance between the sample volumes, and expressed as a percentage of the distance.

3. Atrial wall strain rate. Two sample volumes were placed at a distance of 10–20 mm from each other in the left lateral and septal wall. Peak velocities during atrial contraction were registered. The atrial wall strain rate was defined as the difference in peak velocities divided by the distance between the sample volumes.

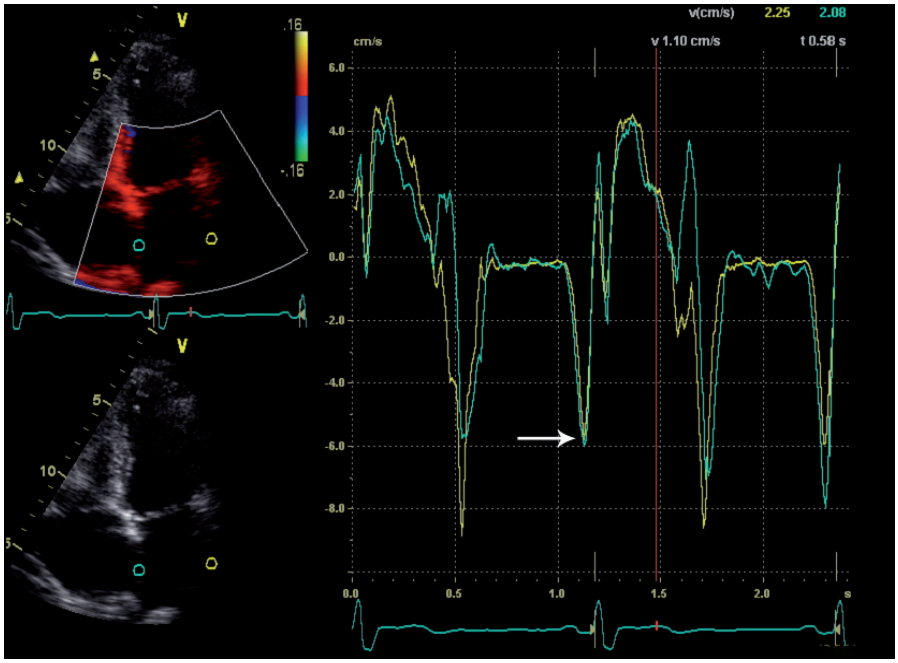


Figure 10. Tissue velocity echocardiography (TVE).
Apical four-chamber view with superimposed TVE image to the upper left. Two sample volumes situated in the left lateral wall and atrial septum, midway between atrioventricular plane and atrial roof. To the right, recordings of tissue velocities in cm/s during two cardiac cycles, with ECG recording at the bottom. The arrow indicates atria wall peak velocity during atrial contraction after the ECG P-Wave.

3.6 Statistics

Data are expressed as the means ± standard deviation (SD) or, in the case of skewed distributions, as medians and interquartile ranges. Categorical variables were compared using chi-square tests or Fisher's exact test, while continuous variables were compared using either Student's *t*-test for independent samples or the nonparametric Mann-Whitney U-test, depending on scale and measurement type. Where appropriate, skewed distributions were transformed to logarithms before application of the parametric tests. Repeated measurements were analysed using Student's *t*-test for paired observations. To illustrate the effect of postoperative AF on long-term survival, Kaplan-Meier cumulative survival curves were constructed and compared by the log-rank test. For all tests, a *p*-value <.05 was considered statistically significant.

Regression analysis was used in several ways in this thesis work. To determine predictors of postoperative AF, multivariable logistic regression was used (in Papers I–III sometimes called "multivariate" or "multiple logistic regression"). Factors determining survival were analysed through Cox proportional hazard analysis. In both models, a series of variables were screened using bivariate analysis, and those which attained a *p*-value of ≤.10 or those which were considered of clinical importance were entered into the regression model. The cofactors remaining in the model were checked for linearity, and if non-linearity was the case, transformation or categorization was used. The modeling strategy was based on Katz [72].

To test the hypothesis that postoperative AF is a risk indicator for later development of AF, *binomial logistic regression* was used and a risk ratio (RR) was calculated. A number of variables were tested pairwise together with postoperative AF; those that changed the estimated RR by >10% were included in the model as possible confounders, and an adjusted RR was calculated. Statistical analysis was performed using SPSS software, version 14 (SPSS, Inc., Chicago, IL, USA), Stata software, version 10 (StataCorp LP, College Station, TX, USA), and Statistica, version 8.0 (StatSoft, Inc., Tulsa, OK, USA).

Regression analysis can be used for two principally different purposes: either to find a model with various variables predicting the outcome (Studies I and II), or to study one factor and control for potential confounders (Study III). From a clinical point of view, both analyses are interesting and consequently, in the survival analysis a model for both predictors of late mortality and control of confounders is presented.

4 Results

4.1 Postoperative atrial fibrillation and C-reactive protein (Study I)

Of the 524 patients in the study cohort, 182 patients (34.7%) developed an episode of postoperative AF. The patient characteristics of the study cohort are shown in *Table 2*. The postoperative AF patients were older and scored higher on both Higgins and EuroSCORE indexes (p <.001).

Table 2. Patient characteristics (Study I).

	Non-AF group (N = 342)	AF group (N = 182)	*p*-value
Age (years)	65.4 ± 10.4	70.6 ± 8.2	< .001
Female (%)	28	25	.45
BMI (kg/m^2)	27.5 ± 4.2	26.9 ± 4.3	.15
Diabetes (%)	23	19	.35
Previous MI (%)	44	41	.66
History of smoking (%)	55	54	.95
COPD (%)	7	10	.25
Betablocker preoperatively (%)	77	64	.003
EF > 65% (%)	80	73	.20
50 – 65% (%)	10	12	
30 – 50% (%)	6	8	
<30% (%)	4	7	
Higgins score	4	5	< .001
EuroSCORE	3	5	< .001

BMI = Body Mass Index ; COPD = Chronic Obstructive Pulmonary Disease ; EF = Ejection Fraction ; MI = Myocardial Infarction.

The median onset of postoperative AF was on day 2 with a median duration of 2 days (interquartile range 1–4 days) (*Figure 11*). C-reactive protein did not differ between patients with postoperative AF and patients without AF, either preoperatively or on the third postoperative day. In fact, the CRP concentrations in both groups were very similar (*Table 3*).

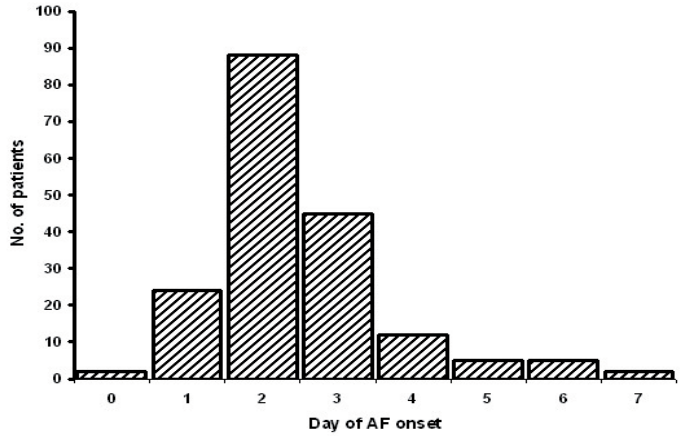


Figure 11. Onset of atrial fibrillation (AF).

Table 3. Operative data and postoperative results (Study I).

	Non-AF group (N = 342)	AF group (N = 182)	*p*-value
Surgical time (minutes)	203 ± 56	227 ± 106	.006[a]
Time on CPB (minutes)	98 ± 53	115 ± 61	.005[a]
Cross clamp time (minutes)	65 ± 31	79 ± 47	.001[a]
Ventilator time (median hours)	5.3	6.7	< .001[b]
CK-MB day 1 (μg /L)	22.5 ± 26.7	33.6 ± 53.1	.009[b]
CRP preoperatively (mg/L)	5.0 ± 6.4	5.6 ± 9.1	.855[b]
CRP day 3 (mg/L)	175.4 ± 64.4	175.3 ± 60.1	.993[a]
Creatinine max postoperatively (mg/L)	99.6 ± 65.8	124.1 ± 112.3	<. 001[b]
Stroke incidence	1.8%	4.6%	.065[c]
Reoperation for bleeding	2.4%	5.2%	.101[c]
Hospital mortality	0%	2.2%	.002[c]

CRP = C- reactive protein ; CK-MB = Creatine kinase. [a] Student's *t*-test; [b] Student's *t*-test on log values; [c] Fisher Exact test

Postoperative CK-MB levels were higher in the AF group, as was the duration of ventilator support and surgery. The hospital mortality in the study cohort was 4/524 patients (0.8%) and was limited to patients in the AF group.

Table 4. Postoperative atrial fibrillation by logistic regression analysis (Study I)

	No.	Bivariate analysis OR [95% CI]	*p*-value	Multivariate analysis [a] OR [95% CI]	*p*-value
CRP pre (mg/L)					
< 5	279				
> 5	97	0.92 [0.57 – 1.51]	.751		
CRP day 3 (mg/L)					
-136	134				
137-176	120	1.14 [0.68 – 1.92]	.615		
177-214	136	1.27 [0.77 – 2.09]	.354		
215-	123	0.95 [0.56 – 1.60]	.847		
Age (years)					
< 61	139				
61 – 68	135	2.02 [1.14– 3.58]	.017	1.75 [0.94 – 3.23]	.075
68 – 76	142	4.66 [2.69 – 8.07]	< .001	4.39 [2.41 – 8.00]	< .001
> 76	108	3.83 [2.14 – 6.85]	<. 001	3.58 [1.89 – 6.78]	< .001
Ventilator time (hours)					
< 4.6	135				
4.6 –5.7	134	1.01 [0.58 – 1.75]	.972	0.76 [0.42 – 1.38]	.37
5.7 – 8	120	2.05 [1.20 – 3.49]	.008	1.33 [0.74 – 2.39]	.34
> 8	128	2.79 [1.66 – 4.70]	< .001	1.50 [0.84 – 2.68]	.18
CK-MB day 1 (μg/L)					
< 70	491				
> 70	22	3.52 [1.45 – 8.56]	.005	3.04 [1.13 – 8.18]	.028
Surgical time (hours)					
< 4	395				
> 4	125	1.80 [1.19– 2.71]	.005	1.84 [1.16 – 2.92]	.009

CRP = C-reactive protein; OR = Odds ratio; CI = Confidence interval; CK-MB = Creatine kinase. [a] With variables age, ventilator time, CK-MB day 1 and surgical time

The logistic regression analysis is summarized in *Table 4*. Preoperative CRP and CRP at postoperative day 3 showed no significant relations to postoperative AF in the bivariate analysis. Age, postoperative CK-MB value >70 μg/L, prolonged respirator time, and time in the operation room were all significant predictors of postoperative AF and since all these variables showed a non-linear relationship, they were categorized. In the multivariable analysis, age remained a significant predictor of postoperative AF, with an OR of 4.39 (2.41–8.00) in the age group 68–76 years and 3.58 (1.89–6.78)

in the age group >76 years compared with the age group <61 years. Patients with a postoperative CK-MB concentration >70 µg/L had an OR for developing AF of 3.04 (1.13–8.18) compared with patients with concentrations <70 µg/L. The multivariate analysis model in the right column of Table 4 had a total misclassification rate of 30.2%, with a specificity and sensitivity for AF of 91.2% and 28.5%, respectively. This means that the majority of the postoperative AF patients could not be detected using the variables in the model.

Comment

The findings indicate no correlation between postoperative AF and pre- or postoperative CRP concentration, treated either as a continuous or as a categorical variable. In this study, elevated levels of CK-MB were found to be a predictor of postoperative AF, a correlation not previously demonstrated. The hospital mortality was low, but it should be remembered that patients with concomitant AF were not included in the study.

4.2 Postoperative atrial fibrillation and late mortality (Study II)

The baseline characteristics of the 1,419 patients in the study cohort from 1997–2000 are shown in *Table 5*. Of the 1,419 patients included, 419 (29.5%) developed postoperative AF. Patients who experienced postoperative AF were generally older, more often hypertensive, and had higher Higgins scores compared with patients in postoperative stable SR. There were no differences in gender or preoperative history of cerebrovascular disease, and the LVEF did not differ between the groups.

Table 5. Clinical characteristics (Study II).

	Non-AF group (N = 1 000)	AF group (N = 419)	*p*-value
Age (years)	64.9±9.5	69.2±8.1	<.001
Female gender (%)	25.8	22.2	.151
BMI (kg/m^2)	26.9±3.9	26.8±3.7	.402
Hypertension (%)	35.1	43.0	.016
Diabetes (%)	17.0	17.4	.847
Previous AMI (%)	56.7	61.6	.089
History of smoking (%)	60.3	55.3	.091
History of CVD (%)	6.7	6.7	.977
CCS angina class IV (%)	33.1	35.6	.371
Ejection fraction (%) [a]	58.4±14.0	57.5±14.0	.281
Higgins score [b]	1 (0–3)	2 (1–3)	<.001

Baseline data of patients in study cohort (N=1419). [a] left ventricular ejection fraction; [b] median (interquartile range)

AF = atrial fibrillation; AMI = acute myocardial infarction; BMI = body mass index; CCS = Canadian Cardiovascular Society; CVD = cerebrovascular disease

Per- and postoperative data are summarized in *Table 6*. Postoperative neurological events were more common in the postoperative AF group (1.7% v. 0.6%, $p = .054$). There was no significant difference in CK-MB release.

Table 6. Per- and postoperative data (Study II).

	Non-AF group (N = 1 000)	AF group (N = 419)	*p*-value
Off-pump surgery (%)	3.3	1.4	.050
Time on CBP (minutes)	106 ± 41	109 ± 31	.169
Cross-clamp time (minutes)	58 ± 18	60 ± 18	.193
CK-MB day 1 (µg/L)	53.1±74.6	59.1±81.0	.193
Neurologic event (%)	0.6	1.7	.054
Medication at discharge (%)			
Amiodarone	0.4	0.8	.370
Sotalol	4.4	67.6	<.001
Other beta blockers	76.7	18.8	<.001
Digoxin	3.4	24.9	<.001
ACE inhibitor	16.5	19.1	.241
AT2 blocker	1.4	1.5	.925
Calcium blocker	11.6	15.6	.047
Diuretics	20.5	30.7	<.001
Statins	40.8	33.9	.017
Warfarin	1.1	3.0	.014
Aspirin	94.7	92.9	.200
Clopidogrel	0.2	0.3	.870

ACE = angiotensin converting enzyme; AF = atrial fibrillation;
AT2 = angiotensin II; CBP = cardiopulmonary bypass; CK-MB = creatine kinase-myocardial band

The median follow-up time was 8.0 years. The total mortality was 191 deaths/1,000 patients (19.1%) in the group with no AF and 140 deaths/419 patients (33.4%) in the AF group (*Table 7*). The Kaplan-Meier survival curves showed a significant difference between the AF group and the non-AF group (log-rank test, $p<.001$) irrespective of whether 30-day mortality rates were excluded or not (*Figure 12 A*).

Cause of death (*Table 7*) was established by autopsy in 57/331 deaths (17.2%), and by clinical examination before death in other cases. Death due to cerebral ischaemia was more common in the postoperative AF group (2.6% v. 0.5%, $p = .001$), as well as death from unspecified cerebrovascular causes (1.7% v. 0.7%, $p = .091$). Myocardial infarction (7.4% v. 3.0%, $p<.001$), sudden death (2.6% v. 0.9%, $p = .012$) and heart failure (6.7% v. 2.5%, $p<.001$) were also more common causes of death among postoperative AF patients. The number of non-cardiovascular causes of death did not differ between the groups.

Table 7. Cause of death (Study II).

Cause of death [a]	Non-AF group (N = 1 000)	AF group (N = 419)	*p*-value
Cardiac			
Myocardial infarction	30 (3.0)	31 (7.4)	<.001
Heart failure	25 (2.5)	28 (6.7)	<.001
Sudden death	9 (0.9)	11 (2.6)	.012
Cerebral			
Cerebral ischemia	5 (0.5)	11 (2.6)	.001
Cerebral bleeding	9 (0.9)	2 (0.5)	.408
Cerebrovascular, undefined	7 (0.7)	7 (1.7)	.091
Other			
Malignancy	56 (5.6)	23 (5.5)	.934
Infection	16 (1.6)	5 (1.2)	.563
Aortic rupture	4 (0.4)	4 (1.0)	.203
Miscellaneous	28 (2.8)	17 (4.1)	.218
Unknown	2 (0.2)	1 (0.2)	1.00
Total mortality	191 (19.1)	140 (33.4)	

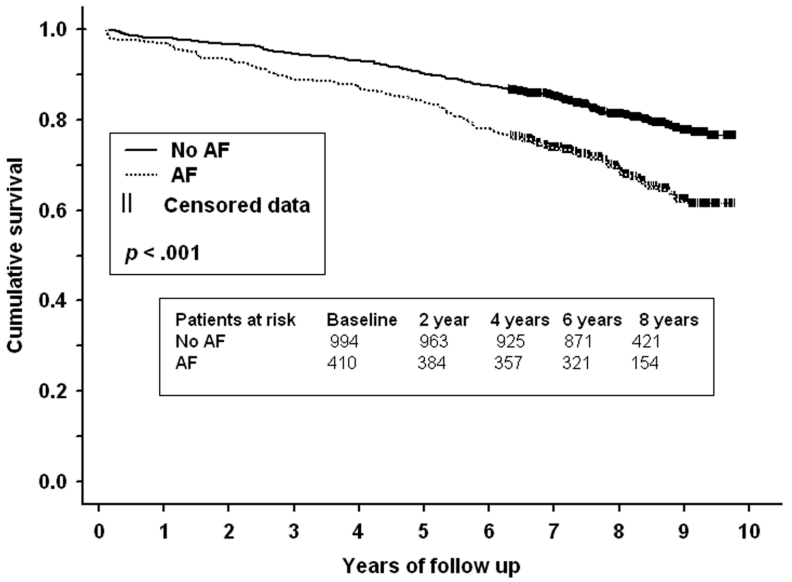
[a] Number of patients (percent in each group).

The Cox regression analysis of patients surviving the first 30 days postoperatively is summarized in *Table 8*. Univariate predictors of late mortality were postoperative AF (p<.001), age (p<.001), diabetes (p = .001), hypertension (p = .022), LVEF (p<.001) and postoperative CK–MB >70 µg/L (p = .012), while female gender had no significant influence on late mortality. In the multivariate analysis, postoperative AF was an independent risk indicator for late mortality (p<.001), with a hazard ratio (HR) of 1.56 (95% CI 1.23–1.98) (*Figure 12 B*, postoperative AF adjusted for age). Age, diabetes, and LVEF were also independent risk factors for late mortality.

Table 8. Predictors of mortality beyond 30 days postoperatively, by Cox regression analysis (Study II).

	Univariate analysis HR (95% CI)	*p*-value	Multivariate analysis HR (95% CI) [a]	*p*-value
Postoperative AF	**1.84 (1.47–2.30)**	**<.001**	**1.56 (1.23–1.98)**	**<.001**
Age	**1.06 (1.05–1.08)**	**<.001**	**1.07 (1.05–1.08)**	**<.001**
Female gender	**0.99 (0.76–1.27)**	**.912**	**0.95 (0.72–1.24)**	**.689**
CK-MB >70 µg/L	**1.38 (1.07–1.79)**	**.012**	**1.32 (0.99–1.74)**	**.056**
Diabetes	**1.58 (1.21–2.06)**	**.001**	**1.76 (1.32–2.34)**	**<.001**
Ejection fraction [b]	**0.98 (0.97–0.98)**	**<.001**	**0.97 (0.97–0.98)**	**<.001**
Hypertension	**1.31 (1.04–1.65)**	**.022**	**1.18 (0.93–1.50)**	**.173**

[a] With all variables in the table; [b] left ventricular ejection fraction
AF = atrial fibrillation; CI = confidence interval; CK-MB = creatine kinas myocardial band; HR = hazard ratio



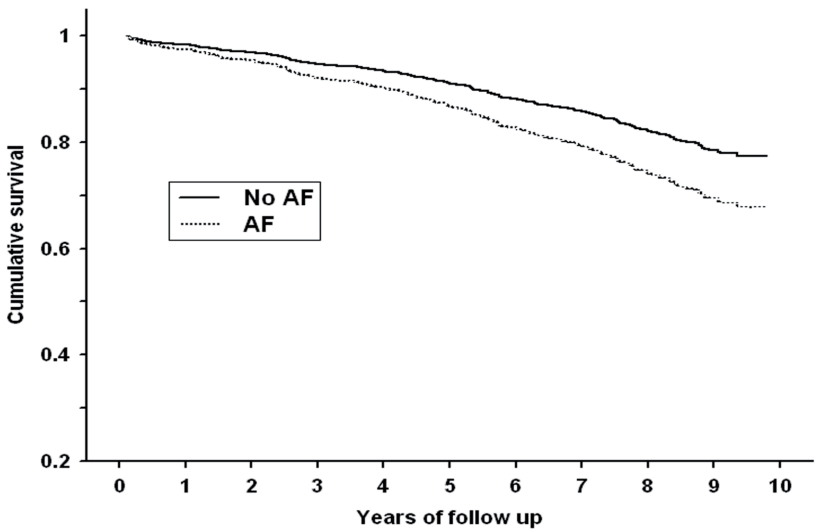


Figure 12 A (upper panel) and B (lower panel). In A, Kaplan-Meier survival curves of patients in cohort, with 30-day mortality excluded, are shown. Log-rank test was used for significance testing. In B, Cox regression plot of postoperative atrial fibrillation adjusted for age is shown.

Comment

Postoperative AF is an independent risk factor for late mortality and postoperative AF patients have a significantly higher risk of death due to cerebral ischemia, MI, sudden death, and heart failure compared with patients without AF.

It should be noted that the correlation between CK-MB and postoperative AF found in Study I could not be demonstrated in this larger study. One interesting finding is, however, that the mean levels of postoperative CK-MB release in Study I are almost half of the values in Studies II and III. The reasons for this are not evident. The patients were operated during different time periods, and Study I included all open-heart surgery patients, while Study II and III focused on CABG patients. The finding is interesting and warrants further investigation.

4.3 Postoperative atrial fibrillation and late arrhythmia (Study III)

Of the 571 patients included in the study, 165 (28.9%) developed postoperative AF. Since the study cohort was a subcohort of the chort from Study II, the baseline characteristics were similar. The postoperative AF patients were older than postoperative patients in stable SR. There were no gender differences, and the LVEF did not differ between the groups (*Table 9*).

Hospitalization was prolonged in patients with postoperative AF. Neurological events during the hospital stay tended to be more common, and 30-day mortality was higher in patients with an episode of postoperative AF.

Table 9. Baseline patient characteristics and postoperative parameters (Study III).

	Non-AF group (N = 406)	AF group (N = 165)	*p*-value
Baseline characteristics			
Age (years)	64.6±9.4	69.2±7.6	<.001
Female gender (%)	22.9	18.8	.279
BMI (kg/m^2)	26.8±3.8	27.0±3.8	.617
Hypertension (%)	30.4	35.8	.211
Diabetes (%)	19.0	17.0	.577
Previous AMI (%)	54.2	58.8	.316
Left ventricular ejection fraction (%)	57.4±14.5	55.7±14.9	.228
S-creatinine (μmol/L)	99.4±69.1	109.8±76.5	.117
Postoperative parameters			
Length of stay (days)	7.4±2.4	9.2±5.8	<.001
Neurological event during hospital stay (%)	0.7	2.4	.111
Death within 30 days (%)	0.2	2.4	.026

Data are presented as means ± standard deviation (SD) for continuous variables, and as percentages for dichotomous variables.
AF = atrial fibrillation; AMI = acute myocardial infarction; BMI = body mass index

Questionnaires were obtained from 450 out of 491 surviving patients (91.6%). Electrocardiogram recordings were obtained from 443 out of 491 surviving patients (90.2%) and from 61 out of 80 deceased patients (76.3%). The median time from surgery to our receipt of the completed questionnaire was 6.3 years, and time from surgery to the latest ECG recording was 5.3 years. The patients who did not answer the questionnaires were slightly younger than patients who did, and were also more frequently female.

The number of patients with AF at follow-up, as documented by a twelve-lead ECG, was ten out of 362 patients (2.8%) without postoperative AF and 20 out of 142 patients (14.1%) with an episode of postoperative AF at surgery ($p<0.001$). Among the 80 deceased patients, none in the non-AF group (0/37) had AF at their most recent ECG, compared with 6/24 (25%) among postoperative AF patients ($p<.001$).

An irregular pulse was reported by 53/120 (44.2%) of the postoperative AF patients, compared with 105/330 (31.8%) of the non-AF patients ($p=.033$). A past history that included hospitalization for heart rhythm problems was also more common among postoperative AF patients, viz. in 27/120 (22.5%) of postoperative AF patients v. 28/330 (8.5%) of non-AF patients ($p<.001$) (*Table 10*).

Table 10. Results of questionnaire.

		No AF group (N = 330)	AF group (N = 120)	*p* -value
Do you experience irregular pulse?				
No, never		**225 (68.2%)**	**66 (55.0%)**	
Yes	**Sometimes**	**97 (29.4%)**	**47 (39.2%)**	**.033**
	Daily	**8 (2.4%)**	**6 (5.0%)**	
No answer			**1 (0.8%)**	
Do you experience chest pain?				
No, never		**209(63.3%)**	**73 (60.8%)**	
Yes, at hard exercise		**98 (29.7%)**	**41 (34.2%)**	**.552**
Yes, in daily activities		**23 (7.0%)**	**6 (5.0%)**	
Have you been hospitalized due to heart rhythm problems?				
Yes		**28 (8.5%)**	**27 (22.5%)**	**< .001**
Have you suffered any stroke?				
Yes		**24 (7.3%)**	**14 (11.7%)**	**.237**

The unadjusted RR for late development of AF when an episode of postoperative AF was documented was 3.88 (95% CI 1.77–8.49). Variables tested as possible confounders were age, gender, previous MI, diabetes mellitus, hypertension, LVEF, preoperative s-creatinine, preoperative BMI, and statin medication at follow-up. The only variable that changed the RR by >10% was age, and the adjusted RR for development of late AF was 3.11 (95% CI 1.41–6.87).

Table 11. Patient medication preoperatively, at hospital discharge and at a six-year follow-up (Study III).

Medication	Preoperatively		At discharge		At follow-up	
	Non-AF group (n = 406)	AF group (n = 165)	Non-AF group	AF group	Non-AF group (n = 330)	AF group (n = 120)
Sotalol	2.0	4.2	3.7	68.5	0.9	5.0
Amiodarone	–	–	0.2	0.6	0.0	1.7
Other AA	–	–	–	–	0.9	0.0
ß blocker	83.0	78.2	82.0	19.5	69.4	66.7
Digitalis	3.9	5.5	4.2	21.2	3.3	9.2
Aspirin	89.4	95.2	95.6	93.9	90.6	87.5
Warfarin	1.2	0.6	1.2	3.6	3.9	8.3
Statins	49.8	48.5	48.3	43.6	71.8	67.5
Diuretics	18.5	29.1	18.7	27.9	25.2	35.0
Ca blocker	26.8	37.6	15.3	15.2	20.0	22.5
ACE inhibitor	22.4	21.2	19.7	21.8	26.4	24.2
AT-2 blocker	4.2	7.3	3.0	3.6	12.7	21.7

Results shown are percentages.
AAs = antiarrhythmics; ACE = angiotensin-converting enzyme;
AF = atrial fibrillation; AT-2 = angiotensin receptor II.

Medication is given in *Table 11*. At discharge, 3.6% of the AF patients and 1.2% of the non-AF patients received warfarin. At follow-up, 8.3% of postoperative AF patients received warfarin, compared with 3.9% of non-AF patients. Medication with sotalol, digitalis, diuretics, and angiotensin II receptor blockers was also more common among postoperative AF patients after 6 years. In total, 6.7% of postoperative AF patients received an antiarrhythmic drug at follow-up, compared with 1.8% of non-AF patients.

Of the 30 patients with AF at follow-up, five patients received warfarin, two received warfarin and aspirin, and eight received aspirin. In six deceased patients, medication was unknown. Consequently, in 9/30 patients with AF at follow-up, no thromboembolic prophylaxis medication was reported.

Comment

The findings from the ECG follow-up and the questionnaire are coherent; the patients with an episode of postoperative AF have a higher risk of developing AF in subsequent years. Together with the findings from Study II, these findings suggest that development of AF may be directly linked to the increased mortality in postoperative AF patients. The findings also indicate that thromboembolic prophylaxis medication is underused in the patients with AF at follow-up.

4.4 Concomitant atrial fibrillation and microwave ablation (Study IV)

Patient characteristics

Preoperative patient characteristics are listed in *Table 12*; 17 of the patients were male, and the mean age was 68 years. The median duration of AF was 4.0 years (0.5–10 years), with nine patients having long-standing persistent AF, seven patients having persistent AF, and four patients having paroxysmal AF. All patients had preoperatively tried at least one anti-arrhythmic drug or beta blocker, and 17 patients received anti-coagulation in some form. The mean left atrial diameter was 49 mm and the mean left atrial area was 29.3 cm^2.

Surgical and ablation procedure

Preoperative and postoperative data are summarized in *Table 13*. Time on CPB was 140 ± 37 minutes, and cross-clamp time was 76 ± 37 minutes (mean ± SD). The total time for the ablation procedure including dissection was 20–40 minutes, and between seven and ten ablation lines were made. In three patients with preoperative atrial flutter, right atrial isthmus lines were made. Left atrial isthmus lines were created in two patients, one because of documented and one because of suspected atypical flutter. Eleven patients underwent valve procedures of some form, eight patients underwent isolated myocardial revascularization either on- or off-pump, and one patient underwent closure of an atrial septal defect (ASD).

There was no hospital mortality, but one patient (patient #12) died 2 months postoperatively from a ruptured abdominal aortic aneurysm. There were two neurological complications. Patient #7 suffered a complete stroke with postoperative left hemiplegia. Postoperative Doppler examination showed an acute occlusion of the right carotid artery, and the patient history revealed several malignant TIAs in the weeks before surgery, which had been misinterpreted as embolic events from paroxysmal AF. Patient #16 underwent an aortic valve replacement and had a postoperative transient paresis of the left arm with full recovery at follow-up. One patient (patient #2) required further surgery 5 months postoperatively due to mitral insufficiency after an aortic valve replacement. This patient underwent a mitral annuloplasty and, because of a recurrent atypical atrial flutter, a completing endocardial ablation of the left atrial isthmus. The postoperative course was uneventful.

No	Age[a]	Sex	BMI[b]	Type of surgery	LA diam[c]	LA area[d]	LVEF[e]	AF type	AF years[f]	Failed drugs[g]	Cardio-version pre[h]	Antiocoagulation status[i]
1	56	Male	29.0	MVR	59	39.8	70	Pers	5	Sotalol	Yes	None
2	72	Male	24.1	AVR	48	25.3	60	Pers	9	Flecainid	Yes	ASA
3	63	Male	24.2	AVR + ASC	47	-	60	Parox	10	Sotalol	No	Warfarin
4	68	Female	28.8	MVrepair	47	27.8	70	Parox	5	-	No	None
5	71	Male	29.4	CABG	53	32.0	20	L pers	1	-	No	ASA
6	56	Male	22.5	MVR	50	23.6	40	L pers	1	-	Yes	Warfarin
7	64	Male	34.0	CABG	47	22.6	60	Pers	8	Sotalol	Yes	Warfarin, ASA
8	71	Male	26.9	AVrepair + ASC	52	35.9	45	L pers	1	Sotalol	Yes	Warfarin
9	73	Male	23.5	MVrepair + CABG	59	42.4	50	L pers	3	-	Yes	ASA
10	72	Male	26.2	AVR	54	32.5	50	L pers	2	-	Yes	None
11	70	Male	31.0	OPCAB	49	30.8	65	L pers	5	-	Yes	Warfarin, ASA
12	73	Male	19.7	CABG	-	-	-	Parox	10	Disopyramid, amiodarone	No	ASA
13	70	Male	21.6	OPCAB	31	17.5	60	Pers	6	Sotalol	Yes	Warfarin
14	78	Male	24.5	CABG	55	42.2	30	L pers	6	-	Yes	Warfarin
15	74	Male	26.0	MVrepair + AVrepair	53	41.4	70	Pers	0.5	Flecainid	Yes	Warfarin
16	72	Male	25.5	AVR	49	22.9	60	L pers	0.5	-	No	Warfarin
17	48	Male	27.1	CABG	-	-	-	Pers	6	Disopyramid	Yes	ASA
18	75	Male	25.2	CABG	44	20.9	70	Pers	0.5	-	No	Warfarin
19	55	Female	27.0	ASD	45	20.7	70	Parox	3	Sotalol	No	ASA
20	79	Female	19.0	AVR	41	19.5	65	L pers	2	-	No	Clopidogrel
Total	68 ± 8.4[k]	3 F / 17 M	25.8 ± 3.7[k]		49 ± 6.6[k]	29.3 ± 8.6[k]	56 ± 14[k]	4/7/9[j]	4.0[m]			

Table 12. Preoperative patient characteristics (opposite side)

[a] years; [b] kg /m^2; [c] in millimetres; patients #12 and #17 had no preoperative echocardiography due to subacute surgery; [d] in cm^2; [e] visually estimated, in percent; [f] duration of atrial fibrillation history; [g] other than beta-blockers; [h] any cardioversion before surgery known at admittance; [i] at admittance; [k] mean ± standard deviation; [l] number paroxysmal/ persistent/ longstanding persistent; [m] median value

AF = atrial fibrillation; ASC = surgery of ascending aorta; ASA = acetyl salicylic acid; ASD = atrial septal defect; AVR = aortic valve replacement; AVrepair = aortic valve repair; BMI = body mass index; CABG = coronary artery surgery bypass; F = female; L pers = longstanding persistent; LA = left atrium; LVEF = left venricular ejection fraction; M = male; MVR = mitral valve replacement; MVrepair = mitral valve repair; OPCAB = off pump coronary artery bypass surgery; Parox = paroxysmal; Pers = persistent; SR = sinus rhythm

Patient characteristics					*Added lesion*[a]			*Heart rhythm*					*Postoperative data*		
No	Age[b]	Sex	Surgery	AF type	LA[c]	RA[d]	LAA[e]	Preop[f]	3 mo[g]	6 mo[h]	12 mo[i]	Cardioversion[k]	Permanent PM[l]	LOS[m]	Major complication
1	56	Male	MVR	Pers	-	-	Lig	SR	AF	SR	SR	Yes	-	5	-
2	72	Male	AVR	Pers	-	-	Lig	SR	AF	SR	SR	Yes	-	9	Atypical flutter, reop MI
3	63	Male	AVR + ASC	Parox	-	-	Lig	AF	SR	SR	SR	No	-	6	-
4	68	Female	MVrepair	Parox	Isthmus	-	Lig	SR	SR	PM	SR	Yes	DDD (17 days postop)	20	-
5	71	Male	CABG	L pers	-	-	Lig	AF	SR	SR	SR	Yes	-	9	-
6	56	Male	MVR	L pers	Isthmus	-	Lig	AF	SR	SR	SR	No	-	6	-
7	64	Male	CABG	Pers	-	Isthmus	Lig	SR	SR	SR	SR	No	-	16	Stroke, carotid occlusion
8	71	Male	AVrepair + ASC	L pers	-	-	Lig	AF	SR	SR	SR	Yes	-	7	-
9	73	Male	MVrepair + CABG	L pers	-	-	-	AF	SR	SR	SR	No	-	7	-
10	72	Male	AVR	L pers	-	Isthmus	Lig	AF	SR	AF	SR	No	-	5	-
11	70	Male	OPCAB	L pers	-	-	-	AF	SR	AF	AF	Yes	-	6	-
12	73	Male	CABG	Parox	-	-	-	SR	SR	-	-	No	DDD (7 days postop)	10	Death 2 months postop, ruptured AAA
13	70	Male	OPCAB	Pers	-	-	-	SR	SR	SR	AF	No	-	6	-
14	78	Male	CABG	L pers	-	-	-	AF	AF	AF	AF	Yes	-	5	-
15	74	Male	MVrepair + AVrepair	Pers	-	-	-	SR	SR	SR	SR	No	-	8	-
16	72	Male	AVR	L pers	-	-	-	AF	SR	SR	SR	No	-	9	Transient postop paresis
17	48	Male	CABG	Pers	-	-	-	AF	SR	SR	SR	No	-	6	-
18	75	Male	CABG	Pers	-	-	-	AF	SR	SR	SR	No	-	6	-
19	55	Female	ASD	Parox	-	Isthmus	-	SR	SR	SR	AF	No	DDD (5 days postop)	7	-
20	79	Female	AVR	L pers	-	-	-	AF	AF	AF	AF	Yes	-	8	-

Table 13. Per- and postoperative data (opposite side)

[a] ablation or ligation added to lesion set in figure 1; [b] years; [c] left atrial endocardial lesion, between left inferior pulmonary vein and mitral annulus; [d] right atrial endocardial lesion; [e] left atrial appendage ligation; [f] rhythm at preoperative echocardiography; [g] rhythm at 3 months postoperatively; [h] rhythm at six months postoperatively; [i] rhythm at 12 months postoperatively; [k] Cardioversion during first postoperative year; [l] implantation of pacemaker postoperatively; [m] length of stay in days

AAA = abdominal aortic aneurysm; AF = atrial fibrillation; ASC = surgery of ascending aorta; ASD = atrial septal defect; AVR = aortic valve replacement; AVrepair = aortic valve repair; CABG = coronary artery surgery bypass; DDD = DDD pacemaker system; L pers = longstanding persistent; Lig = ligated; MI = mitral insufficiency; mo = months ; MVR = mitral valve replacement; MVrepair = mitral valve repair; OPCAB = off pump coronary artery bypass surgery; Parox = paroxysmal; Pers = persistent; PM = pacemaker; reop = reoperation; SA-block = sinoatrial blockage; SR = sinus rhythm

Follow-up

At the 12-month follow-up, 14/19 patients (74%) were in SR without antiarrhythmic drugs (nine patients received amiodarone or sotalol postoperatively, which was discontinued at 3 months). The clinical data on the remaining five patients were as follows: one patient (patient #13) with preoperative persistent AF had occasional paroxysmal attacks at 12 months, one patient (patient #19) with paroxysmal AF preoperatively still had paroxysmal AF (albeit less frequent) at follow-up, and three patients with preoperative longstanding persistent AF remained in AF during the entire follow-up period.

Three patients (patients #4, #12 and #19), all with paroxysmal AF, required DDD-PM implants 6–17 days postoperatively following symptomatic episodes of sinus arrest. Of these, one patient (patient #12) had known episodes of sinus arrests preoperatively and was scheduled for PM implantation.

Echocardiography

Echocardiographic dimensions are summarized in *Table 14*. Left ventricular diastolic diameter was significantly reduced at 6 months postoperatively ($p = .030$), as was left atrial area ($p = .012$). All patients in SR postoperatively showed preserved A-waves on both the left and the right side, and there were no significant differences between A-wave velocities pre- and postoperatively on either side.

Tissue velocity echocardiography, performed on six patients with SR both at preoperative echocardiography and 6 months postoperatively, showed no significant differences in left atrial wall velocities, atrial wall strain, or atrial wall strain rate.

Laboratory findings

Laboratory data are summarized in *Table 15* and *Figure 13*. Overall, serum levels of cardiac natriuretic peptides tended to increase on postoperative day 1 and decrease after 12 months. In *Figure 13*, the preoperative serum levels are subtracted from the levels at 12 months, and the serum level differences are shown in patients with SR and patients with AF at 12 months. In SR patients, levels of ANP, BNP and NT–proBNP tended to decrease compared with AF patients.

Table 14. Echocardiographic findings (Study IV).

Transthoracic echocardiographic dimensions and Doppler measurements	*Preoperatively*	*Postoperatively (6 months)*	*p-value[b]*
Left ventricular ejection fraction (%)	55.2 ± 14.4	53.4 ± 14.9	.591
Left ventricular diastolic diameter (mm)	57.2 ± 9.4	53.9 ± 8.2	.030
Left ventricular systolic diameter (mm)	39.7 ± 10.0	39.2 ± 9.2	.803
Left atrial area (cm^2)	29.3 ± 8.6	24.5 ± 6.6	.012
A wave right (m/s)	0.34 ± 0.14[c]	0.31 ± 0.08[d]	.518
A wave left (m/s)	0.49 ± 0.15[c]	0.75 ± 0.40[d]	.179
Tissue velocity echocardiography[e]			
Atrial wall velocity (cm/s)			
Left	4.3 ± 2.1	3.6 ± 2.0	.350
Septal	5.4 ± 2.2	3.5 ± 1.9	.107
Atrial wall strain (%)			
Left	6.5 ± 7.8	5.9 ± 3.4	.823
Septal	7.4 ± 5.8	6.0 ± 2.1	.603
Atrial wall strain rate (s^{-1})			
Left	1.1 ± 1.2	0.8 ± 0.8	.607
Septal	1.0 ± 0.9	0.6 ± 0.2	.337

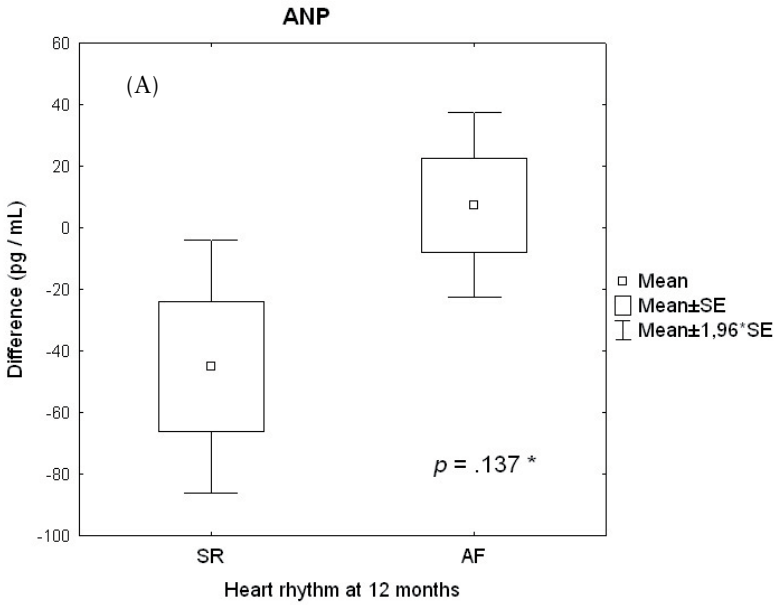
[a] Numbers shown are mean ± standard deviation; [b] paired *t*-test; [c] in all 7 patients with sinus rhythm; [d] in all 14 patients with sinus rhythm; [e] in 6 patients with
sinus rhythm at preoperative and postoperative echocardiography

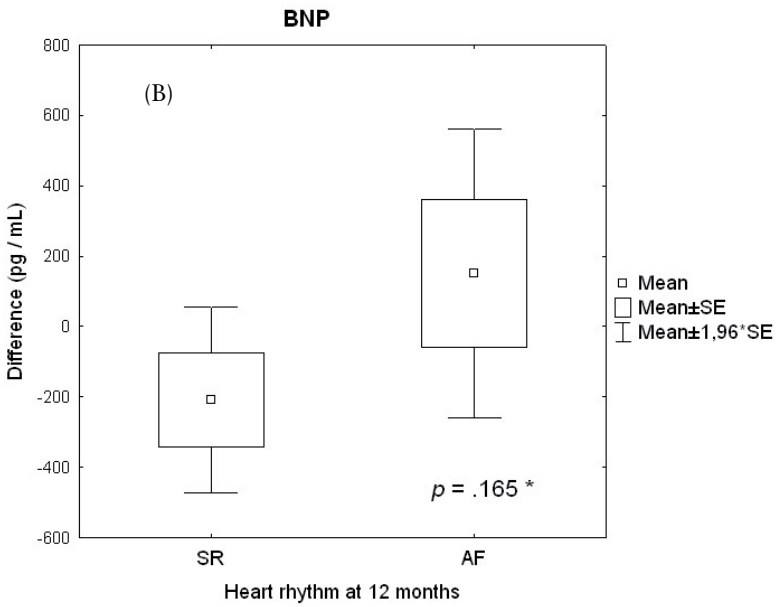
mm = millimeters ; cm = centimeters ; m = meters ; s = seconds

Table 15. Serum concentrations of natriuretic peptides.

	Preoperatively	Postoperative day 1	12 months postoperatively
ANP (pg/mL)	**53.7 (29.7 – 91.8)**	**59.0 (40.1 – 75.2)**	**36.2 (24.0 – 59.2)**
BNP (pg/mL)	**196.8 (118.3 – 512.2)**	**384.6 (238.1 – 488.6)**	**149.3 (119.8 – 239.2)**
NT – proBNP (pg/mL)	**1726.5 (607.6 – 2124.0)**	**1845.5 (1422.1 - 2597.2)**	**545.4 (391.8 – 1410.5)**

Values shown are median (interquartile range) ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; mL = milliliter; NT–proBNP = amino terminal precursor of brain natriuretic peptide; pg = picogram (10^{-12} gram)


ANP
(A)
60
40
20
0
-20
-40
-60
-80
-100
Difference (pg / mL)
p = .137 *
SR
AF
Heart rhythm at 12 months
Mean
Mean±SE
Mean±1,96*SE


BNP
(B)
800
600
400
200
0
-200
-400
-600
Difference (pg / mL)
p = .165 *
SR
AF
Heart rhythm at 12 months
Mean
Mean±SE
Mean±1,96*SE

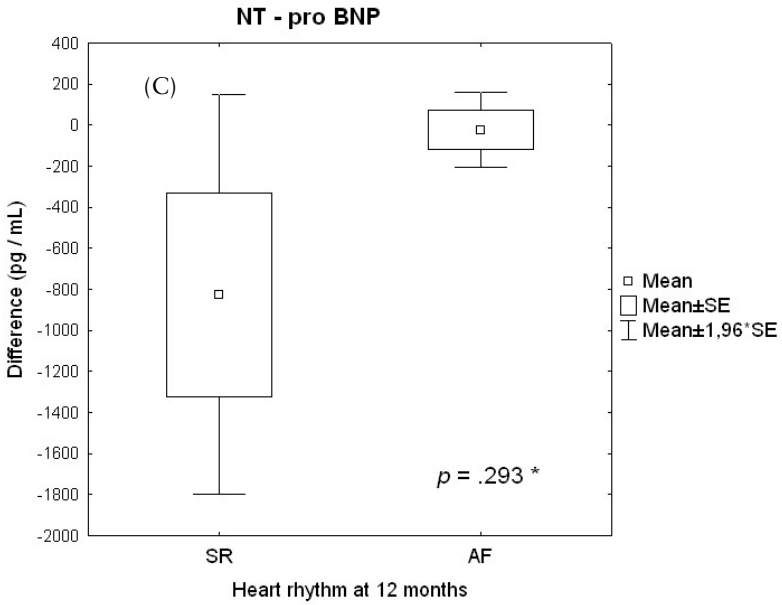


Figure 13 A – C. Serum levels of cardiac natriuretic peptides, preoperative value subtracted from postoperative value at 12 months.

* Student's *t*-test

AF = atrial fibrillation; ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; mL = milliliters; NT-proBNP = amino terminal precursor of brain natriuretic peptide; SE = standard error of mean; SR = sinus rhythm; pg = picogram (10^{-12} gram); postop = postoperatively; preop = preoperatively

Comments

The major finding was that all patients in SR had preserved atrial contractile function 6 months postoperatively, both with Doppler measurements of transmitral and transtricuspid flow and with TVE measurements of left atrial wall velocities, left atrial wall strain, and strain rate. The study also showed that evaluation of atrial function with TVE is feasible although further standardization of the method is needed.

5 General discussion

5.1 Inflammation and postoperative atrial fibrillation

If inflammatory mechanisms are involved in the genesis of AF, it is likely that the model of postoperative AF will lead to some answers. The reasons are that the inflammatory response is pronounced after surgery and that it is correlated with the peak incidence of postoperative AF. However, there are also important methodological considerations. The inflammatory response involves a multitude of systemic reactions and proteins, and statistically, if all are tested, some will, by chance, be significantly correlated to the incidence of AF. To evaluate such findings, a hypothesis of how alterations in concentrations of proteins can affect the incidence of postoperative AF is needed.

In this study, we chose to study the serum concentration of CRP before and after surgery and its relation to postoperative AF. The reasons for this were that several studies of patients with AF in general had shown correlations with CRP [13, 26, 49, 93]. Patients with paroxysmal or permanent AF have been found to have elevated CRP levels compared with controls, and elevated CRP has been shown to act as a predictor of future episodes of AF [13, 26, 49, 93]. Moreover, there was a plausible mechanism for CRP acting as an initiator for AF. The theory behind the arrythmogenic properties of CRP was that CRP binds to phosphocholine in damaged cell membranes; it was postulated that this may contribute to membrane dysfunction and subsequent ion exchange disturbances and arrhythmia [20, 44, 49]. Finally, the relation between CRP and postoperative AF has been previously studied, with conflicting results. In one study, preoperative CRP >3.0 mg/L was correlated to postoperative AF [85], while three other studies found no associations between preoperative CRP levels and AF [6, 51, 68]. Postoperative CRP-complement 4 D complexes on postoperative day 2 were associated with AF in one study [20], but two other studies found no correlations between postoperative CRP and AF [6, 51, 57].

This study showed no correlation between pre- or postoperative concentrations of CRP and the development of postoperative AF. As this is the largest study so far, having the highest power to study the correlations between pre- or postoperative CRP levels and postoperative AF, we conclude that the absence of correlation is a true negative finding.

The results of this study suggest that CRP is only a marker of inflammatory activity and not an aetiological factor for postoperative AF. It is also possible that these results can shed some light on the aetiology of AF in general. The correlation between AF and elevated CRP levels, either as predictor or as marker, has been previously demonstrated in patients with permanent or paroxysmal fibrillation of some duration [13, 26, 49, 93]. A possible explanation for this is that in patients with long-lasting AF this state gene-

rates an inflammatory response, i.e. AF precedes CRP elevation. Also, CRP levels were of a milder magnitude in these studies, with a twofold increase compared with the approximately 30-fold increase seen in the postoperative setting.

The results from this study do not exclude a link between AF and inflammation. The inflammatory response after cardiac surgery is complex and involves, among other proteins, the cytokines interleukin-6 and tumor necrosis factor-α and complement factor C3a. This study only demonstrates the absence of correlation between the inflammatory marker CRP and postoperative AF.

Conclusion

There is no correlation between pre- or postoperative CRP concentrations and the development of postoperative AF.

5.2 Postoperative atrial fibrillation and late mortality

Atrial fibrillation in general is associated with increased long-term mortality [116]. Fatal stroke, heart failure, MI and sudden death are all more common causes of death in AF patients compared with the general population [25, 52, 97, 106, 116, 119, 126]. Stroke and heart failure are closely related to AF, but the increased risk of MI, especially in women, and sudden death in AF patients is harder to explain. It has been proposed that AF is a marker of underlying cardiovascular disease [52], and that increased tendency for fatal arrhythmogenesis may be linked to development of congestive heart failure [25].

Postoperative AF has been defined as a secondary AF of short duration, with no long-term consequences [55]. However, in one large cohort study with 5 years' follow-up, postoperative AF patients had an adjusted OR of 1.5 for long-term mortality [125]. In this study, there was no plausible mechanism linking AF to mortality since causes of death were not available [81]. The findings from this study have not been confirmed; no other long-term follow-up study of postoperative AF has been published so far.

In the present study of 8 years' follow-up, an episode of postoperative AF during the first 7 postoperative days was an age-independent risk factor for late mortality, with an HR of 1.56 (95% CI 1.23–1.98). Despite a lower incidence of postoperative AF in the study by Villareal et al (16%) [125], the results are very similar.

The other important finding of the present study was that postoperative AF patients had a more than doubled risk of dying from cerebral ischaemia, MI, sudden death, and heart failure in spite of equal LVEF at the time of surgery between the groups. This finding resembles the results of mortality

studies of non-secondary AF [25, 52, 97, 106, 116, 119, 126] and implies that the mechanisms may be the same in both types of AF.

The relationship between postoperative stroke and postoperative AF has been studied, but the results are conflicting [67, 75, 78, 100]. In this study, there was no difference in the preoperative prevalence of cerebrovascular disease between the groups. Postoperative neurological events were rare, but tended to be more common in the postoperative AF patients. Consequently, the later development of cerebral thromboembolic disease does not seem to be linked to pre- and peroperative prevalence of the disease.

Other independent risk factors for late mortality in this study were age, diabetes, and LVEF. All are known risk factors for late mortality and heart failure after coronary surgery, and the findings are in agreement with previous studies [19, 115].

Conclusion

Postoperative AF is an age-independent risk factor for late mortality, with an HR of 1.56 (95% CI 1.23–1.98). Postoperative AF patients have a more than doubled risk of death due to cerebral ischaemia, MI, sudden death, and heart failure compared with patients without AF.

5.3 Postoperative atrial fibrillation and late arrhythmia

In most studies so far, postoperative AF has been found to be self-limiting, with a short duration and total prevalence of AF of 1–4% at 1 year [27, 48, 76, 79]. In one small study of 305 non-consecutive CABG patients followed in an outpatient clinic for 2 years, symptomatic episodes of AF requiring medical care were more common in postoperative AF patients (20.4%) than in non-AF patients (3.2%) [9]. Although this finding is interesting, this study suffers from selection bias and the follow-up is poorly described. Apart from this study, no published studies so far have examined the long-term consequences of postoperative AF and heart rhythm.

The present study of 571 consecutive CABG patients had a nearly 90% complete 5-year ECG follow-up. Using a single ECG recording at follow-up to estimate the prevalence of AF, we found that postoperative AF patients had a significantly higher risk of developing AF than did non-AF patients, with an adjusted RR of 3.11 (95% CI 1.41–6.87). To our knowledge, this is the largest study with the longest follow-up time that shows this correlation. The true prevalence of AF at follow-up may be underestimated, since cases of silent paroxysmal AF may be undetected.

In this study, the mean patient age at surgery was 65.9 years. At follow-up, taking into consideration that some patients had died, the mean age was 69 years in non-AF patients and 74 years in AF patients. Epidemiological data from the Framingham Heart Study and the Rotterdam Study indicate that the overall prevalence of AF in this age group is 5–7% [64, 83, 84]. Since patients in these studies were followed with repeated controls, and AF in conjunction with open heart surgery was excluded, it seems unlikely that the 14.1% prevalence of AF at a single time point in this study reflects the "normal" prevalence of AF in this age group. In fact, it may be that the prevalence of AF at follow-up in our study has been underestimated because of our inability to detect patients with paroxysmal AF using a single time measurement.

It was beyond the scope of this study to determine why postoperative AF patients have a higher risk of developing AF. We speculate that major surgery may function as a "stress test" that unmasks a tendency to develop AF. Coronary artery bypass surgery may therefore reveal the risk of developing AF, which might otherwise not be detected until later. Another explanation could be that the surgery causes permanent changes that increase the potential for AF, e.g. by inducing inflammation and atrial scarring.

The findings from this study may also shed light on the mortality findings from Study II. It has been suggested that higher mortality in postoperative AF patients, especially a higher incidence of sudden death, may be related to the use of potentially harmful anti-arrhythmic drugs [81]. In the present

study, only 6.7% of postoperative AF patients received sotalol or amiodarone at follow-up. Therefore, increased use of potentially harmful drugs cannot by itself explain the higher mortality we observed in postoperative AF patients.

Conclusion

In this study we found that patients with an episode of postoperative AF have a higher risk of developing AF in subsequent years. Together with the mortality data from Study II, these findings suggest that development of AF may be directly linked to the increased mortality in postoperative AF patients.

5.4 Atrial function after epicardial microwave ablation of AF

There are two objectives in AF surgery: to restore SR and to reduce the risk of thromboembolic complications. Sinus rhythm without atrial contraction may not reduce stroke risk since thrombus formation as a result of stasis in the left atrium is still possible [87, 95]. While there are data supporting a decreased risk of stroke in Maze surgery patients at follow-up [4, 32], other investigators have found a loss of atrial contraction in patients with SR after the Maze procedure [24, 86, 95]. In a recently published study the decrease in left atrial contractility was sustained several years after the Maze procedure [87], and it has been speculated that loss of atrial contraction leads to maintained risk of stroke [95]. Reduced atrial contractility has also been found after circumferential percutaneous catheter ablation [80]. There is, however, little knowledge regarding the new surgical ablation devices and their influence on atrial contractile function.

In the present study of epicardial microwave ablation all patients in SR had preserved atrial transport function. Doppler measurements of transmitral and transtricuspid flow showed preserved left and right A-waves during atrial contraction 6 months postoperatively. In patients in SR, there were no differences in A-wave velocities before and 6 months after ablation. Tissue velocity echocardiography measurements indicated that left atrial wall velocities, left atrial wall strain, and strain rate were preserved 6 months after ablation.

At the 12-month follow-up, 14/19 patients (74%) were in stable SR. Epicardial microwave ablation has been previously studied in 23 and 29 patients, respectively, with an 86% frequency of SR at 4–6 months [90, 99]. In a prospective randomized trial of endocardial microwave ablation, comparing 43 open-heart surgery patients with a control group, 80% of ablated patients were in SR at 1 year as compared with 33% of controls [111]. The frequency

of SR at 1 year in the present study seems reasonably in accordance with earlier results of microwave ablation techniques.

Decreased levels of BNP have been demonstrated after Cox Maze III surgery [120] as well as after successful pulmonary vein isolation or cardioversion [43, 102]. In the present study the patient material was small and inhomogeneous, and many factors apart from the ablation procedure can affect serum levels of cardiac natriuretic peptides. Nevertheless, there was a tendency of decrease of cardiac natriuretic peptides in patients with SR at 12 months compared with patients still in AF.

Conclusion

In conclusion, epicardial microwave ablation as an adjunct to open-heart surgery seems to achieve a change to SR in the majority of concomitant AF patients, as well as preserving atrial transport function and contractility 6 months after surgery.

5.5 Limitations

Atrial fibrillation registration at the time of surgery

The incidence and timing of postoperative AF in our studies are in concordance with earlier studies [10]. Even the most sensitive method of AF registration, i.e. continuous telemetry, is observer-dependent and we cannot preclude higher prevalence in reality. One of the strongest predictors of postoperative AF is a previous episode of AF [94]. We put a great deal of effort into excluding patients with previous AF, but information bias may have been present and it is therefore possible that patients with previous AF may have been included.

Causes of death registration

Data from the Swedish National Cause of Death Register were complete, but different methods had been used to establish the cause of death. Methods varied from clinical examination before death using a variety of methods (diagnostic radiology, ECG, biochemical analysis) to forensic autopsy. Since these factors were only partly controlled for in the Cause of Death Register, causes of death could be wrongly assigned in this database. The observed difference between the groups concerning cardiovascular and non-cardiovascular death cannot, however, be easily explained by poor validity of the cause of death data.

Residual confounding

In Studies II and III there is a possibility of residual confounding in the multivariate analysis. Age and EF were controlled for, but medication use in these patients was not known. One mechanism explaining a higher mortality could be more frequent use of potentially harmful drugs such as anti-arrhythmics, which could explain a higher incidence of sudden death. This, however, could not easily explain the other causes of death. Congestive heart failure is another possible confounder; because of the complexity and variability of the diagnosis [130] it was not included in our analysis. However, the contribution of postoperative AF to late mortality was independent of the baseline LVEF, which is an important element in congestive heart failure.

Registration of atrial fibrillation at follow-up

Since heart rhythm at follow-up in Studies II and III was only examined on one occasion, intermittent episodes of AF may not have been registered. Ideally, patients with possible AF episodes should be monitored repeatedly or continuously, but this was not possible in the present study because of logistic problems.

Microwave ablation therapy of atrial fibrillation (Study IV)

This was a small, non-randomized study, so the effect of microwave ablation on conversion to SR may have been overestimated; some patients may have converted entirely because of the surgery. The number of patients was small, and there is a risk of a Type II error regarding both atrial mechanical function and biochemical markers. The types of diagnoses leading to surgery and the type and duration of AF also varied.

Conclusions

The major conclusions reached were:

- There is no correlation between postoperative AF and pre- or postoperative serum concentrations of CRP.
- Postoperative AF is an age-independent risk factor for late mortality. Postoperative AF patients have a significantly higher risk of cardiovascular death.
- The patients with an episode of postoperative AF have a significantly higher risk of developing AF in subsequent years.
- Epicardial microwave ablation as an adjunct to open-heart surgery seems to convert a majority of concomitant AF patients to SR, and preserve atrial transport function and contractility 6 months after surgery.

Clinical perspectives

Management of patients with postoperative atrial fibrillation

The findings of this thesis suggest that an episode of postoperative AF after CABG surgery can be regarded as a risk marker for the development of late AF and late cardiovascular death. From a clinical point of view, these findings have several implications:

- The follow-up strategy in patients with postoperative AF should probably be more intense, with the goal of detecting late arrhythmias.
- Anticoagulation therapy should be initiated in high-risk patients with AF.
- If the incidence of postoperative AF can be reduced, will that reduce future risk of AF and cardiovascular death?

The aetiology of postoperative atrial fibrillation

The aetiology of postoperative AF is still an enigma. In a broad perspective, the question arises whether it is a kind of stress test of the myocardium and consequently reveals a tendency that would be overt in subsequent years. Or is it the surgical trauma that induces cellular changes in the myocardium, leading to a substrate for AF?

Surgical treatment of atrial fibrillation

Surgical treatment of AF is today offered to patients with concomitant symptomatic AF undergoing open-heart surgery. The optimal type of lesion set and energy have, however, not yet been defined. There are indications that atrial function is preserved after ablation, but it remains to be proven whether the stroke risk is actually reduced. Finally, new endoscopic techniques are available that need to be evaluated in controlled studies. What are the results for these techniques compared with percutaneous catheter ablation? Today, <1% of patients with AF receive ablation treatment of any kind. Although the majority of AF patients do not meet the criteria for ablation treatment, if we could venture a cautious prophecy we would say that the number of patients treated with AF ablation will increase in the near future as a consequence of well-conducted studies, new and refined techniques and a wider acceptance of elderly symptomatic AF patients.

Acknowledgments

This thesis has been accomplished thanks to the help and support of many people to whom I owe my gratitude. In particular, I would like to express my sincere gratitude to:

Associate Professor **Anders Englund**, my tutor and friend, for your scientific guidance, unsurpassed and rapid intellect, never-ending support and encouragement. Working with you has been a true and continuous pleasure (with the only minor exception when you forced me to participate in Vasaloppet). It is a paradox that finishing this thesis work, in this respect, leaves me in a sentimental mood.

Professor **Lennart Bodin**, statistical expert and co-author, for sharing your extensive knowledge and advice in statistics and epidemiology in many stimulating discussions. There is a risk of flying high in regression analysis, and, with your help, my feet has been kept on the ground.

My co-authors **Peter Linde**, **Peter Rask** and **Espen Fengsrud**, for generously contributing with your time, expertise and knowledge. The collaboration between our specialities has, to a simple surgeon's mind, been a true stimulus.

My colleagues **Lena Sunnermalm** and **Olof Lundblad**, heads of the Department of Cardiothoracic Surgery and Anaesthesiology, for your continuous support and encouragement. Thank you for having made every effort to support me throughout this work, and, by a sound leadership, creating a stimulating, happy and pleasant environment.

My former surgical super-mentor **Vollmer Bomfim**, and my mentors **Domingos Souza** and **Claudio Sobrosa**, for accepting me and introducing me in the field of cardiac surgery, and being, in your own different ways, unsurpassed examples of clinical judgement and technical skills. Everyday, many of the basic rules you taught me still echoes in my mind. In addition to this, your scientific work and thinking has been a true example to me, and, in many ways, much ahead of its time.

All my colleagues and all the staff at the Department of Cardiothoracic surgery and Anaesthesiology, the Department of Cardiology, and the Department of Clinical Physiology, for encouragement and friendship, and making this thesis work possible.

To **Mia Englund**, **Lotta Mazouch**, **Harriet Udd**, **Gunnel Adolfsson**, **Eva Norgren-Holst** and **Amila Bulut** at **Clinical Research Support** for your tremendous work in collecting data from all patients and constructing databases. This work would not, in any way, have been possible without your help and energy.

To **Jane Strand** and **Laila Örtensjö**, for a continuous and strong belief in my capacity to finally finish a thesis project, and for always encouraging and sometimes annoying me by pointing out that violin playing will delay my thesis.

To **Kerstin Persson**, **Lenore Haugland**, **Margareta Sandin** and the study-nurses **Susan Ericsson**, **Ingegerd Pöhner**, and **Madelene Ristman**, for patiently helping me with patient records and data collection.

To **Margareta Landin** for excellent help with literature research and references and to **Heinz Merten** for help with the thesis production.

Finally, I would like to express my deep gratitude to the foundations of my life: my beloved wife **Mette** – for your tremendous love, effort and support – our children **Johan**, **Ida**, **Olle** and **Karl**, my parents **Karl** and **Marlene**, my sisters **Margareta** and **Christina** and their families. Thank you for your continuous love and support which made this thesis work possible.

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