Atrial Fibrillation after Coronary Artery Bypass Surgery

A Study of Causes and Risk Factors

BY

LENA JIDÉUS
ABSTRACT


The aim was to study pathophysiological mechanisms and risk factors for developing atrial fibrillation (AF) after coronary artery bypass grafting (CABG), and the effect of thoracic epidural anaesthesia (TEA).

The study included 141 patients undergoing CABG, including 45 patients randomised for TEA intra- and postoperatively. All patients underwent 24-hour Holter monitoring pre- and postoperatively for the analysis of arrhythmias and heart rate variability (HRV). Catecholamines and neuropeptides (reflecting sympathetic and parasympathetic activity), atrial peptides and echocardiographically assessed atrial arias were obtained pre- and postoperatively.

Logistic regression analysis identified body mass index (BMI), maximum supraventricular beats (SPB) per minute, and total amount of cardioplegia as independent predictors of postoperative AF. Patients developing AF showed limited diurnal variation of HRV preoperatively. All HRV parameters decreased significantly in all patients postoperatively. The significant postoperative increase in atrial areas and atrial peptides did not differ between patients developing AF and those who did not. TEA had no effect on the incidence of postoperative AF, but resulted in lower heart rate, less increase in adrenaline levels, and decreased neuropeptide levels (reflecting sympathetic and parasympathetic activity). AF was initiated by an SPB in 72.4% non-TEA and 100% TEA treated patients, whereas changes in heart rate only were seen in 17.2% non-TEA patients.

The observed risk factors, SPB and cardioplegia, may both induce electrophysiological changes known to increase the susceptibility to AF. The observed postoperative atrial dilatation and autonomic imbalance, indicated by HRV and neuropeptide levels, may further favour the development of AF. The observation that a majority of postoperative AF was initiated by a premature atrial contraction supports our hypothesis that latent atrial foci may be a major trigger mechanism of postoperative AF.

Key words: Atrial fibrillation, catecholamines, coronary artery bypass surgery, heart rate variability, neuropeptides, premature atrial contraction, thoracic epidural anaesthesia.
LIST OF PAPERS

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


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ABBREVIATIONS

A = adrenaline
AF = atrial fibrillation
ANP = atrial natriuretic peptide
ANS = autonomic nervous system
AV = atrioventricular
bpm = beats per minute
CgA = chromagranin A
CgB = chromogranin B
CPB = cardiopulmonary bypass
CABG = coronary artery bypass grafting
ECG = electrocardiogram
HRV = heart rate variability
NA = noradrenaline
NPY = neuropeptide Y
PP = pancreatic polypeptide
SPB = supraventricular premature beat
SVT = supraventricular tachyarrhythmia
TEA = thoracic epidural anaesthesia
VPB = ventricular premature beat
INTRODUCTION

History
Postoperative AF was first described in 1943 as a complication after pneumonectomy [1]. After the first attempts of surgical correction of intracardiac defects in the early 1950s, it became evident that arrhythmias were one of the most common and dangerous complications. This was a serious clinical problem at that time, since heart surgery was performed without supportive systems such as CPB and direct current electroshock [2]. Furthermore, the antiarrhythmic treatment available was ineffective [2, 3]. Several studies were then published concerning the frequency of arrhythmias during and after cardiac surgery and their striking contribution to operative death [4]. These previously fatal problems then changed substantially due to the introduction of extracorporeal circulation in the late 1950s, surgical technique improvements, refinement in the anaesthesia, direct current shock availability, and finally, more effective pharmacological treatment [5]. Few studies were then published as the frequency and significance of arrhythmias during the postoperative period was regarded as rather unimportant [5]. In 1974 a study was published on arrhythmia complications after heart surgery [6]. This extensive study showed that arrhythmias were still frequent after cardiac surgery in spite of the improvements in the surgical procedures. Nearly half of the study group suffered from arrhythmias although intraoperatively occurring arrhythmias were also included. This was further confirmed by Taylor et al reporting a 19% incidence of AF after CABG [7].

Epidemiology
The reported incidence of postoperative AF varies between 5% and 40% during the first postoperative week [8]. These variations in the incidence of AF between patient populations are dependent on the patient populations studied, type of cardiac surgery used, the definition of the arrhythmia, the method used to detect the arrhythmia, and the duration of the observation period [9]. A meta-analysis of 24 controlled and randomised trials confirmed that in trials using 24-hour Holter ECG monitoring the incidence of SVT was higher with (41.3%) than in trials without (19.9%) Holter recordings [10]. Several studies to date have relied on frequency data derived from nurses’ observations of monitor screens and patients’ reports of symptoms when not using Holter monitoring [11].

After the introduction of new surgical techniques without extracorporeal circulation, such as off-pump surgery, early results reported an incidence of AF to be as low as 5% [12], which
is contradictory to other off-pump studies with the same incidence (30%) of AF as previously shown for CABG [13]. Moreover, a more recent study demonstrated, that postoperative AF occurred with similar frequencies irrespective of the method of revascularisation used, after adjusting for differences in baseline and perioperative variables [14]. Today AF is the most common postoperative arrhythmia and also the most frequent complication after open heart surgery despite the refinements in the surgical technique [8, 14].

Postoperative AF, while rarely fatal nowadays, is frequently associated with increased morbidity and discomfort for the patient with a two- to three-fold increased risk of stroke [15]. As postoperative AF may cause congestive heart failure, hypotension and provoke ischemia, treatment with antiarrhythmic drugs or electrical cardioversion is most often required [16]. Therefore, postoperative AF remains a clinical problem causing significant discomfort to the patient and prolonged hospitalisation, with considerable financial implications [15, 17].

**Pathophysiology**

The pathophysiological mechanisms of postoperative AF have been the subject of speculation for decades despite extensive investigations focusing on the identification of risk factors for the initiation of the arrhythmia. There are two major theories advanced concerning the mechanism of AF. These are advanced from investigations in canine and intraoperative human studies, namely re-entry involving one or more circuits, or enhanced automaticity in one or several rapidly depolarising foci [18]. Moe et al advanced the multiple wavelet hypothesis as the mechanism of reentrants AF, postulating that the persistence of AF depends on the average number of wavelets being present in the atria [19], which was later demonstrated in man [20, 21].

Electrophysiologic studies in canine and intraoperative human experiments have further shown that a non-uniform distribution of local atrial refractory periods ("dispersion in refractoriness"), is associated with increased susceptibility to AF [22]. Other studies in patients with paroxysmal AF have shown that prolonged episodes of rapid atrial activity per se induce shortening of the atrial refractory period [23], described as "AF begets AF". Areas with prolonged atrial conduction may also favour re-entry, and thus the initiation of AF, particularly in diseased hearts [24]. Rapidly firing atrial foci, located in the pulmonary veins, were more recently found to trigger AF in patients with paroxysmal AF [25]. Whether this type of focal AF represents a particular form of AF or a triggering arrhythmia is not clear.
Furthermore, in an early study utilised temporarily epicardial placed electrodes to record bipolar atrial electrograms during postoperative AF, AF could be divided into four types on the basis of the electrogram morphology, i.e. Wells’ classification [26]. It was further observed that one type of AF could change to another, in accordance to more recent studies in patients with paroxysmal AF [27]. Thus, the electrophysiologic properties of postoperative AF do not appear to be homogenous.

There are several pre-, intra- and postoperative conditions that per se could predispose to the development of postoperative AF.

**Preoperative risk factors**

Age has been suggested to be the most important independent risk factor in several studies [15, 17, 28]. This was confirmed in a multivariate logistic regression analysis, which studied 1,666 consecutive patients undergoing CABG. [29]. Postoperative AF has been reported in 30% of patients 70 years old or older [28]. Age-related structural changes in the atria could constitute an anatomic substrate that increases the susceptibility to postoperative AF [15] and a history of palpitations has been thought to reflect such atrial abnormalities that predispose to subsequent AF [30].

Both increased sympathetic and parasympathetic tone are known to shorten the atrial refractory period [31]. Advanced age has been associated with increased levels of circulating NA [32], which could indicate increased sympathetic outflow due to imbalance in the ANS, previously proposed to be related to the propensity for postoperative AF [33].

Increased P wave duration, consistent with left atrial enlargement or prolonged intra-atrial conduction defect, have been studied in an effort to predict postoperative AF [34-37]. Increased P wave duration, present in nearly half of the patients before surgery could, however, not be used to identify patients at risk for developing postoperative AF [34]. Another study identified preoperatively prolonged P wave duration to be a predictor of postoperative AF, although patients with antiarrhythmic drugs were included [37]. As definitions of P wave measurements have differed in several studies the need for standardised P wave measurement are important to make results comparable [34-37].

Other triggering factors related to the presence of cardiopulmonary diseases (Table 1), creating the necessary conditions for the development of postoperative AF [30, 33].
Table 1. Disorders associated with AF

- A clinical history of documented SVT
- Heart valve disease
- Cardiomyopathy
- Diabetes mellitus
- Chronic obstructive pulmonary disease
- Chronic renal disease
- Severe reduced ejection fraction
- Thyroid disorders

**Intraoperative risk factors**

The use of CPB may induce a systematic inflammatory response syndrome, which could be associated with increased risk for the development of postoperative AF [38, 39]. In a randomised double-blind study, inhibition of this inflammatory response with corticosteroids was aimed to reduce the incidence of postoperative AF after CABG [39]. Dexamethasone was given after induction of anaesthesia and before skin incision, but resulted in no significant reduction in the incidence of AF among treated patients.

It is well known that optimal myocardial preservation during cardioplegic arrest (during aortic cross-clamp) requires the maintenance of electromechanical arrest. Persistent atrial activity during cardioplegic arrest could be a marker of poor atrial protection and ischemia resulting in increased risk of postoperative AF. By monitoring bipolar atrial electrograms during the aortic cross-clamp period a significantly longer mean duration of atrial activity, suggesting poor atrial preservation, was found in the group with postoperative SVT compared to the group maintaining sinus rhythm, without correlation to the cross-clamp time [40]. Several intraoperative conditions such as prolonged atrial conduction immediately after the aortic cross-clamp period, ineffective cooling of the atria, type of cardioplegia used, the aortic cross-clamp time, and the CPB time have been associated with postoperative SVA [41]. However, a previous extensive study found no such relationship with postoperative AF and intraoperative variables [29].

Many of the intraoperative factors previously considered to be important in the initiation of postoperative AF have been related to CPB and myocardial preservation during the cross-clamp period. However, results from off-pump procedures, which do not require atrial
cannulation, CPB, or cardioplegic preservation, show the same incidence of postoperative AF compared to CABG [13, 14, 42]. These studies further emphasised the importance of the release of endogenous catecholamines after off-pump surgery and its relation to postoperative AF.

Postoperative risk factors

The observed imbalance in the ANS with elevated postoperative plasma NA levels developing after CABG was shown to be independently associated with postoperative AF [33]. In other studies, however, this postoperative release of catecholamine was not associated with AF [43]. Previous studies have also suggested a development of an impaired ANS after open heart surgery, as indicated by an abnormal variability in heart rate [44, 45]. However, the occurrence of or relation to postoperative AF was not addressed. The loss of excessive vagal tone and a moderate increase in sympathetic tone, according to changes in HRV before the onset of postoperative AF, was recently suggested to be important triggering factors [46]. It was further suggested that the variation rather than the autonomic tone, as such, was important before AF initiation. Therefore, the relative importance of the ANS with regard to the initiation of postoperative AF is still unclear.

A previous study showed that patients developing AF after CABG had more frequent atrial ectopies before the onset of AF compared to those not developing AF [44]. However, as some patients remaining in sinus rhythm also had very frequent atrial premature beats, they further suggested that the presence of atrial ectopies per se may not be causally related to the substrate for postoperative AF. Even though the presence of frequent atrial premature beats may be secondary to various factors occurring after cardiac surgery, such as sympathetic stress from the surgical trauma or heart failure, a temporal increase in the number of atrial premature beats may indicate a causal relationship to the initiation of AF. Another previous study reported an increased frequency of atrial premature beats 15 minutes prior to postoperative AF onset, although the proportion of patients with increased frequency of premature atrial contractions was not stated [46].

In summary, there are several pre-, intra- and postoperative factors that could predispose to the development of postoperative AF. Only increased age, however, has remained the most important independent risk factor in several studies [15, 17, 28].
Prophylactic treatment

Antiarrhythmic drugs

Several investigations have focused on the prevention of postoperative AF by reducing the induced intraoperative sympathetic activity by β-blockade. However, Engelman et al found no effect of postoperative β-blocking agents for the prevention AF [43]. Other studies demonstrated that the postoperative use of β-blocking agents was an effective preventive therapy for AF, with no relation to the preoperative use of the drug, although with a reduced efficacy in elderly patients (> 65 years) [29].

As β-blocking agents are frequently used in the treatment of coronary artery disease, many patients continue their ordinary medication until the operation. The general opinion that reinstitution of β-blocking agents decreases the incidence of postoperative SVT has been demonstrated in many studies [10, 11, 47-50]. Other studies have found a two- to fivefold increase in the incidence of AF in patients in whom β-blocker therapy was discontinued compared to patients whose drug treatment was continued postoperatively [11, 51]. It is the hypersensitivity in the atria, induced by the adrenergic stimulation after β-blocker withdrawal, that may induce postoperative SVT [52]. This rebound effect is more pronounced after 24 to 60 hours, when postoperative AF is most likely to occur [8]. Others did, however, not find this connection between the withdrawal of β-blocking agents and increased frequency of postoperative SVT [48, 50, 53]. Although β-blocking agents may cause a reduced incidence of postoperative SVT, there is no defined subset of patients who would benefit from such prophylactic therapy [53]. And still, 32% of patients treated with β-blocking agents develop AF after CABG compared to 43% in non-treated patients, i.e. treatment with β-blocking agents reduces the incidence of postoperative AF with only 25% [50, 54].

Low-dose sotalol, a β-blocking agent with additional class III effects (prolonging the atrial refractory period), has been shown to significantly reduce the incidence of SVT after CABG from 43% to 25% [49], in accordance to other studies [48, 50]. Strikingly, postoperative AF was the only rhythm disturbance observed in patients receiving sotalol [48, 50] and there was no significant reduction in either isolated atrial premature contraction or couplets/runs of supraventricular events by prophylactic low-dose sotalol [50]. Up to date no studies have documented an antiarrhythmic effect using low-dose sotalol. A more recent large study further demonstrated, that sotalol was not superior to atenolol in preventing AF after cardiac surgery [55]. In that study the treatment was initiated after surgery, as in several other studies. In an earlier study sotalol treatment was initiated in the morning before surgery [56] with a target dosage of 160 mg twice a day, it effectively reduced the incidence of postoperative AF...
with 65% compared to the control group, which however had their conventional β-blocking therapy reduced after surgery.

Oral amiodarone, another class III antiarrhythmic drug, was in a randomised double-blind study, shown to significantly lower the incidence of AF after heart surgery from 53% to 25% [57]. However, in that study both valvular heart surgery patients and CABG patients were included. A major limitation with amiodarone in the study was the seven-day preoperative treatment period, which also has been used by others emphasising the safety of low-dose intravenous amiodarone in in patients undergoing CABG [58]. Others using intraoperative amiodarone as a prophylactic therapy against AF after CABG, did not prevent new onset of AF even at high dosages [59]. Furthermore, amiodarone had no effect on the duration of hospitalisation due to a higher incidence of bradycardia requiring temporary pacing and due to later onset of AF.

Verapamil, a Ca\(^{2+}\)-inhibitor, which decreases AV nodal conduction and prolongs AV nodal refractoriness, has also been investigated regarding its prophylactic efficacy against postoperative AF. A randomised double-blind study showed no significant reduction of SVT after CABG in patients treated with verapamil compared to control patients [60]. Due to its adverse effects, especially hypotension, prophylactic treatment with verapamil was suggested to be a treatment that was probably worse than the disease itself. Another randomised double-blind study, investigating the pharmacokinetics of varapamil, found a significantly lower incidence of atrial arrhythmia after CABG in patients with certain verapamil level compared to control patients [61]. These authors concluded that the effect of verapamil therapy was dose-dependent without complicating side effects such as hypotension [61].

Digoxin, which has a vagal effect particularly on the AV node, has been used for decades to prevent AF after cardiac surgery. This prophylactic treatment was until recently generally accepted although previous studies suggested that it might predispose to instead of preventing the development of SVT in patients undergoing CABG [62]. This was confirmed more recently when digoxin was found to decrease the atrial effective refractory period and favour the occurrence of AF [63].

**Prophylactic atrial pacing**

Even though temporary epicardial wires have for many years been proposed for the diagnosis and treatment of atrial arrhythmias after cardiac surgery [64], their use coupled with continuous overdrive pacing to prevent AF after CABG has not been evaluated extensively. Postoperative biatrial synchronous pacing has previously not been successful in preventing
AF after cardiac surgery, primarily due to postoperative deterioration of atrial sensing and its profibrillatory effect [65]. Recently, Blommaert et al found that continuous atrial dynamic overdrive pacing significantly reduced the incidence of postoperative AF from 27% to 10%, without the adjunctive therapy of antiarrhythmic drugs [66]. In that study a specific algorithm was used, which reacted to atrial premature beats and allowed permanent stimulation of the atria just above the patient’s own rhythm. Another study showed that atrial pacing in conjunction with β-blockade, resulted in a significant reduction (55%) of the incidence of AF [67]. In that study, however, a significant proportion of patients with either left atrial or biatrial pacing were excluded due to high pacing thresholds or diaphragmatic stimulation, suggesting that further investigations are mandatory to determine the most effective anatomic pacing site.
AIMS OF THE STUDY

The aims of the investigation were, in CABG patients:

1. to identify pre-, intra- and postoperative predictors of postoperative AF, especially body weight/body mass index, total amount of cardioplegia, atrial areas, atrial peptides and the presence of SVA (paper I).

2. to evaluate in detail the autonomic balance and its role for the development of postoperative AF, by measuring HRV, catecholamines and certain neuropeptides (paper II).

3. to evaluate the effect of TEA on the incidence of postoperative AF, and to evaluate in detail, its effects on the ANS by measuring HRV, catecholamines and certain neuropeptides (paper III).

4. to evaluate the mode of onset of AF, the autonomic tone, and the presence and type of arrhythmias immediately prior to the initiation of postoperative AF, and to compare the findings in those patients treated with TEA (paper IV).
MATERIAL AND METHODS

Patients

A total of 141 patients undergoing elective CABG, during the period of October 1994 to May 1998, were included. In an effort to study postoperative AF in an otherwise healthy population, patients with anti-arrhythmic drug treatment (Class I and Class III antiarrhythmic drugs, digoxin, and verapamil) and patients with disorders that per se could result in changes in conduction and refractoriness, previously shown to be related to the propensity for AF, were not included (Table 1) [8, 30, 33]. These disorders may also be associated with conditions such as atrial wall stretch, ischemia, inflammation, or imbalance in the ANS that could change HRV [68]. Those patients with anticoagulation medication or with disorders that could put them at risk with TEA were also not included [68, 69].

The patients were randomly selected dependent on when the research nurse was on duty and on the availability of Holter recorders. Since the patients had Holter recordings for five days and echocardiographic examinations before and two days after surgery, the day of the operation could only be either a Monday or a Tuesday. During the period of the study approximately 3 000 patients underwent CABG in Uppsala.

The median age was 65.8 years (range 41.8 - 79.6 years). This rather low median age was probably due to the exclusion of patients with associated disorders as several of those are related to an advanced age.

Forty-five patients were randomly selected for TEA and general anaesthesia (TEA group) and the remaining 96 patients received general anaesthesia (non-TEA group).

In the TEA group, four patients were excluded, because TEA did not function or complications occurred that would interfere with the analysis, and because of a hormone-producing tumour detected in one patient during the hormonal analysis. In the control group, 16 patients were excluded due to different surgical procedures, complications that would interfere with the analysis, or severe postoperative anxiety making complete 24-hour Holter recordings impossible.

All studies were approved by the Ethics Committee of Uppsala University and informed consent was obtained from each patient.
Fig 1. The figure shows an SPB (arrow) at the onset of sustained AF from 24-hour Holter-ECG recordings.
Routine procedures before, during and after the operation

A standard 12-lead resting ECG, body weight, blood pressure, and laboratory tests including heart specific biochemical markers (aspartate aminotransferase, creatinine kinase-MB and troponin-t), blood status (hemoglobin, hematocrit and leukocytes), coagulation status (platelet count, antithrombin III, prothrombin complex, and activated partial thromboplastin time), sodium, potassium, and creatinine levels were all obtained pre- and postoperatively, according to the clinical routine. Body mass index (BMI) was calculated as the patient’s weight (kg)/height$^2$ (m$^2$). The left ventricular function was visually qualitatively assessed by the physician performing the preoperative left ventricular contrast angiography, and classified as normal or moderate reduced, as patients with severe dysfunction were not included.

The day of the operation was defined as day 0. The patients’ ordinary medical treatment, including β-blocking agents, was administrated until the morning of the operation and was reinstituted postoperatively, depending on the patients’ clinical status. The premedication used was morphine-scopalamine, and the anaesthesia was induced with intravenous fentanyl, thiopental, and pancuronium. After tracheal intubation, mechanical ventilation was started with oxygen and nitrogen, and anaesthesia was maintained with intermittent doses of fentanyl supplemented by isoflurane. In the TEA group, fentanyl was restricted to the dose given at the induction of the general anaesthesia.

CPB was established, after the patient was heparinised, by cannulation of the ascending aorta and the right atrium (double-stage, single cannula), moderate hemodilution (hematocrit, 20% to 26%), and moderate systemic hypothermia (30 to 32°C). Cold hyperkalemic crystalloid cardioplegia administered intermittently into the aortic root was used for myocardial protection. After the aorta was cross-clamped the cold cardioplegic infusion was begun promptly at a flow rate of 150ml • min$^{-1}$ • m$^{-2}$ for approximately three minutes, resulting in an average dose of about 600 to 700 ml, although more cardioplegia could be administered in the absence of sinus arrest. The distal anastomoses were then constructed during this single period of total aortic occlusion and the cardioplegic infusion was repeated with 100 ml between every single anastomose construction except after the last one, i.e. at the time for the removal of the total occluding clamp. The proximal anastomoses were constructed after removal of the total occluding clamp. The operative technique was consistent among the surgeons. Protamine sulfate, a heparin antagonist, was given after the removal of all cannulae in order to form a heparin-protamine complex obtaining haemostasis. Continuous infusion of propofol was used for postoperative sedation and discontinued slowly before extubation. Repeated doses of ketobemidion were used for postoperative analgesia. In
the TEA group all patients achieved sufficient pain relief with TEA as the only postoperative analgesia. All patients were monitored routinely with telemetry until the morning of day 3.

Definition of postoperative complications

Early death was defined as death from any cause within 30 days postoperatively, perioperative myocardial infarction as the development of new Q waves on the surface 12-lead ECG, and neurologic deficit as symptoms for 6 hours or longer and verified by computed tomography.

24-Hour Holter ECG

All patients underwent continuous 24-hour Holter monitoring starting 24 hours prior to the operation and then from the first postoperative morning for four consecutive days (i.e. 96 hours). The end-point was the first clinically documented episode of sustained AF. This long-term continuous assessment of heart rhythm was used for the detection of AF, analysis of arrhythmias and HRV.

A standard Del Mar Avionics three-channel tape recorder was used. Tapes and batteries were changed every 24-hours period to prevent any failures in the Holter recordings. The recorders were cleaned before use and controlled annually by the manufacturer. We used both new and old recorders and the Department of Biomedical Engineering also checked them before use at our hospital. All tapes were visually scanned, i.e. not scanned with the automatic dart mode, and analysed by an experienced technician. Before the visual scanning (for every single tape) the three different channels were calibrated preventing speed alterations by using an incorporated timing signal and a scanner that recognised and corrected for the timing signal. Artefact and ectopic beats were recognised and further analysed by the author.

Arrhythmia definitions and analysis

AF is an SVT characterised predominantly by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. On the three channel Holter tracings, AF was defined by an absence of consistent P waves before each QRS complex and an irregular ventricular rate. Sustained AF was defined as an episode ≥ 30 seconds, and was used as the end-point in accordance to other studies as non-sustained SVT (lasting less than 30 seconds) are of questionable clinical significance [11]. Occasionally, AF could be difficult to differ from atrial flutter as coarse fibrillation waves can mimic atrial flutter and as a rapid
ventricular response rate may be quite regular masking AF. No attempt was, however, made to differentiate atrial flutter from AF.

An SVT was defined as a narrow and regular or irregular QRS complex tachycardia with three or more consecutive beats with a heart rate above or equal to 100 bpm. Therefore a non-sustained SVT included, among other atrial tachycardias, also non-sustained AF. The other definitions used were in accordance to the Del Mar Model 563 StrataScan Holter Analysis System that was used in our study. An SPB was defined as a narrow QRS complex occurring with 20% prematurity or more and differentiated from sinus arrhythmia on the basis of P wave morphology, cyclic changes in preceding R-R intervals, or both. Bradycardia was defined as a three-interval heart rate less than 50 bpm. A VPB was defined as a broad QRS complex occurring with 20% prematurity or more.

The mode of onset of postoperative AF was studied with regard to presence of an early atrial contraction or a VPB at the onset of AF (paper IV). Although, the detection of early atrial contractions relied on analysis from Holter ECG tracings only, our access to three surface ECG leads (I, II, and III) displayed simultaneously our interpretations (Fig 1). Still, both Holter recordings and surface ECG tracings have inherent difficulties in visualising an SPB during rapid sinus rhythm or at AF onset with rapid ventricular rate, and in discriminating a P wave at the top of a T wave. Another limitation with Holter recordings is the difficulty to distinguish an SPB with aberration from a VPB.

Although intracardiac electrograms obtained through temporary epicardial leads would have been more reliable for the detection of early contraction at AF onset, it was not used for practical reasons and is not routinely used at our department. In an effort to make the results more reliable, the interpretations from two independent and experienced observers, blinded to different tracings of the AF onset from Holter recordings, were used.

The mode of AF onset (Fig 1) was further studied with regard to the presence of non-sustained SVT and changes in heart rate (HR) unrelated to premature beats (HR-8), during the very last 8 beats before the AF onset (paper IV). An increase/decrease in HR was arbitrary defined as present if the HR was 10 bpm above/below the mean HR (i.e. control rhythm) during the last 3 hours before AF onset. In order to assess changes with time, the mean HR was also analysed for each 1-hour period recorded during 3 hours before AF onset, each 15-minute period (recorded during the last hour before AF onset) and each 5-minute period (recorded during the last 30 minutes before AF onset) (paper IV).
The mean number of SPB and the number of episodes of SVT per hour were accordingly analysed for each 1-hour period (recorded during the 3 hours before AF onset), and compared with the corresponding time intervals from day 1 (paper IV).

In study I the following variables were analysed for each 24-hour period recorded: maximal number of SPB and VPB per minute, mean and maximal number of SPB and VPB per hour, the number of episodes of SVT and SVT with maximal bpm (SVT maximal rate).

In study III the following variables were analysed for each 24-hour period recorded: maximal number of SPB per minute, mean number of SPB per hour, the number of episodes of SVT and SVT maximal rate.

**HRV analysis**

The ANS serves mainly to regulate the functions of the internal organs, such as the cardiovascular system, mostly not part of voluntary control. The control mechanisms may be exerted either at the central nervous system level or at the periphery. The peripheral ANS is efferent (to the heart), but autonomic nerves often contain afferent fibers (from the heart) that subserve various reflex functions. Afferent fibers convey the stimuli from pain receptors, and from mechanoreceptors and chemoreceptors of the heart. The ANS provides the efferent fibers to convey the reflex response to such afferent information influencing the function of the heart.

The peripheral ANS consists of two divisions, the sympathetic and parasympathetic division, which are generally anatomically and functionally distinct. In most circumstances, there is tonic activity in both divisions of the ANS, and the net effect on the heart rate represents the balance between the two antagonistic effects. Clearly, the vagal influence is dominant at rest, but with increasing levels of exercise, it declines and the sympathetic influences dominate. Since changes in heart rate, i.e. heart rate variability, are autonomically mediated it reflects autonomic tone and could be determined during periods of ECG monitoring. Therefore, HRV measures the variability in the heart reflecting the ability of the ANS to modulate the heart rate [68]. The heart rate accelerates during inspiration and slows during expiration. The mechanism linking the variability of heart rate to respiration is complex and involves both central and reflex interactions.

Variations in heart rate can be assessed in the time or in the frequency domain. Instantaneous heart rate can be expressed as beats per minute, or more commonly, as a time between the successive heart beats in milliseconds.
There are two classes of time domain variables, those derived directly from the beat-to-beat intervals themselves and those based on the differences between adjacent cycles [68]. Beat-to-beat interval-based variables include mean heart period for the whole recording time, as well as standard deviation of the heart period or cycle length. The square root of mean squared differences of successive values within the time window is an example of the latter approach. In our study the following time domain components were calculated: the standard deviation (SD) of all normal R-R intervals of an entire 24-hour ECG recording (SDNN), the mean of the SD of all normal R-R intervals for all 5-minute segments of a 24-hour ECG recording (SDNN-index) and the square root of the mean of the sum of the squared differences between adjacent normal R-R intervals over the entire 24-hour ECG recording (RMSSD).

Frequency domain analysis, i.e. power spectrum analysis, breaks down a signal to its constituent frequency components and quantifies the variance or power of these components. For optimal reliability and reproducibility of the spectral analysis, the heart rate signals must be properly pre-processed as the values or samples in beat-to-beat cardiovascular time series are not spaced at equal distance in time. Most studies on spectral analysis of HRV make use of short data segments (three to five minutes long) derived from recordings obtained during ambulatory or standardised laboratory conditions. The method used in our spectral analysis with short data segments was based on auto-regressive modelling [70, 71]. A practical compromise has to be made between the length of the time series and the mathematical requirements of stationary. The auto-regressive modelling provides smooth and easily interpretable spectral shapes, and a straightforward decomposition of spectra in root components without the need for predefined spectral bands [68]. In our study, five minutes (300 seconds) epochs of data were re-sampled at 2 Hz, producing a memory of 600 points, using custom-made software. The linear trend was computed by the least-square method and was subtracted from the array of data before the spectral analysis. The calculation was performed in 5-minute segments using the moving average method described by Burg [70]. A number of power determinations are then possible. The total power, a frequency domain measure, is in theory mathematically identical to the variance, which is a time measure. The total power of the signal is represented by the total area under the power spectral curve, and the power of individual frequency components by the area under the portion of the curve related to each component. Determination of these areas permits quantification of total and component power, termed as absolute power.
In our study the power spectrum of frequency domain was divided into four different frequency bands: the total power (TP), 0.0033 - 0.40 Hz (ms²), the very low-frequency (VLF), 0.0033 - 0.04 Hz (ms²), the low-frequency (LF), 0.04 - 0.15 (ms²) and the high-frequency (HF), 0.15 - 0.40 Hz (ms²) [72].

In the neural regulation of circulatory function, the power of the HF component and the RMSSD, supposed to correspond to the HF component, were used in our study as markers of modulation of vagal efferent outflow [68]. The power of the LF component was used as a marker of both sympathetic and parasympathetic modulation [68]. Pagani et al, proposed that the instantaneous balance between sympathetic and vagal nerve activities can be captured by a single ratio, the LF/HF ratio, which was used in our study in order to mirror the sympathovagal balance [68, 73]. However, Eckberg [74] directed criticism to the use of the LF/HF ratio, mainly because spectral powers do not reflect absolute levels of autonomic nerve traffic, and the changes of sympathetic and vagal nerve activities do not always occur reciprocally. The problem of non-stationary of HR modulations of a certain frequency is often discussed with the long-term recording as well as the physiological mechanisms responsible for the LF and HF components that cannot be considered stationary during the 24-hour period. The spectral power will only be able to reflect parasympathetic and sympathetic activity when there is modulation of physiologic levels. For instance, during parasympathetic blockade or at maximal parasympathetic stimulation, there is no modulation of the vagal input to the heart, and the HF component in HRV disappears [68].

We used the HRV as a measure of the autonomic balance, and made comparisons before and after surgery in patients with and without postoperative AF (paper II and III). In an effort to prevent postoperative AF by sympathetic suppression using intra- and postoperative TEA treatment, we hypothesised that there will be no modulation of the sympathetic input to the heart assessed by HRV in those who were treated with TEA compared to those who were not (paper III).

In our study, the HRV was assessed by 24-hour Holter ECG recordings. Despite improvements in computer processing of tapes, human editing is required to detect mislabelled beats and artefacts. Statistics, most commonly markedly perturbed by artefacts and/or ectopic beats, measurements of HRV, attempt to exclude non-normal intervals from the analysis, i.e. intervals between ectopic beats and intervals inaccurately measured because of artefact. In order to make correct analysis of HRV, epochs > 4% of non-normal RR intervals were excluded from further analysis. The ECG signal was then digitised and stored using a commercially available PC-based system. The auto-regressive method was used for
analysing the frequency domain of the time series of R-R intervals [70]. Furthermore, to include a tape, a total of 18 hours, at least 60% of the daytime and 75% of the nighttime recordings had to be analysable [75].

In study II the following time domain and frequency domain measures were calculated: SDNN, SDNN-index, RMSSD, TP, VLF, LF, HF, and LF/HF ratio. The variables from the frequency and the time domain were analysed in 24-hour periods and also in day (7.30 - 21.30) and night (24.00 - 5.00), preoperatively and on day 1 and 2 postoperatively.

In study III only the frequency domain was analysed at the predefined time periods above.

In study IV the frequency domain components were analysed for a 2-hour period immediately before AF onset, each 15-minute period (recorded during the last hour before onset) and each 5-minute period (recorded during the last 30 minutes before onset). The HRV variables during the last 5 minutes were compared with those during the 2-hour period before AF onset. Furthermore, all of the HRV variables were compared to those from either daytime periods (7.30 - 21.30) or nighttime periods (24.00 - 5.00) on day 1, depending on the time of AF onset.

Thoracic epidural anaesthesia

The centres for the sympathetic division of the heart are situated in the upper thoracic regions (T1-T6) of the spinal cord [76]. The centres for the parasympathetic division of the heart are situated in the brain stem supplied by the vagus nerve. Both divisions of the peripheral ANS consist of preganglionic fibers, switching to postganglionic fibers in the ganglia.

Sympathetic postganglionic fibers innervate the entire heart, including the sinoatrial node, the AV conducting pathways, and the atrial and ventricular myocardium. Sympathetic activity results in increased heart rate and shortened duration of contraction [77]. The vagal nerves innervate the sinoatrial node, the AV conducting pathways, and the atrial muscle. Stimulation of the vagus nerves slows the heart and the AV conduction. Moreover, the adrenal medulla is a combination of ganglion and gland, with preganglionic sympathetic fibers (from T6 to L1-2) releasing A and NA into the systemic blood circulation, elicited via enhancement of sympathetic activity, such as pain, cold and heat.

There are several different intraoperative elements, such as median sternotomy and CPB, that can increase the sympathetic activity after CABG, which may explain the hypertension and sinus tachycardia seen during and after cardiac surgery [78, 79]. The most important triggers of this stress response are afferent neurogenic stimuli from the surgical area [79].
High TEA (T1-T5) used with general anaesthesia has been demonstrated to prevent this surgical stress response during CABG by the combination of an afferent nociceptive (sensory) blockade and an efferent blockade of cardiac sympathetic nerve fibers [76]. This type of anaesthesia was further shown to be effective by the improvement in haemodynamic stability and reduced cardiac NA spillover in TEA-treated patients. TEA itself has been shown to reduce A levels after CABG by partial blockade of the efferent and afferent nerve fibers of the adrenal glands (T6-L1-2) [78]. However, the effect of TEA on the incidence of AF was not studied in any of these studies. More recently, a retrospective study showed a significant decrease in new arrhythmias after CABG, in patients treated with TEA compared to those not treated [80]. There were several limitations in that study, as they included patients with preoperative arrhythmias, and those developing atrial flutter/fibrillation, conduction defects and ventricular arrhythmias. Therefore, the antiarrhythmic effect of TEA concerning the incidence of postoperative AF is still unclear.

If the increased sympathetic activity induced by the CABG promotes the initiation of AF, a blockade of this sympathetic outflow would then be expected to reduce the incidence of postoperative AF. Suppression of this increased sympathetic activity by postoperative β-blockade alone reduced the AF-incidence by 25% [54]. This rather poor prophylactic effect of β-blockade against AF observed in several studies, may be due to low plasma concentration, as β-blocking agents are usually administrated approximately three hours before the operation and reinsitituted on the first postoperative day [81]. It has previously been demonstrated that the plasma concentration of β-blocking agents, administrated in the morning before surgery, reached undetectable levels five to six hours later [81]. Therefore, the dosage of β-blocking agents administered intravenously postoperatively should probably be twice that given preoperatively, in order to have any effect on the sympathetic activity [82].

Anaesthesia is loss of sensation and analgesia is inability to feel pain while conscious. It is well known that spinal opioids often provide excellent analgesia without demonstrable motor, sensory or autonomic blockade. Greitz et al demonstrated a model where the cerebrospinal fluid circulation is driven by a pulsative flow that causes effective mixing of the cerebrospinal fluid (CSF) [83]. Opioids are not homogeneously spread throughout the CSF, and it was suggested that enhanced availability of the opioid sufentanil in the CSF was related to the local anaesthetic bupivacaine [84]. In our study we used the combination of bupivacaine and sufentanil as postoperative pain relief, which was insufficient when local anaesthetics was administered alone epidurally [85]. Furthermore, the analgesic efficacy of thoracic epidural sufentanil is enhanced with diminished frequency of sedation when combined with
bupivacaine, compared to sufentanil alone [86]. Therefore, TEA with the combination of local anaesthesia and opioids, with an extension from at least T1 to T8 of the blockade, were used to diminish the sympathetic activity induced by the surgery and postoperative pain in our study.

On the day before surgery, a Portex® 16 G epidural catheter was inserted through a Tuohy needle at the T3 to T5 interstitium. In an effort to avoid complications such as epidural hematoma due to the catheter, this procedure was performed at least 12 hours before the operation. This anaesthetic technique has a potential risk of epidural hematoma, which may occur in patients treated with aspirin who will be fully heparinised during coronary surgery due to CPB [87]. They further concluded that following certain guidelines, as with all other therapeutic interventions, the risk of epidural hematoma was not increased.

The epidural analgesia was induced with 8-14 ml of bupivacaine 5mg/ml. An extension from at least T1-T8 was accepted including the sympathetic centre of the heart (T1-T6) and partial blockade of the efferent and afferent nerve fibers of the adrenal medulla (T6 to L1-2). The effect of the block was tested by the ability to discriminate cold bilaterally at the midclavicular line after 30 to 40 minutes. The blockade was maintained with bupivacaine 5mg/ml, with an infusion rate of 4-8ml/h, supplemented by isoflurane during surgery. After the patients arrived at the intensive care unit, the concentration of bupivacaine was reduced (2mg/ml) and further supplemented by sufentanil (1µm/ml) epidurally (3-7ml/h). From then on, analgesia was achieved by a continuous infusion of bupivacaine and sufentanil epidurally until the end of the study, i.e. 96 hours after surgery, or until clinically sustained AF. All our patients were declared to have sufficient pain relief using TEA as the only analgesia postoperatively.

If postoperative AF was related to an increased sympathetic activity, we hypothesised that TEA treatment, as β-blocking agents, would reduce the incidence of AF. However, it has previously been proposed that TEA has a vagotonic effect on the cardiac ANS according to HRV analysis, since the TEA effect was shown to be attenuated by atropine [88], we further evaluated its effects on the ANS.

Analysis of catecholamines and neuropeptides

The autonomic balance and the level of postoperative sympathetic and parasympathetic activity were evaluated by determining plasma levels of catecholamines and certain neuropeptides.
Specific physiologic changes are followed by a local production of metabolites. The sympathetic nerves stimulate the heart with the primary postganglionic transmitter NA. The parasympathetic division of the heart is supplied by the vagus nerve that generally has the opposite effect to sympathetic stimulation with the primary postganglionic transmitter acetylcholine. The adrenal medulla releases catecholamines, A and NA, into the systemic blood circulation in response to sympathetic activity, such as pain. The adrenal medullary catecholamines are released directly into the blood, to act as hormones, whereas only a small proportion of the NA released from the sympathetic nerves ends up in the plasma [89].

After the introduction of high-performance liquid chromatographic (HPLC) methods, plasma cathecholamine concentrations, as a measure of sympathetic activity, became more frequent used. However, the plasma concentration of NA is determined by the clearance from the circulation in addition to the rate of release into the circulation of NA [90]. The total amount of NA entering the plasma further represents a balance between NA release into and NA re-uptake from the synaptic cleft. It is very difficult to quantify NA release from synaptic neurons but the total rate of entry of NA into the circulation (i.e. NA spillover) and the NA clearance rate can be determined by isotop dilution technique. However, plasma NA levels have been shown to correlate strongly with cardiac NA spillover, despite normal production and plasma clearance of NA, within relatively homogeneous population groups like ours [32, 33], and are useful to identify extensive changes [89] in sympathetic activity, such as that induced by CABG.

We therefore also measured plasma levels of catecholamines to investigate the autonomic balance pre- and postoperatively and if there were any differences between those patients developing AF and those remaining in sinus rhythm (paper II and III).

The sympathetic nervous system can further be activated in a discrete manner resulting in regional differences in NA release, such as an increased sympathetic outflow due to skeletal muscle activity, with local spillover of NA into the venous drainage [89]. In an effort to reduce any iatrogenic stimuli of the ANS, all measurements of catecholamines were taken during sinus rhythm in the morning at rest. As TEA included the centres for the sympathetic division of the heart (T1-T6) and partly the sympathetic fibers of the adrenal medulla (T6 to L1-2), the treatment was expected to reduce the plasma NA level and partly reduce the plasma A level compared to non-TEA patients.

Measuring plasma catecholamine levels alone to assess sympathetic activity is not as accurate as isotop dilution technique, which however, was not used in our study. Other compounds of importance, released with the above-mentioned transmitters, include certain
neuropeptides. To further investigate the level of sympathetic activity, we therefore measured the plasma levels of certain neuropeptides (NPY, CgA and CgB). NPY is released along with NA from sympathetic nerve endings during intense sympathetic stimulation [91]. Beside its direct effects through its own receptors, NPY has cumulative effects on the response of catecholamines to sympathetic activity reducing the cardiac response to vagal activity [92]. Other neuropeptides that are closely connected with NPY, such as CgA and CgB, also reflect a rather strong sympathetic activity. If CABG induces a strong sympathetic activity, followed by increase in neuropeptides levels, they were supposed to remain unchanged postoperatively by TEA treatment.

There are to date no reliable methods for studying acetylcholine release in vivo as it is hydrolysed too rapidly in the vicinity of the synaptic cleft [89]. Therefore, in order to evaluate the parasympathetic activity we measured the plasma level of neuropeptide PP, which is released by stimulation of the vagus nerve, [93]. However, there is also a rapid post-prandial release of PP levels suggesting other control mechanism than the vagus nerve alone [93]. The plasma PP levels were therefore measured in the morning during rest and sinus rhythm to avoid any other stimuli.

Blood samples were taken during sinus rhythm preoperatively, day 1 and 2 in the morning at rest and collected from a cubital vessel in heparin-containing tubes placed on ice until the analysis of NPY, CgA, CgB and PP (paper II and III). The neuropeptides were measured by competitive radioimmunoassays [94-96] and the plasma levels of NA and A at the routine clinical chemistry laboratory using HPLC-techniques.

Echocardiography and analysis of atrial peptides

Atrial wall stretch could result in changes in conduction, previously shown to be related to the propensity for AF [30]. This stretch or dilatation of the atrial wall could be induced by increased atrial pressure or volume overload. In the early postoperative period patients usually increase their body weight, due to the fluid received intra- and postoperatively. To evaluate any postoperative change in atrial areas and its relation to the incidence of postoperative AF, we measured atrial areas at rest preoperatively and on the second postoperative day (paper 1).

Maximal right and left atrial cavity areas were obtained by two-dimensional echocardiographic examinations using planimetry in the apical four-chamber view at the end of systole, defined as the last frame prior to mitral valve opening. All recordings were made during sinus rhythm. Echocardiographic examinations were made by one experienced
technician using a Hewlett-Packard Sonos 1500 or 2500 cardiac ultrasound unit (Hewlett-Packard, Andover, MA), while measurements were performed together with the undersigned.

The results were recorded on VHS videotapes. A 2.5-MHz transducer was used for most of the examinations. Absolute values and values corrected for body surface area, using the Boyd formula, were calculated.

Atrial wall stretch results in atrial secretion of ANP and N-terminal proANP, mainly synthesised in myocytes of the atria [97]. The plasma concentration of ANP could thus be a marker of increased atrial pressure or volume overload postoperatively. Previous observations from canine studies raised the possibility that ANP also acts as a neuromodulator and/or neurotransmitter with effects on the ANS [98]. ANP is further synthesised by the conduction system cells suggesting that ANP also may modulate the electrophysiologic properties of the heart. A recent study observed that infusion of ANP in dogs might give rise to a shortening of the atrial refractory period [99]. Therefore, we also measured plasma levels of atrial peptides during rest and sinus rhythm pre- and postoperatively at day 2, and analysed a possible relation to postoperative AF (paper I). As N-terminal proANP is easy to measure, it was also evaluated in our study.

Blood samples were taken at the same time for the echocardiographic examination and collected from a cubital vessel. ANP in plasma was measured by a commercial radioimmunoassay (RPA512; Amersham, United Kingdom). N-terminal pro-ANP was measured by a two-site Delfia immunoassay. The method is described in detail elsewhere [100].

Statistical Analysis and Power calculation

A large number of significance statistical tests were performed in our study, which could increase the chance of making a type I error (a ‘false positive’ result) which is a problem of mass significance. Several methods have been proposed to deal with this problem such as the Bonferroni method. For large numbers of comparisons its use is highly conservative and one should be aware of the problem of mass significance and interpret the results with some caution regarding variables observed with not very strong significance.

A power calculation was included, in order to obtain the necessary sample size for our study, to have a high probability of finding a true effect of TEA treatment on the incidence of postoperative AF. The power analysis was made before the study began. The prior assumptions were an incidence ratio of 0.35 of postoperative AF without TEA treatment and an improvement of 50% - i.e. to 0.175, with TEA treatment. The rather unrealistic number of
79 patients required in each group, when the power goal was set to 80%, led to the decision to lower the required power to 70%. In other words, 59 patients in each group was sufficient, or e.g. 46 and 92 if groups were unequal. In our case, with a target of 45 and 96 patients, with and without TEA treatment, the power was about 71%.

It is highly desirable that the groups of patients receiving the different treatments are very similar and in most studies it is important that the age distribution of the groups is similar, as in our study, because prognosis is very often related to age. The most widely used method of unbiased treatment allocation, i.e. to ensure that the allocation of treatments to patients is independent of the characteristics of the patients, is to use random allocation to determine which treatment each patient gets. At the start of our study we had intended to randomly select the patients. However, due to changes in our clinical routines and limited access to full time anaesthesiologist, we had to abandon the randomly selection technique after the first 100 patients, in order to finish the study in time.

All data were collected and analysed in a statistical program (STATISTICA 5.5, Stat Soft, Inc., Tulsa, USA) and continuous variables are presented as mean values ± one standard deviation (SD). The associations of all pre-, intra-, and postoperative factors with postoperative AF were analysed using an unpaired t test and \( \chi^2 \) test, as required. Non-normal values were logarithmically transformed before analysis. Double-checking was done using the non-parametric Mann-Whitney U test. The significance of dichotomous variables was tested with Fisher’s exact method. Analysis of variance (ANOVA) for repeated measures was performed to test statistical differences.

Logistic regression was used when the dependent variable was dichotomous and represented an event or a presence/absence relation. Such an event or relation has a probability of occurrence that can also be stated as odds. The probability of the event, \( p \), has the following relation to the concept of odds: odds (event) = \( p/(1-p) \). However, to get a linear relationship between the dependent variable, the event, and the predictors, we have to take the natural log of the odds. Our model then becomes: \( \ln[p/(1-p)] = b_0 + b_1X_1 + \ldots + b_kX_k \). This can easily be rewritten as \( p = 1/(1 + e^{-Z}) \), where \( Z \) is the linear combination of all the predictors: \( Z = b_0 + b_1X_1 + \ldots + b_kX_k \). Values of \( p \) less than 0.05 were considered significant. Discriminant analysis was also used but had some limitations because some of the variables were dichotomous and not suitable as predictors.
RESULTS

Demographics

Postoperative sustained AF occurred with equal frequency, 36.3% (29 patients) in the non-TEA group compared to 31.7% (13 patients) in the TEA group. Thirty-eight patients had clinically recognised AF and were converted by sotalol, whereas four patients were diagnosed by Holter recordings and ended spontaneously within 7 to 562 minutes. There was no diurnal pattern of AF onset (Fig 2). There were no significantly differences in the time of AF onset between TEA treated patients compared to non-TEA patients postoperatively. The extension of TEA did not differ significantly between patients developing AF and those maintaining sinus rhythm (mean extension T1-T11 in both patient groups). The patients’ demographics, surgical, and postoperative data are summarised in Table 2 and 3.

There were no early deaths, and no patient developed perioperative myocardial infarction. No patient required postoperative pacing. One patient in the TEA group suffered perioperative cerebral embolisation, verified by computer tomography and the sequela resolved before discharge.

Patients who developed postoperative AF had lower BMI \( p=0.02 \), received less cardioplegia \( p=0.006 \), and were taken off β-blocking agents more frequently postoperatively \( p=0.001 \) than those maintaining sinus rhythm (paper I) (Table 2).

![Fig 2](image-url). The figure shows the time of AF onset in non-TEA (filled circles) and TEA (unfilled circles) patients.
Table 2. Demographic, surgical and postoperative data\(^a\) in non-TEA patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sinus Rhythm (n = 51)</th>
<th>Atrial Fibrillation (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>65.8 ± 7.8</td>
<td>65.7 ± 7.4</td>
</tr>
<tr>
<td>Male (n)</td>
<td>44 (86%)</td>
<td>23 (79%)</td>
</tr>
<tr>
<td>Duration of angina pectoris (y)</td>
<td>4.0 ± 4.7</td>
<td>4.3 ± 4.1</td>
</tr>
<tr>
<td>Canadian Class</td>
<td>2.5 ± 0.8</td>
<td>2.4 ± 0.6</td>
</tr>
<tr>
<td>NYHA</td>
<td>3.0 ± 0.2</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>No. of previous myocardial infarction</td>
<td>19 (37%)</td>
<td>12 (41%)</td>
</tr>
<tr>
<td>LV function (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>40 (78%)</td>
<td>25 (86%)</td>
</tr>
<tr>
<td>Moderate dysfunction</td>
<td>11 (22%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Family history of CAD (n)</td>
<td>29 (57%)</td>
<td>15 (52%)</td>
</tr>
<tr>
<td>No. of vessels disease (n)</td>
<td>2.7 ± 0.5</td>
<td>2.7 ± 0.6</td>
</tr>
<tr>
<td>Left main disease (n)</td>
<td>12 (24%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Preoperative use of β-blockers (n)</td>
<td>42 (82%)</td>
<td>24 (83%)</td>
</tr>
<tr>
<td>Systemic hypertension (n)</td>
<td>17 (33%)</td>
<td>9 (31%)</td>
</tr>
<tr>
<td>Smoking (n)</td>
<td>27 (53%)</td>
<td>17 (59%)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>27.6 ± 3.8</td>
<td>25.6 ± 3.4*</td>
</tr>
<tr>
<td>Left internal-thoracic-artery grafts (n)</td>
<td>48 (94%)</td>
<td>29 (100%)</td>
</tr>
<tr>
<td>Sapheneous-vein grafts (n)</td>
<td>37/38 (97%)</td>
<td>18/21 (86%)</td>
</tr>
<tr>
<td>Distal anastomoses (n)</td>
<td>3.6 ± 0.7</td>
<td>3.4 ± 1.0</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>44 ± 13</td>
<td>40 ± 13</td>
</tr>
<tr>
<td>Bypass time (min)</td>
<td>82 ± 20</td>
<td>76 ± 22</td>
</tr>
<tr>
<td>Total amount of cold cardioplegia (mL)</td>
<td>957 ± 146</td>
<td>866 ± 119*</td>
</tr>
<tr>
<td>Time for extubation (h)</td>
<td>6.5 ± 2.6</td>
<td>7.0 ± 3.6</td>
</tr>
<tr>
<td>External drainage &gt; Day 1 (n)</td>
<td>10 (20%)</td>
<td>11 (38%)</td>
</tr>
<tr>
<td>Postoperative continuation of β-blockers</td>
<td>39/42 (93%)</td>
<td>15/24 (63%)*</td>
</tr>
</tbody>
</table>

\(^a\) Data are shown as mean ± standard deviation. * \(p < 0.05\)

BMI = body mass index; CAD = coronary artery disease; Distal anastomoses = number of distal anastomoses per patient; h = hour; LV = left ventricular; min = minute; mL = milliliter; n = number of patients; NYHA = New York Heart Association functional class; Sapheneous-vein grafts = graft to right coronary artery; y = years.
Table 3. Demographic, surgical and postoperative data\(^a\) in TEA patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sinus Rhythm (n = 28)</th>
<th>Atrial Fibrillation (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>64.3 ± 8.4</td>
<td>64.5 ± 6.1</td>
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<tr>
<td>Male (n)</td>
<td>22 (79%)</td>
<td>13 (100%)</td>
</tr>
<tr>
<td>Duration of angina pectoris (y)</td>
<td>3.1 ± 3.5</td>
<td>4.3 ± 4.5</td>
</tr>
<tr>
<td>Canadian Class</td>
<td>2.3 ± 0.9</td>
<td>2.4 ± 0.7</td>
</tr>
<tr>
<td>NYHA</td>
<td>2.8 ± 0.5</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>No. of previous myocardial infarction</td>
<td>12 (43%)</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>LV function (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>20 (71%)</td>
<td>8 (62%)</td>
</tr>
<tr>
<td>Moderate dysfunction</td>
<td>8 (29%)</td>
<td>5 (38%)</td>
</tr>
<tr>
<td>Family history of CAD (n)</td>
<td>11 (39%)</td>
<td>7 (54%)</td>
</tr>
<tr>
<td>No. of vessels disease (n)</td>
<td>2.7 ± 0.5</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>Left main disease (n)</td>
<td>1 (3.6%)</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Preoperative use of β-blockers (n)</td>
<td>23 (82%)</td>
<td>12 (92%)</td>
</tr>
<tr>
<td>Systemic hypertension (n)</td>
<td>12 (43%)</td>
<td>5 (38%)</td>
</tr>
<tr>
<td>Smoking (n)</td>
<td>2 (7.1%)</td>
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</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>26.4 ± 2.7</td>
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<tr>
<td>Left internal-thoracic-artery grafts (n)</td>
<td>27 (96%)</td>
<td>12 (92%)</td>
</tr>
<tr>
<td>Sapheneous-vein grafts (n)</td>
<td>22/23 (96%)</td>
<td>11/13 (85%)</td>
</tr>
<tr>
<td>Distal anastomoses (n)</td>
<td>3.6 ± 0.8</td>
<td>3.8 ± 1.0</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>47 ± 14</td>
<td>45 ± 16</td>
</tr>
<tr>
<td>Bypass time (min)</td>
<td>87 ± 23</td>
<td>87 ± 24</td>
</tr>
<tr>
<td>Total amount of cold cardioplegia (mL)</td>
<td>996 ± 235</td>
<td>1078 ± 278</td>
</tr>
<tr>
<td>Time for extubation (h)</td>
<td>5.0 ± 1.5</td>
<td>5.0 ± 1.9</td>
</tr>
<tr>
<td>External drainage &gt; Day 1 (n)</td>
<td>3 (11%)</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Postoperative continuation of β-blockers</td>
<td>16/23 (70%)</td>
<td>6/12 (50%)</td>
</tr>
</tbody>
</table>

\(^a\) Data are shown as mean ± standard deviation. * \(p < 0.05\)

BMI = body mass index; CAD = coronary artery disease; Distal anastomoses = number of distal anastomoses per patient; h = hour; LV = left ventricular; min = minute; mL = milliliter; n = number of patients; NYHA = New York Heart Association functional class; Sapheneous-vein grafts = graft to right coronary artery; y = years.
Arrhythmias

In study I significantly more (70%) patients with postoperative AF had non-sustained SVT runs recorded preoperatively compared to (45%) patients remaining in sinus rhythm ($p=0.03$). Before surgery, the maximum SPB per minute ($p=0.02$) and the recorded non-sustained SVT maximum rate ($p=0.02$) were significantly higher in patients developing postoperative AF compared to patients maintaining sinus rhythm. After surgery, patients developing AF had significantly more SPBs than patients remaining in sinus rhythm.

In study III the mean heart rate significantly increased in the TEA group and control group postoperatively ($p<0.001$), but the increase was significantly less in the TEA group than in the control group ($p<0.001$). After surgery, among patients developing AF, the maximal SPB per minute remained unchanged in the TEA-treated patients but increased significantly in the untreated group ($p=0.01$). Furthermore, the maximal rate during postoperative SVT, among patients developing AF, was significantly lower in the TEA group than in the control group ($p=0.02$).

In study IV in non-TEA patients, the mean HR measured for one hour at hourly intervals 3 hours before AF onset did not differ significantly from that measured on day 1 (Fig 3). Neither was there a difference in mean HR during the 15-minute and 5-minute periods in the last hour before AF onset compared to day 1. During the last 8 beats before AF onset, however, there was an increase in mean HR, which reached significance for the daytime ($97.1 \pm 17.9$ vs $87.6 \pm 10.4$ bpm, $p=0.04$) and the nighttime ($99.8 \pm 18.8$ vs $79.4 \pm 8.9$ bpm, $p=0.02$), respectively. In TEA patients the mean HR did not change significantly during the corresponding time periods above.

The presence of $\geq 10$ SPBs during the last hour before AF onset was observed in 17 (58.6%) non-TEA patients compared to 4 (30.8%) TEA patients ($p=0.10$). The number of SPBs during the predefined time periods before AF onset did not differ significantly from those during comparable time periods at day 1, nor was there any difference between non-TEA patients and TEA patients. However, a more detailed analysis showed that among patients with their onset during the night, non-TEA patients tended to have more SPBs compared to TEA-treated patients ($p=0.06$). Analysis of variance (ANOVA) could not demonstrate that the uneven reinstitution of $\beta$-blocking agent postoperatively in the two patient groups had any effect on the outcome.

Non-sustained SVTs were present during the last hour before AF onset in 48.3% of non-TEA patients and in 23.1% of TEA treated patients ($p=0.13$). Moreover, the number of non-sustained SVTs during the predefined time periods corresponding to the ones above did not
differ significantly between non-TEA patients and TEA patients. No patients had SVT-8 before AF onset.

**Fig. 3.** This figure shows the mean HR distribution of the predefined time intervals, i.e. from day 1 until the onset of sustained AF. Among patients with their AF onset during the daytime, the mean HR was significantly higher in non-TEA (filled circles) than in TEA (unfilled circles) patients at day 1 and also during all the time periods stated in the text, including the first 8 beats of sustained AF (p<0.04). A corresponding comparison of mean HR between non-TEA and TEA patients with their onset at nighttime, however, showed no significant difference in HR during the same time periods.

**Mode of onset of atrial fibrillation (Fig 4)**

In **study IV** an SPB onset was seen in 21/29 patients (72.4%) and a VPB onset in 3 patients (10.3%). Twelve patients (41.4%) had a mixed pattern, thus an SPB onset was combined with an increase (9 patients) or a decrease (1 patient) in HR-8 preceding AF onset, and a VPB onset was combined with an increase (1 patient) or a decrease (1 patient) in HR-8 before AF onset. There were only 5 (17.2%) patients with either increased/decreased or unchanged HR-8 before AF onset, as the only finding.

In non-TEA group, an SPB onset was seen in 12 patients (100%) in whom the recordings permitted such an analysis. The patient with too many artefacts for an analysis of SPB onset showed an increase in HR-8 before AF onset. Furthermore, 3 of these 12 patients (25.0%) had a mixed pattern (SPB onset combined with an increase in HR-8 preceding AF onset).
Fig 4. The figure shows the distribution of mode of AF onset in non-TEA (filled bars) and TEA (unfilled bars) patients. The majority of patients, 33/41 (80.5%), had an SPB onset. The proportion of patients with an HR-8 increase preceding AF onset was larger in the untreated group, although the difference did not reach statistical significance.

Heart rate variability

In study II, preoperatively, when 24-hour recordings were divided into day and night, the parasympathetic HRV components were higher ($p<0.04$) and the LF/HF ratio was lower ($p<0.01$) at night versus in the daytime in patients maintaining sinus rhythm compared to patients developing AF. This difference between day and night (circadian variation) could not be demonstrated preoperatively in patients developing postoperative AF.

After surgery, all patients’ HRV components decreased significantly compared to preoperative measurements ($p<0.001$) and all these variables remained significantly low throughout the study time, with no significantly difference between the two patient groups.

In study III all the HRV components decreased significantly in both the TEA and the control group after surgery ($p<0.001$) with less decrease of parasympathetic components in the TEA group compared to the control group ($p<0.001$) (Fig 5). The postoperative decrease was less in the parasympathetic HRV components during the day- and nighttime in the TEA group compared to the control group ($p<0.001$).

In study IV the frequency domain variables analysed during the 2-hour period and those analysed for 5-minute periods during the last 30 minutes before AF onset did not differ significantly from those analysed during the corresponding day- and nighttime at day 1 in both patient groups. Neither did these variables differ between the two patient groups. The
individual HF component and LF/HF ratio measured the last 5-minute period before AF onset showed no consistent pattern (Fig 6).

**Fig 5.** The figure shows less decrease of parasympathetic components in the TEA group (filled circles) compared to the control group (unfilled circles).

**Fig 6.** The figure shows the individual HF components measured before AF onset without consistent pattern.
Neuropeptides and catecholamines

In study II plasma PP levels, significantly decreased postoperatively compared to preoperative values in both patient groups \((p<0.01)\) but the levels of other neuropeptides remained unchanged after surgery compared to preoperative values. Both NA and A increased significantly postoperatively compared to preoperative values in patients maintaining sinus rhythm \((p<0.02)\), whereas the postoperative increase in NA levels did not reach statistical significance and only A levels increased significantly in patients developing sustained AF \((p<0.01)\). Neither NA nor A differed significantly between the two patient groups pre- and postoperatively. Moreover, PP levels were significantly higher on day 1 in patients developing postoperative AF compared to patients maintaining in sinus rhythm \((p=0.02)\).

In study III the TEA treatment resulted in a significant decrease in NPY postoperatively \((p<0.001)\), while those in patients remained unaffected. However, the CGA and CGB levels remained unchanged postoperatively in both patient groups. Furthermore, an increase of NA was suppressed by TEA postoperatively, so that NA remained unchanged in the TEA group but increased significantly in the control group \((p<0.01)\). The significant increase in A seen postoperatively in both patient groups was significantly lower in the TEA-treated patients compared to the untreated patients \((p<0.02)\).

Echocardiographic examinations and atrial peptides

Both right atrial areas and atrial peptides increased significantly after the operation compared to preoperative values in both patient groups \((p<0.01)\) (paper I). Neither atrial diastolic areas nor atrial peptides differed significantly between patients developing postoperative AF and patients remaining in sinus rhythm. After surgery, left atrial areas remained unchanged in the postoperative AF group but increased significantly in the sinus rhythm group compared to preoperative values \((p=0.4\) and \(p<0.01\), respectively).

Logistic Regression

In study I, presence of AF was considered the dependent variable, and three variables were found to be predictors, including BMI, total amount of cardioplegia, and maximum SPB per minute. The model obtained had a likelihood ratio \(^2\chi\) statistic of 18.64, which, with four degrees of freedom, gave a \(p\) value of 0.00032. The classification table shows that 88% of patients without AF were classified correctly, and the model correctly classified 51.72% of the patients with AF. The overall odds ratio was 7.86, and the overall classification rate was 74.68%, which is substantially greater than the naive classification rate, which was 42.29%. If
a test statistic $Z$ is calculated, a $p$ value less than 0.001 is obtained, which also serves to consolidate the foundation on which the classification rests (Table 4).

### Table 4. Multiple logistic regression analysis; predictors of postoperative sustained AF.

<table>
<thead>
<tr>
<th>Variables</th>
<th>$\beta$</th>
<th>OR</th>
<th>95% CI</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>-0.140</td>
<td>0.870</td>
<td>0.737 - 1.026</td>
<td>0.096</td>
</tr>
<tr>
<td>Total amount of cardioplegia</td>
<td>-0.006</td>
<td>0.994</td>
<td>0.990 - 0.999</td>
<td>0.012</td>
</tr>
<tr>
<td>Max SPB/min</td>
<td>0.154</td>
<td>1.167</td>
<td>1.024 - 1.329</td>
<td>0.021</td>
</tr>
</tbody>
</table>

OR = odds ratio; CI = confidence interval.

In **study II**, in order to use the above findings as an instrument for prediction of AF, only the variables BMI and maximum SPB per minute, which were both measured before surgery, were applied. This model had a likelihood ratio $\chi^2$ statistic of 10.70, which gave a $p$ value of 0.0047. From the classification table, the following results were obtained: 90.00% of cases without AF were correctly classified, but those suffering from AF were only classified correctly to a degree of 31.03%. The odds ratio was 4.05 and the overall classification rate became 68.30%. When the difference between ln LF/HF in the daytime and ln LF/HF at night, measured before surgery, was also included in the model, the likelihood ratio $\chi^2$ statistic turned out slightly less, with a value of 8.16, which gives a $p$ value of 0.04. The classification table improved somewhat, being correct in 92.10% of cases without AF being correctly allocated to that group, while AF patients were now classified correctly in 31.80% of the cases. The odds ratio was now 5.44 and the overall classification rate was 70.00%.

In **study III**, a logistic regression analysis was made with the presence/absence of TEA treatment as the dependent variable. A set consisting of mean heart rate, SPB, SVT maximum rate, NA, A, NPY, and HRV components was used as independent variables. One independent variable remained, i.e. mean heart rate on day 1. This result was obtained regardless of whether a forward or backward method was selected, with a $p$ level <0.01. The effect of sinus rhythm/AF did not have any influence whatsoever.
DISCUSSION

The incidence of AF after CABG at the University Hospital in Uppsala, Sweden, is in accordance to the previously reported incidence of postoperative AF [8, 14]. This study identified pre-, intra- and postoperative factors which could all predispose to the development of postoperative AF.

The patients developing postoperative AF had more frequent premature atrial contractions and diminished circadian variation in HRV before surgery, than those remaining in sinus rhythm, which may be consistent with increased sympathetic activity. However, neither NA nor A differed significantly between the two patient groups pre- and postoperatively. This was also an unexpected preoperative finding in otherwise healthy patients undergoing CABG, since patients with known clinical arrhythmias were excluded in our study.

An increased sympathetic activity has previously been demonstrated among elderly patients [32], which may at least partly explain the increased incidence of AF in elderly patients. Furthermore, several previous studies have reported age as an independent risk factor for developing postoperative AF [15, 17, 28]. In our study, age was not associated with an increased incidence of postoperative AF, most likely because of the narrow age span among the patients included. Moreover, several disorders associated with an increased risk for AF were excluded in our study. These disorders are also related to age, which was probably another possible explanation for the lower distribution in our study.

The observed reduced total amount of cardioplegia received among patients developing postoperative AF suggests that the atria were not sufficiently protected during the cross-clamp period. Although none of our patients had perioperative myocardial infarction, this only indicates that the ventricle was well protected. A previous study demonstrated that the duration of atrial activity during the cross-clamp period had a strong correlation to the incidence of postoperative SVTs, probably due to inadequate atrial protection during global myocardial ischemia [40]. In our study, although there was a correlation between the volume of cardioplegia received and the cross-clamp period, the regression analysis confirmed that patients receiving less cardioplegia were at a higher risk for developing AF. Moreover, more recent studies reported the same incidence of postoperative AF for off-pump surgery as for CABG surgery, which further indicates that the period during CPB is less important for the development of postoperative AF [14]. The finding of lower BMI as a predictor for postoperative AF was unexpected, and difficult to interpret. Although the BMI had a p value
of 0.096, which per definition is non-significant, BMI was still judged to be an independent variable since the model used for the multiple regression analysis had a $p$ value of 0.00032.

The observed higher incidence of premature atrial contractions before and after surgery in patients developing AF compared to those remaining in sinus rhythm, may combined with other factors, such as postoperative increased sympathetic activity, predispose to postoperative AF. Previous studies have observed an increased sympathetic activity during and after cardiac surgery, caused by median sternotomy and CPB [76, 78, 79]. This was confirmed by our study, showing increased postoperative plasma levels of catecholamines, which are highly sensitive to sympathetic stimulus. However, the neuropeptides NPY, CgA and CgB responding to intensive sympathetic stimulation with increased plasma levels, were unchanged after surgery, which was probably due to a rather moderate sympathetic response to surgery. The improved surgical technique and the refined anaesthesia over the last years may at least partly explain this low sympathetic outflow after surgery.

An increased postoperative sympathetic activity could also partly reflect a rebound adrenergic stimulation following the withdrawal of $\beta$-blocking agents. A two- to fivefold increased incidence of AF was reported when $\beta$-blockade was discontinued after CABG [11, 51]. Unfortunately, in our study, the $\beta$-blocking agents were not reinsituted consistently.

The observed postoperative decrease in HRV components may seem contradictory to the increase in postoperative catecholamine levels. As spectral powers do not reflect absolute levels of autonomic nerve traffic, and the changes of sympathetic and vagal nerve activities do not always occur reciprocally [74], our observations indicate that HRV analysis alone is an insufficient method in measuring changes in the autonomic balance during the early postoperative phase. The overall observed postoperative decrease in HRV in our study could, however, indicate a decreased parasympathetic activity, which is supported by others showing that the physiologic explanation for the finding of low HRV is diminished discharge and resistance of cardiac muscarinic receptors to vagal stimulation [101]. This was further confirmed by our demonstrated postoperative decrease in PP levels in our study.

The catecholamines and those neuropeptides expressing sympathetic activity did not differ between the two patient groups, either before or after surgery, but the PP levels were higher in patients developing postoperative AF compared to those remaining in sinus rhythm, which suggests a higher parasympathetic activity in these patients. The observed difference in PP levels after surgery may have been too small to cause a corresponding difference in the postoperative HRV components associated with parasympathetic activity.
All our patients declared sufficient pain relief when TEA was used as the only analgesia postoperatively. Moreover, the extension of the sensory blockade was equal in patients developing postoperative AF and in those remaining in sinus rhythm. High TEA (T1-T5), with local anaesthetics together with general anaesthesia, prevents the surgical stress response during CABG by the combination of an afferent sensory blockade and an efferent blockade of cardiac sympathetic nerve fibers [76]. In our study TEA, with the combination of sufentanil and bupivacaine, sufficiently suppressed the increased sympathetic activity after surgery as evident by the lower heart rate and lower catecholamine levels in the TEA group compared to the control group postoperatively. This was further supported by the observed reduced postoperative levels of NPY in TEA-treated patients. The observation that TEA did not affect the postoperative increase of the A levels in TEA treated patients, despite less increase compared to non-TEA patients, was probably due to insufficient blockade of the adrenal medulla.

It was previously demonstrated that TEA exerts a vagotonic effect on the cardiac ANS, as evident by attenuation of atropine [88]. This concomitant vagal effect of TEA could further explain the higher levels of parasympathetic HRV components in TEA-treated patients compared to the control group. Increased vagal tone has been reported to be a potential trigger for the onset of paroxysmal AF [31]. One may therefore speculate whether the vagotonic effect of TEA, could explain its lack of preventive effect on postoperative AF compared to the prophylactic effect of ß-blocking agents shown in other studies [50, 54]. These findings thus contradict the recent hypothesis that a moderate increase in sympathetic tone and a loss of excessive vagal tone, according to changes in HRV before the onset of postoperative AF, are important triggering factors to the development of postoperative AF [46]. It was also suggested that it is the variation rather than autonomic tone, as such, that is important before AF initiation [46], consistent with our findings as the HRV components showed no consistent pattern before AF onset.

The postoperative atrial dilatation observed in our study was probably related to increased pressure or volume overload after the surgery. Electrophysiologic canine studies have previously found that ANP decreases the atrial refractory period, which is a known risk factor for the development of AF [99]. There are several factors that may cause a shortening of atrial refractoriness: 1) long-term changes in activity or sensitivity of the ANS, 2) stretch of the atrial wall, 3) ischemia of the atrial myocardium, and 4) increase in plasma ANP levels [23]. In our study we demonstrated changes in the autonomic balance before and after surgery, increased atrial dilatation postoperatively, reduced total cardioplegia amount, and increased
plasma ANP levels postoperatively. These coexistent circumstances could therefore change the electrophysiologic milieu and predispose to the development of postoperative AF in already vulnerable patients.

The observed increase of premature atrial contractions in patients developing AF could also reflect an anatomical substrate already present before surgery. One may therefore speculate whether these patients have atrial foci, possibly related to their coronary artery disease, which initiate the AF onset.

Rapidly firing atrial foci, located in the pulmonary veins, have recently been proved to be important triggers for the initiation of AF in patients with paroxysmal AF [25]. While studying possible onset mechanisms of AF in our study, we found that the majority of patients had a premature atrial contraction at the initiation of AF. The observation that the majority of our patients had no change in heart rate before AF onset and that alterations in autonomic balance by TEA did not reduce the incidence of AF, may further support latent atrial foci as the major initiating mechanism in postoperative AF. It is further possible that the postoperative increase of atrial areas, possibly also including the pulmonary veins, may be directly related to an activation of latent atrial foci responsible for the triggering of postoperative AF, which has been observed among patients with paroxysmal AF [25].

Moreover, recent studies have further presented evidence against autonomically mediated AF, as the observed shortening of atrial refractory period induced by AF was not abolished by atropine, and hence could not be mediated by an increased vagal tone [23]. Further evidence against autonomically mediated AF was the finding that a blockade of the β-adrenergic system with propranolol, did not exert a significant effect on the atrial refractory period. Despite these findings, however, one could not completely exclude the role of ANS in the development of long-term shortening of atrial refractoriness [23]. It should be emphasised, though, that neither off-pump surgery [14], TEA treatment, nor β-blocking agents have reduced the incidence of AF.

A previous study demonstrated that the predominant endocrine stress response to surgery commences in the intensive care unit at the end of the anaesthesia [102]. Therefore, some time may be required for some predisposing factors to develop and create a milieu that favours the initiation of postoperative AF.

Even though a premature atrial contraction is a possible trigger mechanism of postoperative AF, one may further speculate whether the inflammatory response initiated by the surgeon, when penetrating the pericardium, may be of importance. In our study we did not evaluate in detail the inflammation response to surgery. It should be emphasised, though, that
the recent observation that atrial overdrive pacing, with an algorithm reacting to atrial premature beats, reducing the incidence of both premature atrial contractions and postoperative AF, may further support latent atrial foci as the major initiating mechanism in postoperative AF [66].
CONCLUSIONS

Our study showed that, among otherwise healthy patients, some are predisposed to develop postoperative AF. The preoperative autonomic imbalance and the increased frequency of SPB before surgery combined with poor atrial protection during the cross-clamp period thus define these patients.

The increased propensity of SVT observed after surgery in patients developing AF combined with the increased sympathetic activity induced by the surgery could also predispose to the development of postoperative AF.

The observed postoperative autonomic imbalance was further confirmed by the overall decrease in HRV components indicating a decreased parasympathetic activity. Our observations further suggest that HRV analysis alone is insufficient in measuring changes in the autonomic balance.

TEA did not affect the incidence of postoperative AF, indicating that the ANS does not play a major role in the development of postoperative AF.

The observed postoperative increase of atrial areas and atrial peptides, could further favour the development of postoperative AF, as ANP has been found to decrease the atrial refractory period.

Furthermore, our study demonstrated that the majority of postoperative AF was initiated by a premature atrial contraction without any changes in the heart rate before the AF onset, supporting our hypothesis of latent atrial foci as the major mechanism in postoperative AF.
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REFERENCES


98. Goodall McC AH. Urinary excretion of adrenaline metabolites in man during intervals of 2 minutes, 5 minutes, and 10 minutes after intravenous injection of adrenaline. Biochem Pharmacol 1965;14:1595.


Errata


Changes to be made:

Page 10 line 17 SVA should be SVT

Page 13 line 8 should be amiodarone in patients
Page 15 line 4 SVA should be SVT

Paper I

Figure 1 text should be All p values are less than 0.05 within the groups, preoperatively and on Day 2, except left area which remained unchanged in patients developing atrial fibrillation.

Table 3 should be

Table 3. Multiple logistic regression analysis; predictors of postoperative sustained AF.

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OR = odds ratio; CI = confidence interval.

Paper IV