Predicting the Risk of Atrial Fibrillation After Coronary Artery Bypass Surgery
Predicting the Risk of Atrial Fibrillation After Coronary Artery Bypass Surgery

Doctoral dissertation

To be presented by permission of the Faculty of Medicine of the University of Kuopio for public examination in Auditorium, Kuopio University Hospital building, on Friday 27th June 2003, at 12 noon

Department of Surgery
University of Kuopio
ABSTRACT

Atrial fibrillation (AF) is the most common arrhythmia after coronary artery bypass grafting (CABG). It is a significant source of morbidity, prolongs hospital stay and increases the costs of the treatment. Preoperative identification of patients at high risk of AF after CABG would be very helpful. Thus, the most effective prophylaxis should be focused on that group of patients.

This study was performed to evaluate if patients at high risk of developing AF after CABG can be identified preoperatively or intraoperatively. The study consisted of four clinical trials. In the first study data of 3676 CABG patients were analysed and logistic regression model was created to predict the risk of postoperative AF. The negative and positive predictive value of the model was 0.72 and 0.55, respectively. In the second study analysis of heart rate variability (HRV) was measured preoperatively in 92 CABG patients in the standardised conditions. No measured parameters of HRV differed between the patients who got AF postoperatively and who remained in sinus rhythm. In the third study atrial sizes were preoperatively measured by echocardiography and atrial natriuretic peptide levels were analysed in 88 CABG patients. A large left atrial size was independent predictor of AF after CABG. High preoperative concentrations of atrial natriuretic peptides correlated with increased risk of postoperative AF, but there were not independent predictor of AF when adjusted for age. In the fourth study a new intraoperative high rate atrial pacing test was developed. Intraoperatively the right atrium was paced with high rate in order to test if AF was inducible. The pacing test was done for 80 patients undergoing CABG. The high-rate atrial pacing test induced AF in 27 patients. Of the 28 patients who experienced AF during postoperative period, 17 patients were inducible in the test. Positive and negative predictive values of the test were 0.63 and 0.79, respectively.

Our study shows that intraoperative high-rate atrial pacing test is simple, safe and fast way to identify the patients at risk for AF after CABG with a sufficient accuracy. Instead, the diagnostic accuracy of logistic regression model is not good enough for clinical use and also the analysis of HRV cannot identify the patients at high risk for AF after CABG. In addition, a large size of left atria is independent predictor of AF after CABG.

Medical Subject Headings: arrhythmia; atrial fibrillation; myocardial revascularization; coronary artery bypass; risk assessment

National Library of Medicine Classification: WG 330, WG 169
to the memory of my parents Elina and Aarne
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ABBREVIATIONS

AF Atrial fibrillation
ANP Atrial natriuretic peptide
BNP Brain natriuretic peptide
BSA Body surface area
CABG Coronary artery bypass grafting
CK-MBm Creatinine kinase-MB mass
COPD Chronic obstructive pulmonary disease
CPB Cardiopulmonary bypass
ECG Electrocardiography
GI Gastrointestinal
HF High frequency
HRV Heart rate variability
IABP Intra-aortic balloon pump
ICU Intensive care unit
LF Low frequency
MIDCABG Minimally invasive direct coronary artery bypass grafting
N-ANP N-terminal natriuretic peptide
NYHA New York Heart Association
OPCABG Off-pump coronary artery bypass grafting
OR Odds ratio
RMSSD Square root of the mean squared differences of adjacent RR intervals
ROC Receiver-operating characteristic
SD Standard deviation
SDNN Standard deviation of normal-to-normal RR interval
SR Sinus rhythm
TIA Transient ischaemic attack
VLF Very low frequency
LIST OF ORIGINAL PUBLICATIONS


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1. INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. With the changing epidemiology of rheumatic disease, the most frequent underlying heart disease in AF is coronary heart disease (Kannel et al. 1982). The prevalence of AF increases with age, with a prevalence of less than 1% at age 50 but more than 9% at age 80 (Feinberg et al. 1995).

AF is most common arrhythmia after cardiac surgery. The patients undergoing valve surgery or combined valve and coronary artery bypass surgery (CABG) have higher incidence of postoperative AF than patients having CABG alone (Cresswell and Damiano 1993, Almassi et al. 1997). AF is especially common after mitral valve surgery, occurring in as many as 64% of patients (Asher et al. 1998). AF after CABG is self-limiting in most cases, but, even when it is uncomplicated, it requires additional medical treatment and a prolonged hospital stay, and it consequently increases the costs of operative treatment (Cresswell and Damiano 1993, Aranki et al. 1996, Borzak et al. 1998). In some cases AF can cause hemodynamic compromise and increase the risk of stroke (Taylor et al. 1987, Creswell et al. 1993).

Prophylactic medical therapy decreases the incidence of postoperative AF after CABG. A meta-analysis of 24 randomised, controlled trials demonstrated that therapy with a β-adrenergic blocker decreases the incidence of AF after CABG by 77% (Andrews et al. 1991). Prophylactic therapy with amiodarone has been shown to be effective in decreasing the incidence of AF after CABG (Daoud et al. 1997, Guarnieri et al. 1999). In addition to medical prevention, atrial pacing may play a significant role in the prevention of AF after CABG, especially when combined with medical therapy (Blommaert et al. 2000, Fan et al. 2000).

The most effective preventive methods, either medical prevention or preventive pacing strategy, require additional nursing and medical resources and expense. Prophylactic treatment to prevent AF with intravenous amiodarone is not cost-effective if given to all patients (Mahoney et al. 2002). In addition, these treatments may have unfavourable side effects. Prophylaxis of the whole patient population
undergoing GABG is not reasonable. Identification of patients who would be at high risk of AF after CABG would be very helpful. In this work we concentrated on methods to predict AF in post-CABG patients.

2. REVIEW OF THE LITERATURE

2.1. ATRIAL FIBRILLATION AFTER CABG

2.1.1. PATHOPHYSIOLOGY

The pathophysiology of AF after cardiac operations is not fully understood. On the basis of experimental animal and clinical studies, underlying electrophysiological abnormality is a necessary substrate for AF. The pathophysiological mechanism is believed to be re-entry, which is facilitated when adjacent atrial regions have widely separated refractory periods. This non-uniform dispersion of refractoriness in the atrial tissue can set up local areas of functional blocks and the depolarising wavefront faces both refractory and excitable myocardium. This makes the re-entry phenomenon possible and can lead to AF (Cox et al. 1991, Cox 1993, Konings et al. 1994). Prolonged atrial conduction may also favour re-entry, and serve as a substrate to AF (Cosio et al. 1983). It is speculated that this electrophysiological substrate is mandatory for the development of AF, which may explain why some patients get AF and some do not after the same surgical intervention (Cox 1993). The explanation is supported by the findings of histopathologic abnormalities such as myolysis and lipofuscin deposition in atrial tissue biopsies before cardiopulmonary bypass in patients who suffered postoperative AF (Ad et al. 2001).

In addition to an electrophysiological substrate, some triggering factor is required to begin the AF. In non-surgical patients this triggering factor is a premature ectopic beat. The pulmonary veins are an important source of ectopic beats, initiating frequent paroxysms of AF (Haissaguerre et al. 1998, Jais et al. 2000). Atrial ectopic activity and tachyarrhythmias are more common just prior to the onset of AF after CABG compared to patients who remain in sinus rhythm. Premature atrial activity may thus serve as a triggering factor for AF (Frost et al. 1995a, Jideus et al. 2000).
Frost et al. also showed that AF could be initiated by atrial ectopic beats that first activate either the right or left atrium (Frost et al. 1995b).

Atrial ischaemia may also play a significant role in the development of underlying substrate and be a triggering factor of AF. Atrial tissue is warmer during cardioplegic arrest than ventricular tissue and electrical activity is often observed as a sign of inadequate atrial protection (Smith et al. 1983, Tchervenkov et al. 1983, Chen et al. 1988). There is a correlation between persistent electrical activity and postoperative atrial arrhythmias (Tchervenkov et al. 1983). Yet, augmented atrial hypothermia during cardioplegic arrest has no effect on the atrial effective refractory period or on the inducibility of AF in canine heart (Sato et al. 1992). There is strong association between arterial insufficiency to the sinoatrial or to the atrioventricular node and the incidence of post-CABG AF, which indicates that atrial ischaemia may play a role in the development of AF after CABG (Kolvekar et al. 1996).

It is believed that increased sympathetic nervous activity increases susceptibility to postoperative AF. Kalman et al. showed that the mean postoperative norepinephrine levels (reflecting sympathetic nervous activity) were significantly higher in patients who developed AF compared to patients who remained in sinus rhythm (Kalman et al. 1995). Hogue et al. studied autonomic balance before the onset of AF after CABG. Either high or low heart rate variability (HRV) was observed before AF. This indicates that in some patients high sympathetic tone is present before onset of AF but in others, either higher vagal tone or dysfunctional autonomic heart rate control is present before AF onset (Hogue et al. 1998).

Total and ionized serum magnesium concentrations are reduced by cardiopulmonary bypass (England et al. 1993). Decreased postoperative magnesium levels are associated with AF after cardiac surgery (Kalman et al. 1995, Zaman et al. 1997). Jensen et al. found that during CABG the potassium levels fell and sodium increased in both right atrium and skeletal muscle, and on the second postoperative day the potassium content in skeletal muscle was not yet restored. Magnesium levels did not change in right atrium and skeletal muscle, but serum magnesium declined
They concluded that the observed electrolyte disturbances might be important in the development of the postoperative AF (Jensen et al. 1996). Magnesium is a cofactor of the myocardial cell membrane Na-K adenosine triphosphatase, which regulates transmembrane sodium and potassium gradients. Magnesium deficiency may predispose to arrhythmias by altering membrane potential and repolarisation via its effect on this enzyme (Fanning et al. 1991).

The reason for the delay from the operation to the onset of AF is not clearly known. After valve replacement significant pericardial effusion increases the risk of postoperative AF (Chidambaram et al. 1992). However, pericardial effusion and exaggerated inflammatory response are associated with postoperative arrhythmia (Bruins et al. 1997) and these factors may explain delay of the onset of AF.

2.1.2. INCIDENCE

The reported incidence of AF after CABG varies widely depending on the particular definition used, the mode of postoperative monitoring of the patients, and the changing profile of the patients undergoing CABG. Table 1 presents atrial arrhythmia incidence after cardiac surgery, for those studies that included 300 patients or more. The incidence of post-CABG AF varied between 17 and 33% in these studies. A meta-analysis of 24 trials (Andrews et al. 1991) the incidence of AF was estimated at 27%. Patients undergoing CABG and combined valve surgery have a higher incidence of postoperative AF than patients having CABG alone (Cresswell and Damiano 1993, Almassi et al. 1997). The peak of AF incidence occurred between the second and fourth days after the operation, with less than 10% on the first postoperative day (Aranki et al. 1996).

The frequency of AF after CABG is not decreasing. The incidence of AF in studies published recently is quite similar to those published a decade ago (Table 1). In series where surgeons, surgical methods and the methods of arrhythmia monitoring were deemed constant, Cresswell and Damiano found that the post-CABG incidence actually increased from 26% in 1986 to 36% in 1991 (Cresswell and Damiano 1993).
The incidence of AF after surgery on the beating heart is presented in the paragraph “Intraoperative predictors” (Section 2.1.3.2).

2.1.3. CLINICAL PREDICTORS
2.1.3.1. PREOPERATIVE PREDICTORS

Old age predicts AF in the general population (Feinberg et al. 1995) and it is the most often reported independent risk factor for post-CABG AF (Table 1). The incidence of AF after cardiac surgery increases by at least 50% per ten years of increased age (Leic et al. 1990, Mathew et al. 1996, Almassi et al. 1997, Mahoney et al. 2002). Aging causes cardiac dilatation, myocardial atrophy, decrease of conduction tissue, and fibrosis in atria (Lie and Hammond 1988, Kitzman et al. 1990). These age-related changes may be responsible for increased risk for AF after CABG.

Preoperative history of AF is a factor which consistently associates with AF after CABG. Patients with a history of AF appear to have the underlying substrate necessary for the development of AF, and they are thus susceptible to postoperative AF (Mathew et al. 1996, Hashimoto et al. 1991, Svedjeholm and Håkanson 2000). The exclusion of patients with a history of AF is probably the reason why preoperative history of AF has not been found to predict postoperative AF in many studies.

Some authors have found preoperative use of digoxin as an independent risk factor for AF after cardiac surgery (Cresswell and Damiano 1996, Almassi et al. 1997). It is apparent that digoxin has been used for heart failure and less compellingly, for prophylaxis of AF as well. The use of digoxin is often associated with sicker hearts.

Hypertension is a predictor of postoperative AF, and this may be related to increased fibrosis and to dispersion of atrial refractoriness (Aranki et al. 1996, Almassi et al. 1997, Svedjeholm and Håkanson 2000). But in many well-conducted studies involving large numbers of patients, hypertension has not been found to be an
Table 1. Atrial Fibrillation studies on after cardiac surgery showing the incidence of postoperative AF together with the suggested independent preoperative predictors of AF. Minimum of 300 patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>CABG patients, n</th>
<th>Incidence of AF, %</th>
<th>Independent predictors of AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fuller et al. 1989</td>
<td>473</td>
<td>28%</td>
<td>Old age, male sex, absence of postoperative β-blockers</td>
</tr>
<tr>
<td>Leic et al. 1990</td>
<td>5807</td>
<td>17%</td>
<td>Old age, COPD, chronic renal failure, preoperative β-blockers</td>
</tr>
<tr>
<td>Hashimoto et al. 1991</td>
<td>800</td>
<td>23%</td>
<td>Old age, previous atrial arrhythmias, preop. atrial premature beats, preop. increased left ventricular pressure</td>
</tr>
<tr>
<td>Cresswell et al. 1993</td>
<td>2833</td>
<td>32%</td>
<td>Old age, male sex, preop. use of digoxin, COPD, PVD, smoking</td>
</tr>
<tr>
<td>Matthew et al. 1996</td>
<td>2048</td>
<td>26%</td>
<td>Old age, male sex, history of congestive heart failure, preop. heart rate &gt;100</td>
</tr>
<tr>
<td>Aranki et al. 1996</td>
<td>570</td>
<td>33%</td>
<td>Old age, male sex, hypertension</td>
</tr>
<tr>
<td>Almassi et al. 1997</td>
<td>3126</td>
<td>28%</td>
<td>Increased age, COPD, preop. use of digoxin, hypertension, pulse rate &lt;80</td>
</tr>
<tr>
<td>Svedjeholm et al. 2000</td>
<td>775</td>
<td>29%</td>
<td>Old age, hypertension, history of AF</td>
</tr>
<tr>
<td>Zaman et al. 2000</td>
<td>326</td>
<td>28%</td>
<td>Increased age, male sex, SAPD &gt;155ms</td>
</tr>
<tr>
<td>Mahoney et al. 2002</td>
<td>8709</td>
<td>18%</td>
<td>Old age, male sex, previous MI</td>
</tr>
<tr>
<td>Majahalme et al. 2002</td>
<td>586</td>
<td>32%</td>
<td>Old age, use of radial artery grafts</td>
</tr>
</tbody>
</table>

AF = Atrial fibrillation, COPD = Chronic obstructive pulmonary disease, MI = myocardial infarction, PVD = Peripheral vascular disease, SAPD = Signal averaged P-wave duration.
independent predictor of AF after CABG (Fuller et al. 1989, Hashimoto et al. 1991, Cresswell and Damiano 1993, Mahoney et al. 2002).

The blood supply to the right atrium, the sinoatrial node and the atroventricular node is mainly conveyed via the right coronary artery. Pehkonen et al. found that patients with a total occlusion or severe stenosis of the proximal right artery had postoperative AF more often when retrograde cardioplegia was used (Pehkonen et al. 1998). In other studies obstructive disease in the sinoatrial nodal and atrioventricular nodal arteries was more common in patients developing AF after CABG than in those who remained in sinus rhythm (Mendes et al. 1995, Kolvekar et al. 1996). Stenosis of the sinoatrial artery (Al-Shanafey et al. 2001) or the right coronary artery (De Jong and Morton 2000) have been found to be independent predictors of AF after CABG by other investigators.

Men appear more likely to develop AF after CABG than women. Sex differences in ion-channel expression and hormonal effects on autonomic tone may explain this difference between genders (Fuller et al. 1989, Aranki et al. 1996, Almassi et al. 1997, Zaman et al. 2000, Mahoney et al. 2002). However, there exist conflicting reports, in which male gender was not an independent predictor of AF (Hashimoto et al. 1991, Cresswell and Damiano 1993).

Chronic obstructive pulmonary disease (COPD) is a predictor of AF after cardiac surgery. COPD patients have frequent premature atrial contractions that act as a trigger for the initiation of AF (Leich et al. 1990, Cresswell and Damiano 1993, Almassi et al. 1997, Ad et al. 1999).

When long-term β-blocking medication is abruptly discontinued, a phenomenon called β-blocking withdrawal effect follows. It is characterised by increased catecholamine concentration in plasma. A withdrawal effect has been proposed as a possible cause of AF after cardiac operation when β-blocking medication has been stopped at the time of surgery (White et al. 1984, Kalman et al. 1995).
Several other factors have been found independently to predict the risk of AF after CABG: previous congestive heart failure (Mathew et al. 1996), previous myocardial infarction (Mahoney et al. 2002), resting pulse rate less than 80 (Almassi et al. 1997), precardiopulmonary heart rate over 100 (Mathew et al. 1996), peripheral vascular disease (Creswell and Damiano 1993), smoking (Cresswell and Damiano 1993), three vessel coronary artery disease (Ducceschi et al. 1999), lower body mass index (Jideus et al. 2000), and left atrial enlargement (Ducceschi et al. 1999).

Long duration of P wave in signal-averaged electrocardiography (SAECG) as a predictor of AF will be discussed in paragraph “Signal average P-wave ECG” (Section 2.2.1.).

2.1.3.2. INTRAOPERATIVE PREDICTORS

There are conflicting data about the association between aortic cross-clamp time and postoperative AF. Some (Caretta et al. 1991, Creswell and Damiano 1993, Mathew et al. 1996, Mahoney et al. 2002) studies show that long cross-clamp time increases the risk of postoperative AF, but in other studies the correlation was not found (Fuller et al. 1989, Hashimoto et al. 1991, Aranki et al. 1996). The type of cardioplegia does not seem to have effect on the incidence of postoperative AF (Butler 1993a, The warm heart investigators 1994, Pehkonen et al. 1995). Insulin-enhanced blood cardioplegia does not decrease the incidence of postoperative AF when compared with standard blood cardioplegia (Hynynen et al. 2001).

A strong correlation was found between the duration of atrial activity during the cross-clamp time and the incidence of postoperative AF (Tchervenkov et al. 1983). In a recently published study the total volume of cardioplegia was significantly less in patients with AF compared with patients with sinus rhythm (Jideus et al. 2000).

During the last few years a growing number of coronary surgeries have been completed without using cardiopulmonary perfusion. From the theoretical standpoint, patients undergoing CABG without cardiopulmonary bypass (CPB) would not be subject to some precipitating factors of postoperative AF, i.e. atrial ischaemia,
cannulation trauma to the atrium, and CPB itself (Cresswell and Damiano 2001). There is conflicting information about the incidence of postoperative AF among patients after off-pump CABG. Table 2 presents studies comparing postoperative AF incidence after off-pump and conventional CABG. Unfortunately most of these studies are retrospective and involve only small number of patients.

Ascione et al. reported a randomised study of 200 patients, with a postoperative AF incidence of 49% after conventional CABG, compared with 14% after off-pump CABG. The incidence of AF after conventional CABG was very high but the use of β-blocking medication was not reported (Ascione et al. 2000). Buffolo et al. reported a retrospective study involving 1,067 patients. They also found the incidence of atrial arrhythmias significantly lower after off-pump CABG compared with conventional CABG (Buffolo et al. 1996). Allen et al. reported no postoperative arrhythmias in a small group of patients who underwent single vessel redo off-pump CABG with the left anterior thoracic artery (Allen et al. 1997). Subramanian et al. reported their experience of minimally invasive direct coronary artery bypass grafting (MIDCABG) (Subramanian et al. 1997). They used minithoracotomy, subxiphoid and lateral thoracotomy incisions, and the incidence of AF was only 8% (14/185 patients). No difference in the frequency of postoperative AF was found in a small case-controlled study after MIDCABG and conventional CABG (Cohn et al. 1999). Similarly, no significant difference was found in a study comparing the incidences of AF after conventional CABG, MIDCABG and OPCABG (Siebert et al. 2000). In another study by Siebert et al, no difference was found between the incidence of AF after on-pump and off-pump CABG during ICU stay (Siebert et al. 2001). There are also other negative studies, which did not reveal any difference in the incidence of AF after CABG with or without CPB (Saatvedt et al. 1999, Abrey et al. 1999, Mueller et al. 2001). Tamis-Holland et al. compared 208 patients having MIDCABG or conventional CABG, and they concluded that the reason of low incidence of AF after MIDCABG is due to different clinical characteristics of patients compared to conventional CABG patients (Tamis-Holland et al. 2000).
Table 2. Studies comparing the incidences of postoperative AF after on-pump and off-pump CABG.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Total number of patients</th>
<th>Type of Study</th>
<th>On pump AF, %</th>
<th>Off pump AF, %</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buffalo 1996</td>
<td>1067</td>
<td>Retrospective, OFFPUMP-ONPUMP</td>
<td>12.6%</td>
<td>5.5%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Allen 1997</td>
<td>35</td>
<td>Retrospective, only LIMA-LAD REDO</td>
<td>58%</td>
<td>0%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cohn 1999</td>
<td>110</td>
<td>Case-control, MIDCAB-CABG</td>
<td>20%</td>
<td>24%</td>
<td>NS</td>
</tr>
<tr>
<td>Saatvedt 1999</td>
<td>704</td>
<td>Retrospective ONPUMP-OFFPUMP</td>
<td>36%</td>
<td>37%</td>
<td>NS</td>
</tr>
<tr>
<td>Ascione 1999</td>
<td>80</td>
<td>Prospective randomised ONPUMP-OFFPUMP</td>
<td>38%</td>
<td>15%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Abrey 1999</td>
<td>781</td>
<td>Retrospective, OFFPUMP-ONPUMP</td>
<td>26%</td>
<td>12%</td>
<td>0.06</td>
</tr>
<tr>
<td>Tamis-Holland 2000</td>
<td>209</td>
<td>Retrospective, MIDCAB-ONPUMP</td>
<td>39%</td>
<td>23%</td>
<td>&lt;0.05 but NS</td>
</tr>
<tr>
<td>Ascione 2000</td>
<td>200</td>
<td>Prospective randomised ONPUMP-OFFPUMP</td>
<td>49%</td>
<td>14%</td>
<td>0.001</td>
</tr>
<tr>
<td>Siebert 2000</td>
<td>87</td>
<td>Retrospective ONPUMP-OFFPUMP</td>
<td>27%</td>
<td>18%</td>
<td>NS</td>
</tr>
<tr>
<td>Mueller 2001</td>
<td>183</td>
<td>Retrospective, only LIMA-LAD</td>
<td>18%</td>
<td>22%</td>
<td>NS</td>
</tr>
</tbody>
</table>

AF = Atrial fibrillation, CABG = Coronary artery bypass grafting, LAD = Left anterior descending artery, LIMA = Left anterior mammarian artery, MIDCABG = Minimally invasive direct coronary artery bypass grafting.
2.1.3.3. POSTOPERATIVE PREDICTORS

Postoperative pneumonia and mechanical ventilation longer than 24h have been shown to be independent postoperative predictors of AF (Aranki et al. 1996), as well as atrial pacing (Mathew et al. 1996), and need of postoperative inotropic agents (Almassi et al. 1997). Svedjeholm and Håkanson found that low postoperative mixed venous oxygen saturation and the need for postoperative mechanical circulatory support were independent predictors of post-CABG AF (Svedjeholm and Håkanson 2000). In addition, a high central venous pressure at the time of admission to intensive care is predictive of a higher risk of AF (Frost and al. 1995c).

2.1.4. IMPACT ON OUTCOME AND RESOURCE UTILIZATION

Most of the postoperative AF cases are temporary and the morbidity related to them is low. However, there is evidence that AF associates with adverse events, patient discomfort, the need for additional medication and treatment, decrease in cardiac output, hypotension, and congestive heart failure (Lamb et al. 1988, Creswell and Damiano 1993, Aranki et al. 1996, Paul et al. 1997).

The most serious complication of AF is stroke. Chung et al. found in their retrospective analysis of 8,389 CABG patients that postoperative AF independently increases the risk of embolic stroke 1.8 fold (Chung 1995). The same association has been found also in other studies (Taylor et al. 1987, Fuller et al. 1989, Creswell and Damiano 1993).

Increase in hospital stay relates to postoperative AF in many studies (Creswell and Damiano 1993, Lazar et al. 1995, Mathew et al. 1996, Aranki et al. 1996, Chung et al. 1996, Borzak et al. 1998, De Jong and Morton 2000). Aranki et al. noted that AF lengthens hospital stay by 4.9 days, which increased the costs of operation more than 10,000 USD. Mathew et al. noted that length of hospital stay increased from 10.2 to 12.8 days with AF. The above-mentioned studies were based on patients who were operated between 1991 and 1994.
A recently published study by Tamis et al. AF recorded a lengthening of the hospital stay after CABG by 3.2 days, and this effect was independent of other variables (Tamis et al. 2000). In another recently published study the impact of postoperative AF was found to be only 1 to 1.5 days (Kim et al. 2001). In a study by Hravnak et al. the new onset atrial fibrillation after CABG increased the total cost of treatment by more than 6,000 USD (Hravnak et al. 2002). The authors concluded that the economic impact of AF after CABG has been underestimated.

However, there is also a published study in which the postoperative AF did not affect the length of stay or costs (Gupta et al. 1996).

2.1.5. TREATMENT

Spontaneous conversion of AF to sinus rhythm (SR) after cardiac surgery is common. 15% of patients convert to SR in two hours (VanderLugt et al. 1999) and 80% in 24 hours (Cochrane et al. 1994) when either placebo or digoxin was given.

Two management strategies are available to treat AF after CABG: rate control and rhythm control. In addition, anticoagulant therapy must be remembered to reduce the risk of embolic complications (Ommen et al. 1997). There are no specific data on when anticoagulation therapy should be started on patients who have AF after CABG. Two reviews of postoperative AF recommend anticoagulant therapy with heparin and warfarin either if the AF persists for 24 hours (Ommen et al. 1997) or more than 48 hours (Maisel et al. 2001).

β-blockers are considered first-line therapy for rate control when ventricular response is rapid (Andrews et al. 1991). Digoxin may slow down the ventricular response at rest, but seldom adequately when sympathetic tone is high. When β-blockers alone inadequately control the heart rate, calcium channel blockers may be administered to achieve adequate rate control (Maisel et al. 2001). Infusion of amiodarone can also be used for adequate rate control in AF (Cochrane et al. 1994).

Early electrical cardioversion may be necessary in hemodynamically compromised patients. Unfortunately, AF tends to relapse after cardioversion
(Ommen et al. 1997). Reports on the use of various antiarrhythmic drugs to restore SR in patients with AF after CABG show diverse results. This is partly due to spontaneous restoration of SR. Some of the drugs (dofetilide, procainamidi, intravenous quinidine) used in studies are not available in many countries, including Finland.

When antiarrhythmic therapy is indicated, drug-induced proarrhythmia should be avoided. Patients with a history of myocardial infarction, reduced ejection fraction, or high age are at particularly high risk for proarrhythmias (Friedman and Stevenson 1998).

The efficacy of flecainide, class IC antiarrhythmic agent for converting AF to SR after cardiac surgery has been shown (Cavaghan et al. 1988, Wafa et al. 1989). Since flecainide increases mortality after myocardial infarction, this drug should not be first choice for long-term oral therapy in patients with postoperative AF (Ommen et al. 1997).

Intravenous amiodarone therapy converts AF to SR within 12 to 24 hours in 40% to 90% of patients, and amiodarone therapy provides effective rate control (McAlister et al. 1990, Cochrane et al. 1994). Another drug with class III antiarrhythmic properties, sotalol, leads to conversion to SR in 85% of patients in 12 hours (Campbell et al. 1985). Ibutilide, a class III antiarrhythmic agent, given intravenously converted 44% of AF patients to SR after cardiac surgery compared of 15% of patients who were given placebo, but ibutilide infusion was associated with an up to 3% risk of torsades de pointes proarrhythmia (Vander Lugt et al. 1999).

Overall, although many antiarrhythmic options are available to convert AF to SR after CABG, the combination of reasonable efficacy and low risk of proarrhythmia favours amiodarone as the drug of choice for patients requiring antiarrhythmic drug treatment (Ommen et al. 1997).

Less than 10% of patients with postoperative AF after CABG who are discharged in SR will have recurrent AF in six weeks after discharge, and
prophylactic treatment with calcium-channel blockers, quinidine, or amiodarone after discharge does not reduce to the rate of recurrence (Yilmaz et al. 1996).

2.1.6. PREVENTION

2.1.6.1. BETA-BLOCKING THERAPY

There are a large number of studies concerning the efficacy of β-blockers in the prevention of AF after CABG. Three meta-analyses have confirmed the efficacy of β-blockers in AF prophylaxis (Andrews et al. 1991, Kowey et al. 1992, Crystal et al. 2002). Meta-analyses published in 1991 and 1992 showed that the incidence of postoperative AF decreased from 34% and 20% to 8.7% and 9.8%, respectively. The β-blocking agent used, the time of the initiation, or the dose administered did not influence the efficacy of the prophylactic therapy. In a recently published meta-analysis (Chrystal et al. 2002) comprising 27 prospective randomised trials and 3,840 patients, the incidence of AF decreased from 33% in the control group to 19% in the β-blocking group. The β-blocking agent used, the proportion of patients on β-blocker preoperatively, study size, or the method of electrocardiographic monitoring did not influence the efficacy of the prophylactic therapy.

Yazicioglu et al. reported recently a prospective randomised study consisting of 160 patients. The incidence of AF after CABG was only 5% in the group treated prophylactically with the combination of atenolol and digitalis compared with incidence of 15% to 25% in the groups treated with either of these medicines alone or placebo (Yazicioglu et al. 2002).

Sotalol has been shown to decrease significantly the incidence of postoperative AF compared with placebo (Pfisterer et al. 1997, Weber et al. 1998, Gomes et al. 1999). Three prospective randomised clinical trials have compared the efficacy between sotalol and other β-blockers in the prevention of postoperative AF. Suttert et al. compared low-dose sotalol (40 mg every 8 hours) and high-dose sotalol (80mg every 8 hours) to low- and high-dose propranolol (10 and 20 mg every 6 hours). They found a tendency of less supraventricular tachyarrhythmias in patients treated with
sotalol, and significantly fewer adverse effects were noted in both low-dose groups (Sutton et al. 1990). Parikka et al. compared sotalol 120 mg daily to metoprolol 75 mg daily postoperatively in 191 consecutive CABG patients (Parikka et al. 1998). AF occurred in 16% of sotalol patients and 32% of metoprolol patients (p<0.01). Proarrhythmic adverse effects did not appear. In another study comparing sotalol to metoprolol the incidence of supraventricular tachyarrhythmias were 2.4% and 15.3%, respectively (Janssen et al. 1986). Although previously mentioned papers showed that sotalol is more effective than other β-blockers in prevention of postoperative AF there is a concern over its potential to create proarrhythmic side effects. In a review of non-surgical patients the proarrhythmic risk associated with sotalol has been reported to be from 4.3% to 5.9% in patients receiving sotalol after myocardial infarction (Soyka et al. 1990).

In a pilot study by Balcetyte-Harris et al. intravenous esmolol was compared to oral β-blocker therapy in prevention of AF after CABG (Balcetyte-Harris et al. 2002). They found intravenous esmolol less tolerated and the drug did not offer any advantages to standard β-blocker therapy.

In conclusion, the routine early postoperative administration of β-blockers is considered standard therapy to reduce the risk of AF after CABG (Eagle et al. 1999).

2.1.6.2. AMIODARONE THERAPY

The feasibility of amiodarone for prevention of AF after cardiac surgery has been interesting. Daoud et al. reported that amiodarone lowered the incidence of atrial fibrillation after bypass and valve surgery by 53% (Daoud et al. 1997). They started oral amiodarone therapy (600 mg per day for seven days, then 200 mg per day) for a minimum of seven days before elective cardiac surgery and continued it until the day of discharge from the hospital. Two individual oral amiodarone regimens were compared in a double-blind prospective trial (White et al. 2002). When amiodarone therapy (7 g oral amiodarone in ten days) was started five days before cardiac surgery it reduced significantly the incidence of AF, of symptomatic AF, and of AF lasting
more than 24 hours. If the therapy (6 g oral amiodarone in six days) was started one
day before surgery it reduced the risk of symptomatic AF, of AF lasting more than 24
hours, and showed a trend for prevention of any AF. Giri et al. randomised 220
patients, older than 60 years, to receive either oral amiodarone or placebo starting 1
(6 g amiodarone over six days) or 5 days (7 g amiodarone over ten days) before
surgery. Concomitant β-blocking therapy was given to 90% of the patients. Both
regimens were effective in the prevention of AF. The incidence of AF in the
amiodarone group was 22.5% compared to 38% in the placebo group (p=0.01). There
was also significant difference in favour of amiodarone in the preventing of
cerebrovascular accidents and postoperative ventricular tachycardia.

Several studies have focused on the feasibility of intravenous amiodarone for
prevention of postoperative AF after CABG (Hohnloser et al. 1991, Butler et al.
1993b, Guarnieri et al. 1999, Lee et al. 2000). Hohnloser et al. reported a significant
reduction in the incidence of AF when amiodarone, compared with placebo, was
given for two days postoperatively (5% vs. 21%, respectively). Overall the incidence
of AF was low in this study. Guarnieri et al. also gave intravenous amiodarone or
placebo for two postoperative days with a significant reduction of AF (35% vs. 47%
respectively). The incidence of AF was high in the placebo group, which may have
been related to a high β-blocker withdrawal rate. Butler et al. gave a 24-hour
intravenous amiodarone infusion (15 mg/kg) after operation and oral amiodarone
(600 mg daily) therapy for five days. The overall incidence of supraventricular
tachyarrhythmias did not differ between amiodarone and placebo groups but the
arrhythmias requiring therapy were reduced in amiodarone group. More bradycardia
occurred in amiodarone treated patients. Lee et al. started intravenous amiodarone
therapy three days before CABG and continued it for five days after surgery. They
found a significant reduction in the incidence of AF (12% vs. 34%), ventricular rate
during AF, and the duration of AF, compared to placebo group.

Conflicting results in the efficacy of amiodarone for preventing postoperative
AF have been found by Dörge et al. 2000 and Redle et al. 1999. Dörge et al.
randomised 150 patients to receive intravenous amiodarone (two regimens) or placebo during three days after CABG. There was no difference in the incidence of AF between the groups. Redle et al. used a 1-4 day (2g) preoperative loading and continued with 400 mg amiodarone daily for 7 days postoperatively in CABG patients. They achieved a non-significant 25% reduction in AF incidence. Treggiari-Venzi et al. gave intravenous amiodarone (900 mg per 24 h) for 72 hours in a double-blind controlled study. The reduction of AF incidence was not significant (14% vs. 27%) in the amiodarone group, but the administration of amiodarone was associated with a longer duration of cardiovascular instability, and an extended need for intensive care (Treggiari-Venzi et al. 2000).

In a meta-analysis of prospective randomised trials comprising 9 studies and 1,384 patients, amiodarone reduced the percentage of patients with AF from 37% in the control group to 22.5% in the amiodarone group (Crystal et al. 2002).

Mahoney et al. assessed the cost-effectiveness of intravenous amiodarone therapy (Mahoney et al. 2002). They found routine use of intravenous amiodarone after CABG not to be cost-effective. Older patients undergoing valve surgery with concomitant CABG, or who had had COPD, were likely to benefit most from intravenous amiodarone therapy.

In conclusion, routine amiodarone administration to all patients for reduction AF after CABG cannot be recommended. Instead, amiodarone should be given to patients at high risk for AF after CABG.

2.1.6.3. MAGNESIUM SUBSTITUTION

Majority of the studies have shown that prophylactic administration of magnesium reduces the incidence of atrial arrhythmia after cardiac surgery (Fanning et al. 1991, Colquhoun et al. 1993, Wistbacka et al. 1995, Toraman et al. 2001, Wilkes et al. 2002). Fanning et al. randomised 99 patients to receive either 178 mEq of magnesium or placebo over the first four postoperative days. Significantly fewer episodes of AF occurred in the group receiving supplemental magnesium. Wistbacka et al. compared high dose (4.2g before CPB followed by an infusion of 11.9 g until first morning and a further 5.5g until second postoperative morning) and low dose (2.9 g at the first postoperative morning and 1.4 g at the second postoperative morning) magnesium supplementation in prevention of AF after CABG. A significant reduction of AF incidence was found in the high dose group compared to the low dose group (7.3% vs. 25%, respectively). It is remarkable that also the patients in the low dose group were normomagnesemic postoperatively. Toraman et al. randomised 200 CABG patients to receive either 6 mmol magnesium on the day before surgery, just after CPB and once a day for four days postoperatively or placebo. The incidence of AF in the magnesium group was astonishingly low, only 2%, on the contrary, in the placebo group, it was 21% (p<0.0001). In a study by Jensen et al. the magnesium substitution reduced the duration of atrial fibrillation or flutter but not the number of patients developing these arrhythmias (Jensen et al. 1997).

On the contrary there are studies, which have shown that prophylactic administration of magnesium does not decrease the incidence of AF after CABG. Parikka et al. showed that administration of 70 mmol of magnesium in the first 48 hours after cardiac surgery did not decrease the incidence of postoperative AF (Parikka et al. 1993). They reported that high plasma magnesium concentration perioperatively led to a higher incidence of AF. In that study the patients in the magnesium group were significantly older, had more prior episodes of AF, and used digoxin more often before the surgery. Karmy-Jones et al. showed that administration of 14.4 g of magnesium in the first 24 hours after the cardiac operation did not reduce the incidence of supraventricular tachyarrhythmias (Karmy-Jones et al. 1995).
One retrospective study compared the effectiveness of magnesium supplementation in preventing atrial tachyarrhythmias in patients undergoing off-pump CABG (Maslow et al. 2000). The incidence of postoperative atrial arrhythmias was significantly lower in magnesium group compared to control group (12% vs. 29%, respectively).

The role of magnesium in the prevention of AF after CABG remains unclear.

2.1.6.4 OTHER MEDICAL THERAPY

Digoxin administered prophylactically does not reduce the incidence of AF after CABG (Tyras et al. 1979, Andrews et al. 1991, Kowey et al. 1992). Prophylactic use of verapamil was not shown to be different from controls in reducing the likelihood of AF after CABG according to a meta-analysis (Andrews et al. 1991).

Intravenous postoperative administration of diltiazem reduced significantly the risk of postoperative AF after CABG compared with intravenous nitroglycerin administration in four studies (Hannes et al. 1993, Seitelberger et al. 1994, el-Sadel and Krause 1994, Malhotra et al. 1997), without evidence of haemodynamic compromise. No placebo-controlled trials have evaluated diltiazem for prevention of AF after CABG.

The effect of perioperative triiodothyronine supplementation was studied in one prospective double-blind study involving 142 CABG patients with depressed left ventricular ejection fraction (Klemperer et al. 1996). Triiodothyronine-treated patients had statistically significant lower incidence of AF postoperatively (24% versus 46%).

In a meta-analysis of 52 randomised trials various prophylactic therapies against postoperative AF after cardiac surgery were analysed. β-blockers, sotalol and amiodarone all reduced the risk of postoperative AF with no marked difference between them (Crystal et al. 2002).
2.1.6.5. PREVENTION BY ATRIAL PACING

Few studies have investigated the role of atrial pacing for the prevention of AF after cardiac surgery. Table 3 summarises the controlled trials of atrial pacing for the prevention of AF. Gerstenfeld et al. found continuous right or biatrial pacing in the postoperative setting safe and well tolerated (Gerstenfeld et al. 1999). Although the incidence of AF episodes in the paced groups was the same as that in the control group, the authors noted that the combination of β-blocking medication and preventive pacing significantly reduced the incidence of AF. In another study Gerstenberg et al. found that biatrial pacing together with β-blocking therapy after CABG reduces the incidence of postoperative AF. Particularly patients over 70 years appeared to benefit most of this combination therapy (Gerstenfeld et al. 2001). Greenberg et al. randomised 154 patients to four groups: one control group and three groups treated with permanent atrial overpacing with different pacing sites (Greenberg et al. 2000). The proportion of documented AF episodes was only 17% in the paced groups versus 37% in the control group. Blommaert et al. tested the effectiveness of right atrial pacing with continuous atrial dynamic overdrive pacing to ensure effective atrial capture in >90% of heart cycles (Blommaert et al. 2000). The incidence of documented AF episodes was significantly lower in the paced group (10%) compared to control group (27%). In Fan et al’s study biatrial pacing proved significantly more effective than single site right atrial or single site left atrial pacing (Fan et al. 2000). In another study, biatrial pacing was compared with no pacing at all, and a marked decrease in the incidence of AF was reported in the paced group (Levy et al. 2000). In a double-blind, randomised study 118 patients who underwent open heart surgery were assigned to right atrial pacing at 45 bpm (AAI), right atrial triggered pacing at a rate of >85bpm and biatrial pacing at a rate of >85bpm. The incidences of postoperative AF were 28%, 32% and 10%, respectively. There was a statistically significant difference indicating benefit to the biatrial paced group (Daoud et al. 2000).
Table 3. Controlled studies of atrial pacing for the prevention of AF after cardiac surgery.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>PACING MODE</th>
<th>PACING SITE</th>
<th>CONCLUSION OF THE STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurtz et al. 1999</td>
<td>21</td>
<td>10 bpm over native HR</td>
<td>BAP</td>
<td>Study was stopped due to proarrhythmic effect of BAP</td>
</tr>
<tr>
<td>Gerstenfelt et al. 1999</td>
<td>61</td>
<td>100 bpm</td>
<td>RAP, BAP</td>
<td>No difference between groups in AF incidence</td>
</tr>
<tr>
<td>Daoud et al. 2000</td>
<td>118</td>
<td>85 bpm or 10 bpm over native HR</td>
<td>RAP, BAP</td>
<td>Significant reduction of AF in BAP group</td>
</tr>
<tr>
<td>Levy et al. 2000</td>
<td>130</td>
<td>80 bpm</td>
<td>BAP</td>
<td>Significant reduction of AF in paced group</td>
</tr>
<tr>
<td>Fan et al. 2000</td>
<td>132</td>
<td>90 bpm or 10 bpm over native HR</td>
<td>LAP, RAP, BAP</td>
<td>AF decreased in study groups; BAP was the most effective</td>
</tr>
<tr>
<td>Blommaert et al. 2000</td>
<td>69</td>
<td>Dynamic atrial Overdrive pacing</td>
<td>RAP</td>
<td>Significant reduction of AF in paced group</td>
</tr>
<tr>
<td>Greenberg et al. 2000</td>
<td>154</td>
<td>100-110 bpm</td>
<td>LAP, RAP, BAP</td>
<td>AF decreased in study groups; RAP was the most effective</td>
</tr>
<tr>
<td>Chung et al. 2000</td>
<td>100</td>
<td>10 bpm over native HR</td>
<td>Not mentioned</td>
<td>No difference between groups in AF incidence</td>
</tr>
<tr>
<td>Gerstenfelt et al. 2001</td>
<td>118</td>
<td>100</td>
<td>BAP</td>
<td>Trend toward reduction of AF in paced group</td>
</tr>
</tbody>
</table>

Abbreviations: BAP = biatrial pacing, BPM = beats per minute, HR = heart rate, LAP = left atrial pacing, RAP = right atrial pacing
There are also two studies, which have shown that atrial pacing does not decrease incidence of AF after CABG. 100 patients were randomised to AAI pacing at 10 beats/min or more above the resting heart rate and to control group with no pacing (Chung et al. 2000). There was no difference in the incidence of AF between the study groups and, paradoxically, atrial ectopy was more frequent in the paced group. Kurz et al. compared medical therapy with biatrial pacing via epicardial wires for prevention of postoperative AF in a prospective randomised study. After 21 of the planned 200 patients, the study was prematurely aborted because of the proarrhythmic effect of biatrial pacing; 6 of the 12 patients treated with biatrial pacing developed sensing failure, which provoked AF in 5 of these 6 patients (Kurz et al. 1999).

In conclusion, temporary atrial pacing may play a significant role in the prevention of AF after cardiac surgery. Further studies are needed to confirm the feasibility of atrial pacing in the prevention of postoperative AF and to find the most effective pacing algorithms and pacing sites.

### 2.1.6.6. POSTERIOR PERICARDIOTOMY

Posterior pericardiectomy was firstly reported by Mulay et al. to reduce the incidence of AF after CABG (Mulay et al. 1995). Echocardiographically observed pericardial effusion decreased from 40% in a control group to 8% in the pericardiotomy group, with a reduction in the incidence of supraventricular tachyarrhythmias from 36% to 8%. The effect of pericardiotomy on the incidence of AF after CABG was confirmed in another randomised prospective study of 150 patients. A 4-centimeter longitudinal incision of posterior pericardium reduced the incidence of postoperative AF from 32% in the control group to 9% in the pericardiotomy group (Farsak et al. 2001). Also Kuralye et al. confirmed the efficacy of posterior pericardiotomy in prevention of AF after CABG in a prospective randomised study (Kuralye et al. 1999).
In contrast, a prospective, controlled trial involving 100 patients by Asimakopoulos et al., posterior pericardiotomy had no effect on the incidence of AF after CABG (Asimakopoulos et al. 1997).

2.2. CURRENT METHODS FOR PREDICTING THE RISK OF ATRIAL FIBRILLATION AFTER CABG

2.2.1. SIGNAL AVERAGE P-WAVE ECG

Recent studies have demonstrated that signal-averaged P-wave ECG analysis is useful in identifying patients at high risk for developing AF after cardiac surgery. Specifically, abnormal atrial conduction, defined by a prolonged filtered P-wave duration in signal-averaged P-wave ECG analysis, has been shown to be an independent predictor of postoperative AF (Steinberg et al. 1993, Klein et al. 1995, Zaman et al. 1997, Stafford et al. 1997, Aytemir et al. 1999, Caravelli et al. 2002). Table 4 summarises the studies of signal-averaged P-wave ECG analysis in predicting the risk of AF after cardiac surgery.

In these studies the abnormal P-wave duration varied from 122 ms to 155 ms. Sensitivity of signal-averaged P-wave duration in identifying the patients who developed AF postoperatively was 68%-86%, and specificity was 39%-88%. The positive predictive value and negative predictive value varied from 34% to 76% and from 83 to 85%, respectively.

The predictive value of the signal-averaged P-wave duration is further enhanced when it is combined with ejection fraction. When P-wave duration was >140ms and ejection fraction <40% the risk for postoperative AF was nearly nine times higher compared to the situation when both were normal (Hutchinson and Steinberg 1996).

Similarly, the combination of P-wave duration (>155 ms) and low serum magnesium concentration (<0.7mmol) on the first postoperative day increased the positive predictive value from 37% to 62% (Zaman et al. 1997).
When P-wave duration (>122.3 ms) and the presence of right coronary artery lesion were combined, the positive and negative predictive values were subsequently 81% and 76% (Aytemir et al. 1999).

Table 4. Comparison of signal-averaging P wave studies for predicting the risk of AF after cardiac surgery.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>P-DURATION</th>
<th>SPECIFICITY</th>
<th>SENSITIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steinberg et al 1993</td>
<td>130</td>
<td>140 ms</td>
<td>55%</td>
<td>77%</td>
</tr>
<tr>
<td>Klein et al 1995</td>
<td>45</td>
<td>155 ms</td>
<td>79%</td>
<td>69%</td>
</tr>
<tr>
<td>Hutchinson and Steinberg 1996</td>
<td>272</td>
<td>140 ms</td>
<td>39%</td>
<td>82%</td>
</tr>
<tr>
<td>Zaman et al 1997</td>
<td>102</td>
<td>155 ms</td>
<td>45%</td>
<td>86%</td>
</tr>
<tr>
<td>Stafford et al 1997</td>
<td>201</td>
<td>141 ms</td>
<td>48%</td>
<td>73%</td>
</tr>
<tr>
<td>Aytemir et al 1999</td>
<td>53</td>
<td>122 ms</td>
<td>88%</td>
<td>68%</td>
</tr>
<tr>
<td>Caravelli et al 2002</td>
<td>129</td>
<td>135 ms</td>
<td>73%</td>
<td>84%</td>
</tr>
</tbody>
</table>

N=Number of the patients studied, ms=milliseconds, P-duration= Cut off value of P-wave duration used in the study
2.2.2. STANDARD ELECTROCARDIOGRAPHY

There are conflicting data concerning the standard ECG as a tool for predicting the risk of AF after cardiac surgery. Buxton and Josephson first reported that patients developing AF after CABG had a significantly longer P-wave duration in the standard ECG (Buxton and Josephson 1981). In a recently published study (Chang et al. 1999) the presence of prolonged P-wave duration (>100ms in lead II) was an independent predictor of AF with 1.9-fold risk compared to a P-wave duration less than 100 ms. The P-wave duration in both the signal averaged ECG and in the surface ECG were prolonged in patients who had AF after CABG (Dimmer et al. 1998). In the latter study a significant correlation was found between the P-wave duration in standard ECG and signal-averaged ECG. In a study published by Aytemir et al. lead II P-wave duration and left atrial enlargement in the electrocardiograph were determined from standard ECG. In multivariate analysis left atrial enlargement (relative risk 2.7 fold) but not the P-wave duration was an independent predictor of AF after CABG (Aytemir et al. 1999). Passman et al. found that P-wave duration in lead V1 was an independent predictor of AF after CABG (Passman et al. 2001). The age-adjusted odds ration (OR) for AF was 2.30 when P-wave duration in lead V1 was >110 milliseconds. Tsikouris et al. measured P-wave dispersion and maximum P-wave duration on the 12-lead ECG preoperatively and on postoperative day 1-4 in patients undergoing open-heart surgery (Tsikouris et al. 2001). They found that P-wave dispersion is greatest on days 2 and 3 and the longest atrial conduction time is greatest on day 3 after open-heart surgery, findings that coincide with the time of greatest risk of AF.

Steinberg et al. did not find a statistically significant difference of long P-wave duration in the standard ECG between patients who progressed to AF and those who remained in SR after CABG. Stafford et al. analysed lead II P-wave duration, total P-wave duration, and P-terminal force in standard ECG. No significant differences were observed in any of these variables between patients who developed AF and who did
not after CABG (Stafford et al. 1997). Similarly, no difference was reported on P-wave duration on standard ECG between the patients with AF and without AF after CABG in recently published study (Caravelli et al. 2002).

2.2.3. ECHOCARDIOGRAPHY

Two papers have shown left atrial enlargement to predict AF after open-heart surgery (Ducceschi et al. 1999, Giri et al. 2001). In a study by Ducceschi et al. the left atrial enlargement in transthoracic echocardiography was the strongest predictor of postoperative AF in CABG patients. The same finding was determined by Giri et al. in patients undergoing CABG, valve surgery or both. Asher et al. found left atrial enlargement to be an independent predictor of AF early after cardiac valvular surgery (Asher et al. 1998).

There are also contrary findings. In two studies the left atrial enlargement was not found to be independent predictor of AF after CABG (Stafford et al. 1997, Jideus et al. 2000). In addition, the study by Zaman et al. did not reveal any difference in the size of left atrium in echo assessment between the patients who had AF and those who remained in SR, but their study included only 64 patients and was subgroup of a larger study population (Zaman et al. 2000).

2.3. HEART RATE VARIABILITY

2.3.1. HEART RATE VARIABILITY AS PROGNOSTIC PREDICTOR IN CORONARY HEART DISEASE

The clinical implications of HRV analysis have been recognised in only two clinical conditions: as a predictor of risk of arrhythmic events or sudden cardiac death after acute myocardial infarction, and as a clinical marker of evolving diabetic neuropathy (Stys and Stys 1998).

In a multicentre postinfarction study involving 1,284 patients a strong correlation has been found between reduced HRV and total post-infarction mortality.
The observedly reduced HRV was independent of other prognostic factors and the
prognostic value was further enhanced in the subgroup of patients with a left
ventricular ejection fraction of less than 30% (La Rovere et al. 1998). In an
observational follow-up study involving 715 patients with recent myocardial
infarction, reduced HRV was associated with a 2-3 fold relative increased risk for
sudden cardiac death (Bigger et al. 1992). In an observational follow-up study by
Hartikainen et al., sudden arrhythmic death was associated predominantly with
depressed HRV and ventricular tachycardia runs (Hartikainen et al. 1996). In a
recently published observational follow-up study analysis of the fractal characteristics
of short term R-R interval dynamics was found to give more powerful prognostic
information than traditional measures of HRV among patients with depressed
ejection fraction after acute myocardial infarction (Huikuri et al. 2000).

In a case controlled study, 22 survivors of out-of hospital cardiac arrest, which
was not associated with acute myocardial infarction, were compared with 22 control
patients matched with respect to age, sex, previous infarctions, ejection fraction and
the severity of coronary artery disease. HRV parameters were reduced in cardiac
arrest patients compared to controls (Huikuri et al. 1992).

Pozzati et al. analysed eight patients who succumbed to ischaemic sudden death
during ambulatory ECG monitoring. They found a marked decrease in HRV
immediately before the onset of the ST-shift, which precipitated the ischaemic
sudden death (Pozzati et al. 1996). The records of implanted cardioverter-
defibrillators were analysed in 58 patients (Pruvot et al. 2000). A state of sympatho-
excitation was suggested by significant reduction in HRV before the ventricular
tachyarrhythmias.

The specificity and predictive accuracy of altered HRV in predicting fatal
arrhythmic events is relatively low. Therefore, widespread clinical application of this
method has not been established for monitoring the heart-rate behaviour in individual
patients (Lombardi et al. 2001).
Vikman et al. measured traditional time and frequency domain HRV indices, along with the short-term scaling exponent a and approximate entropy before the episodes of AF in 22 patients without structural heart disease (Vikman et al. 1999). Traditional HRV measures showed no significant changes before the onset of AF. But they observed that a decrease in the complexity of R-R intervals and altered fractal properties in short-term R-R interval dynamics preceded the spontaneous onset of AF.

2.3.2. HEART RATE VARIABILITY AS PREDICTOR OF ATRIAL FIBRILLATION IN THE RECOVERY PHASE AFTER CABG

Two studies have evaluated HRV preceding onset of AF after CABG with somewhat divergent results. Dimmer et al. analysed the HRV preceding onset of AF after CABG. They found that the LF/HF ratio was initially significantly lower in the AF group compared to the SR group, and there followed a significant increase in LF/HF ratio compared with the initial values in the AF patients (Dimmer et al. 1998). They concluded that a shift in the autonomic balance, with a loss of vagal tone and a moderate increase in sympathetic tone, are observed before the onset of AF. Also, Hogue et al. performed HRV analysis before the onset of AF in patients after CABG. They observed either lower or higher measures of HRV before AF, a finding consistent with a divergent autonomic condition before AF onset. They thought that in some patients heightened sympathetic tone is present before AF, but, in others, either higher vagal tone or dysfunctional autonomic heart rate control is present before AF onset (Hogue et al. 1998).

2.4. ATRIAL PEPTIDES

2.4.1. CLINICAL IMPORTANCE OF ATRIAL PEPTIDES

Atrial natriuretic peptide (ANP) is produced primarily in the cardiac atria. Increased atrial wall tension, reflecting increased intravascular volume, is the dominant stimulus for its release. ANP is synthesised from prohormone. Endocrinological active peptide ANP and its N-terminal prohormone fragments (N-ANP) are found in
plasma. Brain natriuretic peptide (BNP) is synthesised from prohormones mainly in cardiac ventricles (Levin et al. 1998).

It is well established that circulating ANP levels are increased in patients with chronic congestive heart failure in proportion to the severity of the disease and are elevated in patients with asymptomatic left ventricle dysfunction. Also the prognostic implications of ANP have been established in heart failure patients (Bonow 1996).

During the subacute phase of myocardial infarction, the cardiac natriuretic peptides are well-documented markers for identifying heart failure and they are powerful predictors of morbidity and mortality (Mair et al. 2001).

Natriuretic peptides have an excellent negative predictive value, particularly in high-risk patients. An increase in BNP is serious enough to warrant follow-up examinations. The measurement of natriuretic peptides can be used for quid therapy in heart failure and for risk stratification in heart failure and myocardial infarction (Mair et al. 2001).

In 911 healthy subjects high BNP and N-ANP were associated with old age, female gender, low diastolic blood pressure, low BMI, and high left atrial size (Wang et al. 2002).

### 2.4.2. ATRIAL PEPTIDES AND ATRIAL FIBRILLATION

It has been shown that AF is an independent determinant of high N-ANP levels, but, conversely high BNP levels are not uniquely associated with AF (Rossi et al. 2000). Longstanding AF causes depletion of ANP and N-ANP in patients with congestive heart failure. This finding suggests that longstanding AF leads to impaired ability of atria to produce these hormones because of the inherent degenerative processes (van der Berg et al. 2001).

ANP or N-ANP levels are not predictors of conversion to SR in AF patients (Hornestam et al. 1998, Shotan et al. 2001). Instead, elevated ANP level is an independent predictor of AF paroxysms in chronic heart failure. ANP levels higher
than 60 pg/ml had a hazard ratio of 8.6 for AF in 75 patients who had congestive heart failure but no previous AF (Yamada et al. 2000).

### 2.4.3. ATRIAL PEPTIDES AND CARDIOPULMONARY BYPASS

The concentration of ANP decreases during aortic cross-clamping, and a rebound increase occurs after removal of the clamp (Northridge et al. 1992). It has been shown that CPB decreases the molar ratio of cyclic guanosine monophosphate to ANP, which may represent the ANP biological activity (Hayashida et al. 2000). Kaukinen et al. showed that in patients with occluded right coronary artery both ANP and N-ANP concentrations were higher, and right ventricle ejection fraction was lower than in the patients with patent right coronary artery during the postoperative course after CABG (Kaukinen et al. 1997). They concluded that ventricular expression of ANP may be stimulated by right ventricular distension.

Human ANP was given for 24 hours from the start of CPB (Sezai et al. 2000). The patients who received human ANP showed significantly higher glomerular filtration rates, lower levels of renin, angiotensin-II, aldosterone, and pleural effusion and larger urine volume, compared with control patients. The authors concluded that the administration of human ANP compensated for the shortcomings of CPB by decreasing the peripheral vascular resistance, by suppressing the renin-angiotensin-aldosterone system, and by exerting a strong diuretic effect.

### 2.5. INTRAOPERATIVE SCREENING TEST

Intraoperative testing to determine the local refractory period of a particular site in the atrium is not technically feasible (Cox 1993). The value of intraoperative induction of AF has been studied in 50 patients who underwent CABG (Lowe et al. 1991). The intraoperative induction of atrial fibrillation with alternating current had a sensitivity of 94% and a specificity of 41% for the occurrence of postoperative atrial
arrhythmias. The negative and positive predictive values of the test were 0.93 and 0.47, respectively.
3. **AIMS OF THE PRESENT STUDY**

The aim of this study was to evaluate if patients at high risk of developing AF after CABG can be identified preoperatively or intraoperatively.

The specific aims were:

1. To determine the risk factors of postoperative AF in a large group of patients undergoing CABG and to create predictive model of postoperative AF after CABG. A secondary aim of this study was to evaluate the effects of AF on patients’ outcome (I).

2. To measure HRV preoperatively in CABG patients in order to test the hypothesis that increased sympathetic tone before surgery predicts AF after CABG (II).

3. To test the hypothesis that increased atrial sizes and increased level of atrial peptides would be predictors for AF after CABG. Secondarily we measured atrial peptides in the early postoperative period (III).

4. To test whether AF induced by intra-operative atrial high-rate pacing can be used to identify patients at risk for postoperative AF (IV).
4. PATIENTS AND METHODS

4.1. PATIENTS

4.1.1. STUDY I

The study was conducted at Kuopio University Hospital, having been approved by the Ethical Committee. The need for informed consent was waived, because the data used for the study had already been collected for clinical purposes. The retrospective material consisted of 3,676 patients having undergone CABG requiring cardiopulmonary bypass between January 1, 1992 and December 31, 1996. Patients who had AF in the preoperative ECG or some accompanying procedures in addition to CABG were excluded. The preoperative, perioperative and postoperative data were collected from the patient records and stored in the cardiac surgical database. The association of pre- and perioperative factors to postoperative AF were assessed, as were the occurrence and consequences of postoperative complications being associated with development of AF.

The regression model predicting postoperative AF was tested in the prospectively collected material. The prospective material consisted of 1,107 CABG patients operated between September 1, 1998, and December 30, 1999. The exclusion criteria were the same as in the retrospective material. Detailed pre-, peri- and postoperative data were collected by a cardiologist and were entered into a cardiac surgical database. There were no apparent differences in operative techniques or postoperative protocols between the retrospective and prospective patient series.

4.1.2. STUDY II AND STUDY III

The patient population was the same in study II and study III. One hundred patients were randomly enrolled into the study between November 1999 and November 2000 providing they fulfilled the inclusion criteria: elective primary isolated CABG using cardiopulmonary bypass. The exclusion criteria were: previous AF episodes, acute myocardial infarction within a month before surgery and ejection fraction less than 50% measured with echocardiography or left ventricle kine-angiogram. All
procedures used in this study were approved by the Kuopio University Ethical committee. Informed consent was obtained from every patient before entering the study.

4.1.3. STUDY IV
Eighty patients scheduled for elective cardiopulmonary bypass requiring CABG in Kuopio University Hospital between August 2000 and June 2001 were included in the study. Patients with a history of AF were excluded. Also patients with additional procedures or with unstable angina pectoris were not included. The study protocol was approved by the Kuopio University Ethical committee. Informed consent was obtained from every patient before entering the study.

4.2. DESCRIPTION OF PROCEDURES
4.2.1. OPERATIVE TECHNIQUE
The ascending aorta was cannulated for arterial line and a single stage venous cannula was inserted through the auricle of the right atrium. Aortic root venting was used routinely. Cardiopulmonary bypass with moderate systemic hypothermia (temperature of venous blood 32°C) and moderate haemodilution (haematocrit >0.22) was used with flow rates of 2.2-2.4 l/m² and mean perfusion pressure of 50-85 mm Hg. Intermittent cold crystalloid cardioplegia was administered through the antegrade route. Peripheral and central anastomoses were constructed during single aortic occlusion. Cardioplegia solution consisted of magnesium 16 mmol/l and no extra magnesium substitution was given.

4.2.2. POSTOPERATIVE CARE AND FOLLOW UP
After the operation patients were followed in the intensive care unit (ICU) and were weaned off the ventilator when they fulfilled the following criteria: hemodynamic stability, peripheral temperature more than 32°C, co-operativity, and no major bleeding. Chest drains were removed on the first postoperative day and the patients
were moved to the surgical ward when their hemodynamics and respiration were stable. In studies II, III and IV, postoperative continuous ECG monitoring was carried out during the whole period of hospital stay to detect all episodes of AF and twelve-lead ECG was used to confirm the rhythm abnormality. The ECG recordings were checked daily by the surgeon. Postoperative potassium level was measured twice a day during the study period and potassium was administered as needed to keep the potassium serum concentration within normal range. Aspirin was administered 100 mg daily starting on the first postoperative day. In studies II, III and IV, β-blocking medication (metoprolol) was continued in every patient starting on the first postoperative day, and the dosage was titrated for a resting heart rate 60-90. No other anti-arrhythmic medication was given. In study I, β-blocking medication was used in patients who had no contraindications such as bradycardia or severe asthma.

4.3. STUDY SETTINGS

4.3.1. LOGISTIC REGRESSION MODEL

Data from 3,676 consecutive patients were retrospectively analysed. Detailed pre-, peri- and postoperative data had been prospectively collected by a cardiologist and had been entered into a cardiac surgical database. On the basis of these data a multivariate logistic regression model was created. This model was validated prospectively in 1,107 patients.

4.3.2. ANALYSIS OF HEART RATE VARIABILITY

Function of the autonomic nervous system was evaluated by short-term measurements of HRV. HRV measurement was performed in the Department of Clinical Physiology the day before surgery. A commercial software package (CAFTS, version 3.3.9 Medicro Inc., Kuopio, Finland) was used for all data acquisition and analysis. Continuous ECG recording was performed in three different conditions:
1) Spontaneous breathing: ECG was recorded for a 10 min period during normal spontaneous breathing in supine position.

2) Controlled breathing: ECG was recorded for a 10 min period during fixed breathing frequency of 0.2 Hz in supine position.

3) After 2 min recording in supine position with normal breathing, the subject was passively tilted up to a 70 degree angle position for a period of 10 min.

Data were analysed by the CAFTS software package. The time domain analysis of HRV included standard deviation of normal-to-normal RR intervals (SDNN) and the square root of the mean squared differences of adjacent RR intervals (RMSSD) during a 5 min period free from ectopic beats. For the power spectral analysis, an autoregressive modelling with fixed model order of 14 was used. Spectral analysis of HRV included total power, high-frequency (HF) component (0.15 to 0.40Hz), low-frequency (LF) component (0.04 to 0.15 Hz) and very low-frequency (VLF) component (0 to 0.04 Hz ). Thereafter, the LF/HF ratio and HF power in normalised units (HF nu), i.e. HF power/(Total power-VLF power)*100, was calculated. LF power was normalised as well (LF nu), i.e. LF power/(Total power-VLF power)*100.

4.3.3. MEASUREMENT OF ATRIAL SIZES AND CONCENTRATIONS OF ATRIAL PEPTIDES

Preoperatively each patient had a transthoracic echocardiographic evaluation study by a cardiologist (HP Sonos 2500, Hewlett Packard, USA). The sizes of the left and right atria were measured in the apical four-chamber view.

Venous blood samples from the cubital vein, for the analysis of atrial natriuretic peptide (ANP), N-terminal natriuretic peptide (N-ANP) and brain natriuretic peptide (BNP), were taken preoperatively, and 18 hours and 28 hours postoperatively. ANP and BNP were extracted from plasma using SepPak C18 cartridges. N-ANP was
assayed directly from unextracted plasma. The radioimmunoassay protocols have been described previously for ANP (Vuolteenaho et al. 1985) and N-ANP (Vuolteenaho et al. 1992). The BNP assay was performed with the same protocol as ANP. The sensitivities of the ANP, N-ANP, and BNP assays were 1.0, 40 and 0.5 pmol/l plasma, respectively. The ‘within and between’ assay coefficients of variation in each assay were <10 and <15%, respectively. The different assays were specific for the particular peptide. The ANP and N-ANP assays cross-reacted fully with proANP and the BNP assay with proBNP. With these methods, the following plasma levels (mean ± SD) were detected in healthy adult volunteers aged 20-55 years: ANP 10.9 ± 4.0 pmol/l, BNP 3.8 ± 3.4 pmol/l and N-ANP 227 ± 84 pmol/l (Vuolteenaho et al. 1992)

4.3.4. HIGH-RATE ATRIAL PACING TEST

After cannulation, but before starting the cardiopulmonary bypass, two epicardial pacing electrodes (Flexon-0, Tyco Healthcare Finland, Helsinki, Finland) were sutured into the right atrial wall. One electrode was sutured to the sinoatrial node region and the other two centimetres away from it to the lateral wall of the right atrium. The interelectrode distance was the same for all patients. The right atrium was paced with an output programmed at two times the capture threshold using a rate of 200 beats per minute for 10 seconds. The rhythm was determined after the high-rate pacing was stopped. Patients were ECG-monitored during the test and the test was determined positive if the pulse rate was irregular and there were no p-waves before the QRS complexes. If the patient was in sinus rhythm the test was repeated after one minute with a rate of 250 beats per minute. If sinus rhythm was still present after the pacing the test was repeated after one minute with a pacing rate of 300 beats per minute. Thereafter, the cardiopulmonary bypass was initiated.
4.4. STATISTICS

All the statistical procedures were performed by SPSS 9.0 statistical package (SPSS Inc., Chicago, Illinois, USA). Values are expressed as mean±SD unless otherwise indicated. In study II the distribution of power spectral analysis values was skewed and, therefore, log-transformed before statistical analysis. Differences in continuous and categorised variables were tested by unpaired t-test and chi-square, or Fischer’s exact test, respectively. Paired t-test was used to test differences of pre- and postoperative values of atrial peptides (study III). Correlation between those variables that were significant in the univariate analyses was tested by Pearson’s correlation (continuous variables) or Spearman’s rank order correlation (categorised or nominal variables). Only one clinically relevant variable was chosen for multivariate analysis in the case of correlation (p<0.05). If a variable predicted AF in univariate analysis it was entered into backward stepwise logistic regression analysis in order to assess the independent predictors of AF (studies I-III). In study I, model calibration (precision) was evaluated by the goodness-of-fit statistics (Hosmer and Lemeshow 1989). The discrimination abilities (accuracy) of the predictive model were assessed with the area under the receiver-operating characteristic (ROC) curve (Hanley and McNeil 1983). The limit for statistical significance was p<0.05.
5. RESULTS

5.1. LOGISTIC REGRESSION MODEL

The majority of the patients were men (76.1%) and the mean age was 60.5 ± 8.5 years. Age distribution of the patients is presented in Figure 1. There were only four patients over 80 years of age. The overall incidence of AF was 31%. The mean age of the patients with AF was 63.9 compared with 58.9 years for the patients that remained in sinus rhythm (SR). The incidence of AF in age groups is presented in Figure 1.

Univariate analysis identified several preoperative patient-related factors which had high association with postoperative AF. The preoperative demographics data are shown in Table 5 for patients with and without postoperative AF.
Figure 1: Age distribution of patients and the incidence of postoperative AF in each age group.
Table 5. Statistically significant preoperative and perioperative variables in univariate analysis associated with postoperative atrial fibrillation.

<table>
<thead>
<tr>
<th>Preoperative variable</th>
<th>All patients</th>
<th>Sinus rhythm</th>
<th>Atrial fibrillation</th>
<th>p value; Patients in sinus rhythm vs. AF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=3,676</td>
<td>N=2,535</td>
<td>N=1,141</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) or % of subgroup, N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>60.5 (8.5)</td>
<td>58.9 (8.6)</td>
<td>63.9 (7.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.89 (0.17)</td>
<td>1.90 (0.17)</td>
<td>1.89 (0.17)</td>
<td>0.044</td>
</tr>
<tr>
<td>EF %</td>
<td>63 (14.1)</td>
<td>63.6 (13.8)</td>
<td>61.8 (14.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative haemoglobin g/l</td>
<td>142.4 (12.8)</td>
<td>142.7 (12.7)</td>
<td>141.5 (12.9)</td>
<td>0.007</td>
</tr>
<tr>
<td>Heart volume ml/m²²</td>
<td>468 (82.3)</td>
<td>462.2 (82.1)</td>
<td>481.2 (81.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>76.1%, 2,798</td>
<td>77.4%, 1,961</td>
<td>73.3%, 837</td>
<td>0.008</td>
</tr>
<tr>
<td>Female</td>
<td>23.9%, 878</td>
<td>22.6%, 574</td>
<td>26.6%, 304</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.1 (0.7)</td>
<td>3.1 (0.7)</td>
<td>3.2 (0.7)</td>
<td>0.010</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>28.7%, 1,056</td>
<td>27.3%, 693</td>
<td>31.8%, 363</td>
<td>0.005</td>
</tr>
<tr>
<td>Current or ex-Smoker</td>
<td>54.3%, 1,996</td>
<td>55.6%, 1,410</td>
<td>51.3%, 586</td>
<td>0.016</td>
</tr>
<tr>
<td>Serum creatinine level &gt;119 µmol/l</td>
<td>4.8%, 177</td>
<td>4.2%, 107</td>
<td>6.1%, 70</td>
<td>0.012</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>59.2%, 2,178</td>
<td>61.5%, 1,560</td>
<td>54.2%, 618</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Digoxin use preoperatively</td>
<td>4.9%, 180</td>
<td>3.6%, 92</td>
<td>7.7%, 88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diuretic use preoperatively</td>
<td>11.9%, 438</td>
<td>10%, 256</td>
<td>16%, 182</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of TIA</td>
<td>5.5%, 202</td>
<td>4.9%, 124</td>
<td>6.8%, 78</td>
<td>0.017</td>
</tr>
<tr>
<td>History of COPD</td>
<td>1.6%, 59</td>
<td>1.1%, 29</td>
<td>2.6%, 30</td>
<td>0.001</td>
</tr>
<tr>
<td>EF &lt; 50%</td>
<td>15.5%, 569</td>
<td>14.2%, 359</td>
<td>18.4%, 210</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Perioperative or early postoperative variables

| Need of IABP or inotropic support when weaning off the pump | 4.1%, 149 | 3.3%, 84 | 5.7%, 65 | 0.001 |
| Number of peripheral anastomoses | 4.5 (1.2) | 4.5 (1.2) | 4.6 (1.2) | 0.012 |
| Pump time | 117.2 (41.5) | 115.4 (40.9) | 119.1 (41.2) | 0.012 |
| Clamp time | 100.1 (34.7) | 98.8 (33.9) | 101 (35.4) | 0.037 |
| IABP or inotropic medication during the first 24 hours | 9.4%, 346 | 7.1%, 181 | 14.1%, 161 | <0.001 |
| Temporary conduction disturbance | 7.3%, 270 | 6.6%, 168 | 8.9%, 102 | 0.013 |
| Resternotomy because of bleeding | 3.7%, 137 | 3.3%, 84 | 4.6%, 53 | 0.049 |

BSA = body surface area; EF = ejection fraction; NYHA = New York Heart Association; TIA = transient ischaemic attack; COPD = chronic obstructive pulmonary disease; IABP = intra-aortic balloon pump.
Increased age, high volume of the heart in preoperative chest x-ray, preoperative use of digoxin, and preoperative use of diuretics had the strongest association with postoperative AF. Other factors with significant association were ejection fraction less than 50%, female gender, unstable angina pectoris, no ex- or current smoking, increased level of serum creatinine and smaller NYHA class.

Perioperative and early postoperative data are presented in Table 5. Univariate analysis showed that increased number of peripheral anastomoses, long pump time, and long aortic cross-clamp time were highly associated with high incidence of postoperative AF. The need for inotropic support and temporary conduction disturbance had association with AF.

Multivariate analysis identified five independent factors as predictor of postoperative AF (Table 6).

Table 6. Multivariate predictors of postoperative atrial fibrillation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>P value</th>
<th>B</th>
<th>OR</th>
<th>95% CI of OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age (continuous)</td>
<td>&lt;0.001</td>
<td>0.774</td>
<td>1.08</td>
<td>1.07 – 1.09</td>
</tr>
<tr>
<td>Increased body surface area (categorised)</td>
<td>0.006</td>
<td>0.0641</td>
<td>1.07</td>
<td>1.02 -1.12</td>
</tr>
<tr>
<td>Decreased ejection fraction (categorised)</td>
<td>0.048</td>
<td>0.0711</td>
<td>1.07</td>
<td>1.00 -1.15</td>
</tr>
<tr>
<td>Digoxin use preoperatively</td>
<td>0.003</td>
<td>0.4986</td>
<td>1.64</td>
<td>1.18 -2.29</td>
</tr>
<tr>
<td>IABP or inotropic medication during the first 24 hours</td>
<td>0.013</td>
<td>0.3180</td>
<td>1.37</td>
<td>1.07 – 1.77</td>
</tr>
<tr>
<td>Constant</td>
<td>–6.0296</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hosmer-Lemeshow goodness of fit p=0.0684, Chi-square 14.5549, and degrees of freedom 8.

CI = Confidence interval, IABP = Intra-aortic balloon pump, OR = Odds ratio

Old age was statistically the strongest predictor of AF with an odds ratio (OR) of 1.1 for each increasing year above the lower border of the age range. Preoperative use of digoxin increased the risk of postoperative AF 1.6 fold. The need of an intra-aortic
balloon pump (IABP) or the need of inotropic medication in the weaning off cardiopulmonary bypass, or during the first 24 hours postoperatively, increased the risk of postoperative AF 1.4 fold. For the regression analysis, body surface area (BSA) was divided into ten (10) categories: <1.5\(m^2\), 1.5-1.6 \(m^2\), 1.6-1.7 \(m^2\), and >2.3 \(m^2\). The ejection fractions were arbitrarily grouped as well as follows: >60\%, 50-60\%, 40-50\%, 30-40\% and less than 30\%. Increasing body surface area and low ejection fraction were independent risk factors for postoperative AF.

Model calibration (precision) statistics are shown in Table 6 and the results of ROC analysis in Figure 2. The area under the ROC curve was 0.690, 95\% confidence interval 0.657-0.724, and \(p<0.001\). The negative predictive value of the model was 71.5\% and the positive predictive value was 54.7\% (cut off level 0.5). The retrospective derivation patient series was not quite comparable with the prospective validation series: the prospective patients were older (62.9 ± 9.3 vs. 60.3 ± 8.5 years, \(p<0.001\)), they had lower preoperative haemoglobin values (138.6 ± 13 vs. 142.6 ± 12.7, \(p<0.001\)), shorter perfusion time (94.3 ± 31.1 vs. 114.4 ± 38.2 min, \(p<0.001\)), shorter aortic cross clamp time (82.6 ± 25.6 vs. 97.9 ± 32.2 min, \(p<0.001\)), and the number of peripheral anastomoses was lower (4.1 ± 1.1 vs. 4.5 ± 1.2, \(p<0.001\)).
Figure 2. Discrimination power of the regression model predicting postoperative AF from data of preoperative phase and of the first 24 postoperative hours. The model described in Table 2 was tested in the prospective validation patient series, N=1,107. The area under the ROC curve was 0.690, 95% confidence interval 0.657-0.724, and p<0.001.

Figure 2: ROC curve showing the discrimination power of the regression model predicting postoperative AF.
Postoperative outcome of the patients with and without AF is presented in Table 7. Postoperative AF was associated with increased risk of complications. Patients with postoperative AF had a 2.3-fold increased incidence of stroke than patients without AF. The rate of confusion or postoperative psychosis was also significantly higher in the patients with AF. The patients with AF had a significantly greater number of serious gastrointestinal complications (pancreatitis, cholecystitis, ischaemic bowel complications or gastrointestinal bleeding).

### Table 7. Relationship of postoperative events to atrial fibrillation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>Sinus rhythm</th>
<th>Atrial fibrillation</th>
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<tr>
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<td>N = 2,535</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) or % of subgroup</td>
<td>Mean (SD) or % of subgroup</td>
<td>Mean (SD) or % of subgroup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative stroke</td>
<td>0.8%</td>
<td>0.6%</td>
<td>1.4%</td>
<td>0.008</td>
</tr>
<tr>
<td>Confusion or psychosis</td>
<td>1.8%</td>
<td>1.0%</td>
<td>3.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative TIA</td>
<td>0.5%</td>
<td>0.4%</td>
<td>0.7%</td>
<td>0.152</td>
</tr>
<tr>
<td>Multiple organ failure</td>
<td>0.7%</td>
<td>0.7%</td>
<td>0.6%</td>
<td>0.742</td>
</tr>
<tr>
<td>Anuria</td>
<td>0.9%</td>
<td>0.8%</td>
<td>1.1%</td>
<td>0.300</td>
</tr>
<tr>
<td>Severe GI complication</td>
<td>0.5%</td>
<td>0.3%</td>
<td>1.0%</td>
<td>0.005</td>
</tr>
<tr>
<td>Readmission to ICU</td>
<td>2.2%</td>
<td>1.1%</td>
<td>4.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>1.4%</td>
<td>1.6%</td>
<td>1.0%</td>
<td>0.121</td>
</tr>
<tr>
<td>Postoperative length of stay in ICU, days</td>
<td>1.6 (3.4)</td>
<td>1.4 (2.8)</td>
<td>2.2 (4.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative length of hospital stay, days</td>
<td>6.8 (4.7)</td>
<td>6.3 (3.7)</td>
<td>7.8 (6.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*TIA= Transient ischaemic attack; GI= gastrointestinal; ICU= Intensive care unit*
Readmission rate to the intensive care unit (ICU) of the patients with AF was more than 4-fold compared to the patients without AF. The length of the stay in the ICU as well as in the hospital was also significantly longer in the patients with postoperative AF.

5.2. ANALYSIS OF HEART RATE VARIABILITY

HRV was assessed in 100 patients. Four patients were excluded from the analysis because they were operated on with beating heart without cardiopulmonary bypass due to extensive calcification of the ascending aorta. Four patients had to be excluded from the HRV analysis, because there were not sufficiently long periods free of ectopic beats for the analysis. Therefore 92 patients formed the final study population.

The majority of the patients were males (n=70). Seventeen patients had diabetes and 2 patients used digoxin preoperatively. The average age was 61.7±9.9 yrs (range 40-85 yrs). All the patients had β-blocking agent medication preoperatively. Thirty (32.6%) patients developed AF postoperatively while 62 (67.4%) remained in SR. The time of occurrence of postoperative AF was 59±23 hours (range 12-115 hours) from the operation. There were no postoperative deaths in the study group. One perioperative stroke occurred. There were 4 perioperative myocardial infarctions (new Q-wave and increases in serum levels of MB isoenzyme of creatinine kinase); 3 of these were in the AF group and 1 in the SR group. The clinical and operative characteristics of the patients with and without postoperative AF are presented in Table 8.
Table 8. Clinical characteristics of patients with AF and with SR after CABG.

<table>
<thead>
<tr>
<th>Preoperative Characteristic</th>
<th>SR Patients, N=62</th>
<th>AF Patients, N=30</th>
<th>univariate p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59.7±9.7</td>
<td>66.0±9.0</td>
<td>0.004</td>
</tr>
<tr>
<td>Gender (men/women)</td>
<td>48/14</td>
<td>22/8</td>
<td>0.667</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.0±3.1</td>
<td>28.5±3.7</td>
<td>0.047</td>
</tr>
<tr>
<td>Current tobacco use</td>
<td>6, (9.7%)</td>
<td>4, (13.3%)</td>
<td>0.597</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8, (12.9%)</td>
<td>9, (30.0%)</td>
<td>0.048</td>
</tr>
<tr>
<td>COPD</td>
<td>2, (3.2%)</td>
<td>4, (13.3%)</td>
<td>0.066</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26, (41.9%)</td>
<td>18, (0.60%)</td>
<td>0.104</td>
</tr>
<tr>
<td>Digoxin therapy</td>
<td>1, (1.6%)</td>
<td>1, (3.3%)</td>
<td>0.596</td>
</tr>
<tr>
<td>History of MI</td>
<td>28, (45.2%)</td>
<td>10, (33.3%)</td>
<td>0.280</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>5, (8.1%)</td>
<td>3, (10.0%)</td>
<td>0.757</td>
</tr>
<tr>
<td>History of claudication</td>
<td>3, (4.8%)</td>
<td>4, (13.3%)</td>
<td>0.150</td>
</tr>
<tr>
<td>Creatinine (µg/ml)</td>
<td>91±11</td>
<td>94±17</td>
<td>0.321</td>
</tr>
<tr>
<td>Haemoglobin g/l</td>
<td>14±11</td>
<td>135±13</td>
<td>0.020</td>
</tr>
<tr>
<td>Perioperative Characteristic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary bypass time, min</td>
<td>90±28</td>
<td>99±38</td>
<td>0.239</td>
</tr>
<tr>
<td>Cross-clamp time, min</td>
<td>80±25</td>
<td>85±30</td>
<td>0.438</td>
</tr>
<tr>
<td>Number of bypass grafts</td>
<td>4.2±1.2</td>
<td>4.3±1.2</td>
<td>0.567</td>
</tr>
<tr>
<td>CK-MB mass (µg/l)</td>
<td>30±19</td>
<td>30±18</td>
<td>0.996</td>
</tr>
</tbody>
</table>

*COPD = chronic obstructive pulmonary disease, CK-MB mass = First postoperative creatinine kinase-MB mass, MI = myocardial infarction, the values are mean ± SD, univariate p is between the SR and AF groups.*

Univariate analysis showed that increased age, low preoperative haemoglobin value, diabetes, and high body mass index were associated with high incidence of postoperative AF. Multivariate analysis identified two independent factors as predictors of postoperative AF. Old age was the strongest predictor of AF with an odds ratio (OR) of 1.06 for each increasing year above the lower border (46 years) of the age range (p=0.03, 95% CI 1.0061-1.1248). Body mass index (BMI) was the other independent predictor of postoperative AF (OR 1.18 per unit, p=0.02, 95% CI 1.0259-1.3739)
Heart rate, SDNN or RMSSD did not differ significantly between AF and SR groups when tested either with spontaneous or controlled breathing. None of the spectral analysis measures (total power, VLF power, LF power and HF power) differed significantly either. In both groups, heart rate increased and SDNN decreased after tilting towards upright position, but there was no statistical difference between the groups. In power spectral analysis, total power and all of its components decreased after tilting up both in AF and SR groups but there was no statistical difference between the groups. There was no statistical difference between the groups in LF/HF ratio in any of the differing conditions. The results of HRV analysis are summarised in Table 9. Multivariate analysis did not identify any parameter of HRV analysis as an independent predictor for postoperative AF. Exclusion of diabetic patients from analysis of HRV did not significantly affect the result. Also exclusion of the patients who had history of myocardial infarction did not affect the result. Exclusion of the patients with unstable angina pectoris did not affect the result either.
Table 9. Result of HRV analysis in AF and SR patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SR Patients, n=62</th>
<th>AF Patients, n=32</th>
<th>univariate p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spontaneous breathing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>61.8±9.2</td>
<td>58.6±8.5</td>
<td>0.088</td>
</tr>
<tr>
<td>SDNN</td>
<td>28.3±15.7</td>
<td>33.0±16.1</td>
<td>0.192</td>
</tr>
<tr>
<td>RMSSD</td>
<td>21.5±14.6</td>
<td>26.4±18.3</td>
<td>0.172</td>
</tr>
<tr>
<td>Total power</td>
<td>6.3±1.1</td>
<td>6.7±1.0</td>
<td>0.137</td>
</tr>
<tr>
<td>VLF power</td>
<td>5.6±1.2</td>
<td>5.9±1.0</td>
<td>0.131</td>
</tr>
<tr>
<td>LF power</td>
<td>4.8±1.3</td>
<td>4.8±1.3</td>
<td>0.988</td>
</tr>
<tr>
<td>HF power</td>
<td>4.5±1.4</td>
<td>4.9±1.5</td>
<td>0.228</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>1.1±0.4</td>
<td>1.0±0.3</td>
<td>0.196</td>
</tr>
<tr>
<td>LF nu</td>
<td>8.3±5.3</td>
<td>11.0±11.0</td>
<td>0.203</td>
</tr>
<tr>
<td>HF nu</td>
<td>7.4±4.3</td>
<td>10.6±9.6</td>
<td>0.105</td>
</tr>
<tr>
<td><strong>Controlled breathing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>63.2±9.0</td>
<td>59.7±9.9</td>
<td>0.093</td>
</tr>
<tr>
<td>SDNN</td>
<td>27.2±14.2</td>
<td>26.8±15.1</td>
<td>0.894</td>
</tr>
<tr>
<td>RMSSD</td>
<td>21.7±17.4</td>
<td>22.0±18.6</td>
<td>0.947</td>
</tr>
<tr>
<td>Total power</td>
<td>6.2±1.1</td>
<td>6.1±1.1</td>
<td>0.626</td>
</tr>
<tr>
<td>VLF power</td>
<td>5.4±1.0</td>
<td>5.2±1.0</td>
<td>0.417</td>
</tr>
<tr>
<td>LF power</td>
<td>4.5±1.2</td>
<td>4.2±1.4</td>
<td>0.349</td>
</tr>
<tr>
<td>HF power</td>
<td>4.7±1.5</td>
<td>4.8±1.5</td>
<td>0.880</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>1.0±0.3</td>
<td>0.9±0.3</td>
<td>0.231</td>
</tr>
<tr>
<td>LF nu</td>
<td>7.2±4.4</td>
<td>6.6±4.1</td>
<td>0.544</td>
</tr>
<tr>
<td>HF nu</td>
<td>7.1±4.0</td>
<td>7.2±4.6</td>
<td>0.924</td>
</tr>
<tr>
<td><strong>Standing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71.1±10.8</td>
<td>68.9±9.4</td>
<td>0.351</td>
</tr>
<tr>
<td>SDNN</td>
<td>26.1±12.9</td>
<td>23.0±10.0</td>
<td>0.269</td>
</tr>
<tr>
<td>RMSSD</td>
<td>15.2±14.8</td>
<td>11.8±7.0</td>
<td>0.248</td>
</tr>
<tr>
<td>Total power</td>
<td>6.2±1.0</td>
<td>5.9±0.9</td>
<td>0.272</td>
</tr>
<tr>
<td>VLF power</td>
<td>5.5±1.0</td>
<td>5.5±0.9</td>
<td>0.912</td>
</tr>
<tr>
<td>LF Power</td>
<td>4.6±1.3</td>
<td>4.0±1.1</td>
<td>0.059</td>
</tr>
<tr>
<td>HF power</td>
<td>3.6±1.4</td>
<td>3.2±1.3</td>
<td>0.210</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>1.4±0.5</td>
<td>1.3±0.5</td>
<td>0.604</td>
</tr>
<tr>
<td>LF nu</td>
<td>11.4±8.4</td>
<td>12.8±7.3</td>
<td>0.458</td>
</tr>
<tr>
<td>HF nu</td>
<td>8.2±5.0</td>
<td>9.6±5.1</td>
<td>0.262</td>
</tr>
</tbody>
</table>

The values of power spectral analysis are logtransformed. HF = high frequency, LF = low frequency, nu = normalised unit, RMSSD = the square root of the mean squared differences of adjacent RR intervals, SDNN = standard deviation of normal-to-normal RR intervals, VLF = very low frequency.
5.3. MEASUREMENT OF ATRIAL SIZES AND CONCENTRATIONS OF ATRIAL PEPTIDES

Twelve patients were excluded from the analysis. The reasons for exclusion were: 4 patients had unplanned mitral valve procedure, 5 patients unexpectedly were operated on without cardiopulmonary bypass with beating heart due to calcification of ascending aorta, and 3 patients had incomplete data of atrial peptides. Thus, 88 patients formed the study population.

Seventy eight percent of the patients were male and their average age was 61.8 ± 9.9 years. All patients had β-blocking medication preoperatively. Postoperative AF occurred in 31 of 88 (35.2%) patients. The average time from the operation to the first AF episode was 56 ± 22 hours. The patients` demographics and operative data are summarised in Table 10. There were no hospital deaths in the study group. Two patients, both in the sinus rhythm (SR) group had to be reoperated due to postoperative bleeding. There were no perioperative myocardial infarctions or postoperative low output syndromes in the study group. Two perioperative strokes occurred, one in each group. One superficial sternal wound infection occurred in the AF group.

Atrial dimensions and other results of transthoracic echocardiographic assessment and the values of ANP, N-ANP and BNP levels are presented in Table 11. Results of the analysis of atrial areas are illustrated in Figure 3.
Table 10. Demographic, operative and postoperative data and univariate p value.

<table>
<thead>
<tr>
<th>Variable</th>
<th>SR group</th>
<th>AF group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=57, (%)</td>
<td>N=31, (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.6±9.9</td>
<td>65.9±8.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Female gender (n, %)</td>
<td>12, (21.1%)</td>
<td>7, (22.6%)</td>
<td>0.87</td>
</tr>
<tr>
<td>BMI</td>
<td>27.4±3.1</td>
<td>28.7±3.7</td>
<td>0.07</td>
</tr>
<tr>
<td>BSA (m^2)</td>
<td>1.92±0.17</td>
<td>1.97±0.19</td>
<td>0.21</td>
</tr>
<tr>
<td>COPD (n)</td>
<td>2, (3.5%)</td>
<td>3, (9.7%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>22, (38.6%)</td>
<td>18, (58.1%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Diabetes (n, %)</td>
<td>7, (12.3%)</td>
<td>9, (29.0%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Prior MI (n, %)</td>
<td>24, (42.1%)</td>
<td>12, (38.7%)</td>
<td>0.76</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.5±0.7</td>
<td>2.8±0.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Preop. digitalis (n, %)</td>
<td>0, (0.0%)</td>
<td>1, (3.2%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Preop. haemoglobin value (g/l)</td>
<td>141±11</td>
<td>136±13</td>
<td>0.062</td>
</tr>
<tr>
<td>Preop. creatinine value (µmol/l)</td>
<td>90±15</td>
<td>95±18</td>
<td>0.23</td>
</tr>
<tr>
<td>Smoking (n, %)</td>
<td>5, (8.8%)</td>
<td>4, (12.9%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Urgent operation (n, %)</td>
<td>4, (7.0%)</td>
<td>3, (9.7%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Number of Anastomoses (n)</td>
<td>4.2±1.2</td>
<td>4.3±1.2</td>
<td>0.76</td>
</tr>
<tr>
<td>Perfusion time (min)</td>
<td>91±27</td>
<td>94±30</td>
<td>0.75</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>82±24</td>
<td>82±28</td>
<td>0.92</td>
</tr>
<tr>
<td>RCA by-pass (n, %)</td>
<td>46, (80.7%)</td>
<td>25, (80.6%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Postop. CK-MB mass (µg/l)</td>
<td>27±16</td>
<td>29±18</td>
<td>0.59</td>
</tr>
<tr>
<td>Ventilation &gt; 24 h (n, %)</td>
<td>0, (0.0%)</td>
<td>1, (3.2%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Resternotomy (n, %)</td>
<td>2, (3.5%)</td>
<td>0, (0.0%)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

BMI=body mass index, BSA = body surface area, COPD = chronic obstructive pulmonary disease, NYHA=New York Heart Association, CK-MB mass = creatinine kinase-MB mass, the values are mean ± SD or n (%).
Table 11. Atrial areas and values of ANP, N-ANP and BNP and univariate p value.

<table>
<thead>
<tr>
<th>Variable</th>
<th>SR group</th>
<th>AF group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrium, cm²/m²</td>
<td>8.9±1.8</td>
<td>10.2±2.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Left atrium, cm²/m²</td>
<td>9.2±2.3</td>
<td>10.9±2.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Diameter of left ventricle wall, mm</td>
<td>11.8±2.2</td>
<td>12.8±2.5</td>
<td>0.06</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>52.0±6.7</td>
<td>50.7±6.5</td>
<td>0.37</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>33.8±5.4</td>
<td>32.4±6.1</td>
<td>0.26</td>
</tr>
<tr>
<td>Preop. ANP, pmol/l</td>
<td>57±28</td>
<td>79±58</td>
<td>0.016</td>
</tr>
<tr>
<td>Preop. N-ANP, pmol/l</td>
<td>337±147</td>
<td>426±230</td>
<td>0.03</td>
</tr>
<tr>
<td>Preop. BNP, pmol/l</td>
<td>10±10</td>
<td>14±16</td>
<td>0.15</td>
</tr>
<tr>
<td>1. postop. ANP, pmol/l</td>
<td>125±56</td>
<td>155±78</td>
<td>0.04</td>
</tr>
<tr>
<td>1. postop. N-ANP, pmol/l</td>
<td>536±244</td>
<td>697±315</td>
<td>0.01</td>
</tr>
<tr>
<td>1. postop. BNP, pmol/l</td>
<td>36±19</td>
<td>36±17</td>
<td>0.93</td>
</tr>
<tr>
<td>2. postop. ANP, pmol/l</td>
<td>110±41</td>
<td>148±91</td>
<td>0.008</td>
</tr>
<tr>
<td>2. postop. N-ANP, pmol/l</td>
<td>558±237</td>
<td>772±397</td>
<td>0.002</td>
</tr>
<tr>
<td>2. postop. BNP, pmol/l</td>
<td>35±19</td>
<td>33±15</td>
<td>0.650</td>
</tr>
</tbody>
</table>

LVEDD=left ventricle end diastolic diameter, LVESD= left ventricle end systolic diameter, ANP=atrial natriuretic peptide, N-ANP=N-terminal natriuretic peptide, BNP=brain natriuretic peptide, preop=preoperative, postop=postoperative. Values are expressed as mean ± SD.

Old age and increased left and right atrial dimensions were associated in univariate analysis with increased risk for postoperative AF. Increased level of ANP and N-ANP both preoperatively and postoperatively were also associated with increased risk for AF. There was no significant association between the level of BNP and the risk for postoperative AF. The level of all atrial peptides increased significantly after the operation compared with preoperative concentrations. There was a significant correlation between age and the level of N-ANP (r=0.451 and p<0.01). The correlation is illustrated in Figure 4.
Figure 3. Results of analysis of atrial areas.
Black boxplots represents patients who remained in sinus rhythm and open boxplots represents patients who went into atrial fibrillation. P-values are less than 0.05 between AF and SR groups both in the areas of right and left atrias.

Figure 4. Correlation between patient’s age and value of preoperative N-ANP.
Diabetes associated in univariate analysis with increased risk for postoperative AF and there was a trend indicating association between high body mass index and postoperative AF, as well as between low preoperative haemoglobin value and postoperative AF.

The sizes of the left and right atria correlated significantly (r=0.59, p<0.001) and only the size of left atrium was taken to multivariate analysis. The left atrium was chosen because of left atrial predominance in the initiation and maintenance of AF (Haissaguerre et al. 1998). Atrial size did not correlate with the level of ANP or N-ANP. The correlation between ANP and N-ANP was strong (r=0.64, p<0.001). Therefore only preoperative N-ANP value was taken to multivariate analysis.

Two variables were found to be independent predictors of postoperative AF. Age was one predictor of AF with an odds ratio (OR) of 1.07 for each increasing year above the lower border of the age range (p=0.02 and 95% CI 1.01-1.12). The other independent predictor was the cross sectional area of the left atrium. Each increasing cm$^2$ of left atrial area increased the risk of AF 1.29 fold (p=0.01 and 95% CI 1.05-1.57). Diabetes was not an independent predictor for postoperative AF in multivariate analysis.

5.4. **HIGH-RATE ATRIAL PACING TEST**

The mean age of all patients was 63.4 ± 8.3 years (range 41-77 years). Seventeen (21%) patients were female. All except 2 patients had β-blocking medication preoperatively and β-blocking medication was given to all patients postoperatively. All patients underwent CABG without additional procedures and the mean number of distal anastomoses was 4.1 ± 1.0. There was no mortality in the study group. One patient (1.3%) had a perioperative stroke and another patient (1.3%) returned to the operating room because of postoperative bleeding.

During the postoperative period AF developed in 28 patients (35%). The first AF episode appeared on average 52 hours postoperatively (range 5-100 hours). AF was
treated medically and all the patients were in sinus rhythm at the time of discharge. Patients who developed AF tended to be older ($p=0.09$), to have a higher creatinine kinase-MB mass postoperatively ($p=0.05$) and were more often female ($p=0.08$) compared to patients who remained in sinus rhythm (Table 12).

Table 12. Preoperative, perioperative and postoperative characteristics of patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SR, N=52, (%)</th>
<th>AF, N=28, (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.3±8.2</td>
<td>65.5±8.1</td>
<td>0.09</td>
</tr>
<tr>
<td>Female gender (n)</td>
<td>8, (15.4%)</td>
<td>9, (32.1%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>64±14</td>
<td>66±12</td>
<td>0.65</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>28, (53.8%)</td>
<td>19, (67.9%)</td>
<td>0.22</td>
</tr>
<tr>
<td>COPD (n)</td>
<td>1, (1.9%)</td>
<td>1, (3.6%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Diabetes (n)</td>
<td>11, (21.1%)</td>
<td>7, (25.0%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Pump time (min)</td>
<td>83±29</td>
<td>90±34</td>
<td>0.37</td>
</tr>
<tr>
<td>Cross-clamp time (min)</td>
<td>76±30</td>
<td>79±29</td>
<td>0.62</td>
</tr>
<tr>
<td>Number of anastomoses (n)</td>
<td>4.1±1.0</td>
<td>4.1±1.0</td>
<td>0.85</td>
</tr>
<tr>
<td>Right coronary bypass</td>
<td>47, (90.4%)</td>
<td>23, (82.1%)</td>
<td>0.29</td>
</tr>
<tr>
<td>CK-MB mass (µg/l)</td>
<td>29±18</td>
<td>46±58</td>
<td>0.05</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation, COPD = chronic obstructive pulmonary disease, CK-MB mass = First postoperative creatinine kinase-MB mass, SR = sinus rhythm. The values are mean ± SD or N (%).
High-rate atrial pacing test induced AF in 27 (33.7%) patients (Figure 5). Nine patients were inducible with the pacing rate of 200 beats per minute, 14 patients with the rate of 250 per minute, and 4 patients with the rate of 300 per minute. Of the 28 patients who developed AF during the postoperative period, 17 patients were inducible to AF in the test. Thus, the sensitivity of the test was 0.61. Of the 52 patients who did not develop AF postoperatively, 42 patients were non-inducible in the pacing test, giving a specificity of 0.81. The positive and negative predictive values of the test were 0.63 and 0.79, respectively. The rate of pacing which induced the AF, did not influence the sensitivity or specificity, when analysed separately.

Figure 5. Results of high rate atrial pacing test.

AF = Atrial fibrillation, SR = Sinus rhythm.
6. DISCUSSION

6.1. MATERIALS

In study I the retrospective patient population comprised all patients who had isolated CABG during the study period, apart from those patients who had AF preoperatively. The number of patients in our study is one of the biggest published patient material concerning AF after CABG. Because of the large number of patients, the sample is a good representation of the general patient population undergoing CABG. The group of 1,107 patients, in which the logistic regression model was validated, was not completely comparable in regards to age, preoperative haemoglobin values, perfusion time, aortic cross clamp time, and the number of peripheral anastomoses. This may be one reason why the discriminating power of the model was not exceptionally good.

In studies II and III the patients with the history of myocardial infarction less than one month preoperatively and the patients whose left ventricular ejection fraction were less than 50% were excluded. We did exclusions in order to minimise the factors, which might have influenced HRV and atrial peptide concentrations, and to achieve as uniform a study population as possible. A consequence of these exclusions the study cohort (II and III) does not represent completely the patient population undergoing CABG nowadays. A similar conclusion can be drawn in study IV in which the patients with unstable angina pectoris were excluded for safety reasons.

6.2. EVALUATION OF THE METHODS

Surgical and anaesthesiological methods that we used in the patients’ treatment are generally accepted and widely used. We used antegrade crystalloid cold cardioplegia for all patients in the study groups. In many other cardiac surgical centres other forms of cardioplegia are used, but the type of cardioplegia does not seem to have an effect on the incidence of postoperative AF (Butler 1993a, The warm heart investigators 1994, Pehkonen et al. 1995).
HRV was measured in the Department of Clinical Physiology under standardised physiological conditions. In HRV measurement, transthoracic echocardiographic evaluation, and analysis of concentrations of ANP, N-ANP and BNP, we used methods that are widely utilised in clinical practise.

We performed an intraoperative high-rate atrial pacing test just before starting cardiopulmonary perfusion. Some intra-operative factors might have an influence on the incidence of postoperative AF, therefore the diagnostic accuracy of the test would be even better if it were performed after finishing cardiopulmonary perfusion. But just after cardiopulmonary bypass myocardium is vulnerable and the AF induced by high-rate pacing test would be very harmful. There was no morbidity related to the pacing test in our study.

6.3. PREDICTORS OF AF AND ITS IMPACT ON OUTCOME

We found old age to be an independent predictor of postoperative AF (I, II, III). Old age has consistently predicted a high incidence of AF after CABG (Table 1). Increased age causes cardiac dilatation, muscle atrophy, conduction tissue decrease, and fibrosis in atria (Lie et al. 1988, Kitzman et al. 1990). These age-related changes may be responsible for increased risk for AF after CABG.

Decreased left ventricle ejection fraction was an independent predictor for post-CABG AF in our study (I). Poor left ventricular function is associated with a greater risk for the development of AF in non-surgical patients (Kannel et al. 1982), but, surprisingly, no other study has reported it as predictor of AF after CABG.

The need for IABP or the need for inotropic medication either when weaning off cardiopulmonary bypass, or anytime during the first 24 hours after operation was an independent risk factor for postoperative AF in our study (I). This correlation has also been found by other authors (Aranki et al. 1996, Almassi et al. 1997). Probably the increased risk of AF among patients requiring IABP therapy is not caused by IABP
itself, but it is related to other factors concurrent to IABP therapy: the use of inotropic agents, increased sympathetic activity, and heart. Thirty-day mortality was not different between patients with and without failure.

Preoperative digoxin use was independent predictor for postoperative AF in our study (I). This association between preoperative digoxin use and post-CABG AF has been found by some authors (Creswell et al. 1993, Almassi et al. 1997), but there are also contrasting findings (Hashimoto et al. 1991). It is apparent that in our study (I) digoxin was used for AF prophylaxis for many patients and, therefore, it actually reflects the increased risk related to previous episodes of AF paroxysm. Unfortunately, the previous AF paroxysms were not recorded in the cardiac surgical database.

We found that a large BSA was an independent predictor of postoperative AF (I). The large number (3676) of patients in the analysis make it unlikely that the caused by chance. We are not aware of any other study in which BSA was tested as a predictor of AF. We cannot find a plausible explanation as to why larger BSA predicts postoperative AF.

High body mass index was independent predictor for postoperative AF in study II but not in study I. Contrary to our result, Jideus et al. found that low BMI was independent predictor of AF after CABG (Jideus et al. 2000). However, the results of Jideus et al. and our own in study II are not conclusive and may be simply a result of the small number of patients in the studies. In our analysis of 3,676 patients (I) BMI did not differ between AF and SR groups either in univariate or multivariate analysis.

More postoperative complications were found in AF patients (I). The most serious complication of postoperative AF was stroke. The limitation of our study (I) was that we were not able to determine the exact timing of postoperative AF and stroke from our data, so it is difficult to draw conclusion if AF was predisposing factor for stroke, or whether the AF occurred after the stroke. However, postoperative AF was associated with a 2.3 fold increased risk of stroke (I). This is in agreement with other studies where postoperative AF has been an independent risk factor for
systemic embolic events and postoperative stroke (Creswell et al. 1993, Chung 1995, Aranki et al. 1996, Almassi et al. 1997). We also found that postoperative confusion or psychosis is related to postoperative AF (I). One possible explanation is that AF decreases the cardiac output and leads to hypoxemia, which might be the root cause of the confusion. The patients with AF had significantly more gastrointestinal complications than patients who remained in sinus rhythm (I). The plausible explanation for this is that low cardiac output during AF leads to ischaemia of the splanchnic area, and ischaemia is an initiating factor for gastrointestinal complications postoperative AF (I). Postoperative AF was associated with both a greater readmission rate to the ICU and longer stays in the ICU and the surgical ward (I). This finding has been reported by other investigators (Creswell et al. 1993, Aranki et al. 1996, Mathew et al. 1996, Almassi et al. 1997).

6.4. LOGISTIC REGRESSION MODEL

The accuracy of the predictive model was good according to Hosmer-Lemeshow statistics, but its discriminative power was not very good since the area under the ROC curve was below 0.75. There were significant changes in the age of the patient population, the duration of the operation from years 1992-1996 to 1998-1999 and the number of peripheral anastomoses. Some systematic changes of these variables might have influenced the discriminative power of the model. It is evident that there are other factors influencing the occurrence of postoperative AF than those included in the model. The positive predictive power of our model is comparable to the predictive power of signal averaged P-wave duration (0.55 vs. 0.34-0.65, respectively, Table 4.), but the negative predictive power is lower (0.72 vs. 0.82-0.87, respectively).

Discriminative power of the model appears at the moment to be not high enough for clinical purposes. In addition, one factor in the model (IABP or inotropic use during the first 24 hours after CABG) is not known preoperatively and that makes the clinical use of the model difficult in practice. According to the literature (Table 4)
signal averaged P-wave duration is clearly a predictive factor for postoperative AF, and, in addition, left atrial size in preoperative echocardiography predicts postoperative AF (III). If these two variables were included in the regression model, the discriminate power of the test would be higher.

6.5. HEART RATE VARIABILITY

We showed that a short-term preoperative analysis of HRV under standardised physiological conditions couldnt reliably identify patients at high risk for AF after CABG. The HF component of HRV corresponds to respiratory induced variations of heart rate and is mainly under vagal influence. The LF component of HRV is considered to be mainly a measure of cardiac sympathetic control (Malliani et al. 1991). The LF/HF ratio is thought to be marker of the sympathovagal balance. In our study values of LF/HF increased both in AF and SR groups in due to sympathetic activation induced by passive tilt but there was not a difference between groups.

Two earlier studies evaluated preoperatively the risk of postoperative AF after CABG with HRV. Frost et al. analysed HRV of a 24-hour preoperative Holter monitoring performed in 102 CABG patients (Frost et al. 1995d). They calculated the percentage of successive RR interval differences >6% (vagal index) and found it significantly lower in patients developing AF while the overall HRV was the same between AF and SR groups. They concluded that isolated reduction in the basic vagal modulation causes an autonomic imbalance in patients prone to develop AF after CABG. Our results are not in agreement with the results of Frost et al. While the vagal index correlated with the power of the HF component in spectral analysis of HRV, we did not recognise a difference in HF power between the AF and SR groups. Frost et al. performed their analysis of HRV in 24-hour monitoring and we in 5 minutes periods under three different conditions. This difference in the length of recording periods does not explain the different results, since both studies measured short-term HRV related to respiration. Jideus et al. did not find any difference in preoperative time and frequency domain variables between the patients who went
into AF and those who remained in SR (Jideus et al. 2001). This is in agreement with our study. However, they found that a diminished circadian variation in HRV before surgery indicated propensity for AF. The above-mentioned studies were based on the 24-hour monitoring of HRV. Long-term measures of HRV represent responses of cardiac autonomic regulation to challenges of daily life and a limitation to interpreting these findings is that these challenges are not controlled, the recordings are not stationary and the recording conditions cannot be standardised. These standardisation problems could be solved by using an assessment of short-term HRV. In addition, in the risk assessment of post-CABG, AF long-term HRV measurement requires additional resources and, therefore, it is not clinically feasible.

Two other studies have evaluated HRV preceding onset of AF after CABG (Dimmer et al. 1998, Hogue et al. 1998). Dimmer et al. found that LF/HF ratio was initially significantly lower in their AF group compared to the SR group and it was followed by a significant increase compared to the initial values in AF patients. This study showed that changes of autonomic tone rather than autonomic tone itself were important indicators before AF onset. Because these changes of autonomic tone happened within minutes or an hour, it is obvious that they cannot be recognised when analysing HRV a day before surgery as we did. Hogue et al. observed either lower or higher measures of HRV before AF after CABG, a finding consistent with divergent autonomic conditions before AF onset. They thought that in some patients heightened sympathetic tone is present before AF but in others, either higher vagal tone or dysfunctional autonomic heart rate control is present before AF onset. In order to find those patients at high risk of AF after CABG, postoperative assessment of HRV is not feasible. It shows the risk of AF just prior to its onset, when any prophylactic actions would be too late and, furthermore, it requires so many resources, that it is practically impossible to apply clinically.

Diabetic autonomic neuropathy may impact heart rate dynamics (Freeman et al. 1991). Exclusion of diabetic patients from the analysis did not significantly affect the results in our study. The LF power decreases during treatment with β-blocking agents
(Akselrod et al. 1981). All patients in our study group were on β-blocking medication on the time of HRV analysis. It is possible that withdrawal of β-blockade before HRV testing would have affected the results but, practically, it was not feasible. In this respect our study group was uniform and corresponds well with the clinical setting as most of the patients coming to CABG have β-blocking medication preoperatively. It has been shown that myocardial infarction may decrease HRV (Bigger et al. 1992). We also analysed HRV after exclusion of patients with a history of myocardial infarction, without significant effect on the result.

6.6. ATRIAL SIZES

Left atrial enlargement was an independent predictor of postoperative AF in the present study (III). Atrial dilatation is associated with structural changes in the atrial wall and, therefore, it is argued that the distribution of atrial refractoriness is not uniform. Abnormal dispersion of refractoriness makes the atria more vulnerable to development of AF after cardiac surgery (Sato et al. 1992). Our results are in agreement with Ducceschi et al. who found that left atrial enlargement in transthoracic echocardiographic assessment was the strongest predictor of postoperative AF in CABG patients (Ducceschi et al. 1999). The same finding was reported by Giri et al. in patients undergoing CABG, valve surgery, or both. Asher et al. found left atrial enlargement to be an independent predictor of AF occurring early after the cardiac valvular surgery (Asher et al. 1998).

There are also opposite findings. Jideus et al. did not find atrial enlargement to predict AF after CABG in a study involving 80 patients (Jideus et al. 2000). We cannot find a plausible explanation for this difference between the results of their study and ours. Zaman et al. also did not find association between atrial enlargement and AF after CABG, but their study comprised only 64 patients and the study was a subgroup of larger study (Zaman et al. 2000). Neither was a difference found in left atrial transverse diameter measured using transthoracic echocardiography between
patients who went into AF after CABG compared to patients who remained in SR (Stafford et al. 1997).

It is evident that the predictive value of left atrial size alone is not accurate enough for clinical purposes to identify the patients at high risk for AF after CABG. However, if left atrial size were included in the regression model (I), the discriminate power of the model would be higher.

6.7. ATRIAL PEPTIDES

Preoperative concentration of ANP and N-ANP were predictors of postoperative AF with univariate analysis, but they did not remain independent predictors of AF with multivariate analysis. We found a correlation between the patients’ age and the level of N-ANP, and this correlation was found also in the N-ANP assessment of healthy subjects (Wang et al. 2002). Thus, both the patient’s age and the level of N-ANP could not be taken into the same multivariate analysis. The main stimulus of release of N-ANP prohormone from the atrium is atrial wall stress (Edwards et al. 1988). The association between elevated N-ANP levels and postoperative AF is caused by left atrial wall stress. Age-related changes like fibrosis in the atria increases atrial wall stress and stimulates the release of ANP prohormone. This may explain the correlation between increased age and increased level of N-ANP. Another reason might be the decrease in the clearance of natriuretic peptides from plasma in elderly patients, even in the absence of renal dysfunction (Wang et al. 2002).

In non-surgical patients, plasma ANP and N-ANP have been reported to be raised in patients with heart failure and to increase further as the severity of the disease progresses (Burnett et al. 1986, Raine et al. 1986). N-ANP is a marker for symptomless left ventricular dysfunction (Lerman et al. 1993). Therefore, we excluded patients who had an ejection fraction of less than 50% from our study, in order to exclude known left ventricular dysfunction as a reason for any increased level of ANP. In addition it is known that ANP and N-ANP levels are markedly increased in patients with acute myocardial infarction (Jougasaki et al. 1990,
Svanegaard et al. 1992) and thus we also excluded patients who had had myocardial infarction within 30 days prior to the operation. Yamada et al. have shown in non-surgical patients that elevated ANP level is a predictor of paroxysmal AF in patients with congestive heart failure (Yamada et al. 2000). However, in our study ANP and N-ANP correlated with age, and they were not independent predictors of AF when adjusted for age. Jideus et al. did not find any association between preoperative values of ANP or N-ANP and AF after CABG (Jideus et al. 2000).

The level of N-ANP and ANP increased significantly after the operation compared with the preoperative values. This finding was in agreement with the result of other investigators (Jideus et al. 2000). Surgical trauma of atria and atrial wall stress because of fluid retention are the most plausible explanations for this change.

Preoperative atrial enlargement and concomitantly elevated preoperative plasma levels of atrial natriuretic peptides indicate an existence of pathophysiologic substrate for postoperative AF. The elevated levels of ANPs suggest that any pathophysiologic mechanism leading to an increase in atrial wall stress confer predisposition to electrical chaos and fibrillation. Increased postoperative level of the peptides indicates the same mechanism is significant at initiation of the AF. The patients with left ventricular systolic dysfunction were excluded in the present study (III). However, not only systolic but also diastolic dysfunction may cause an increase in filling pressure and an increase in atrial wall stress. Due to the wide overlapping of the plasma concentrations of the atrial peptides between the patients who went into AF and those who remained in SR, the preoperative peptide measurements offers only limited value for the assessment of the risk of postoperative AF.

6.8. HIGH-RATE ATRIAL PACING TEST

We developed a new intra-operative screening test for identifying the patients at high risk for postoperative AF (IV). The intra-operative high-rate atrial-pacing test turned out to be useful tool for identifying patients at high risk for AF after CABG. AF may begin as a rapid atrial tachycardia from the pulmonary veins, with
tachycardia remodelling promoting the transition to multiple-circuit re-entry AF (Haissaguerre et al. 1998, Hobbs et al. 1999). Re-entry and atrial fibrillation is facilitated when adjacent atrial regions have widely disparate refractory periods (Sato et al. 1992, Cox 1993). Our study suggests that high-rate atrial pacing mimics the rapid atrial tachycardia and thus identifies the patients vulnerable to AF. Atrial pacing with high rate induces AF in the presence of increased dispersion of refractoriness i.e. where some parts of atrial tissue are repolarised while the adjacent tissue is still depolarised.

Only one other study has tried intraoperatively to predict the risk of AF after CABG (Lowe et al. 1991). In contrast to our study, Lowe et al. did not use high-rate pacing but stimulated the mid-right atrium with a bipolar probe and alternating current to induce AF. The test induced AF in 36 of 50 patients. The sensitivity and negative predictive values of their test were better than those in our test (0.94 vs. 0.61 and 0.93 vs. 0.79, respectively). On the other hand, in our study, the specificity, positive predictive value, and accuracy were better (0.81 vs. 0.41, 0.63 vs. 0.47, and 0.74 vs. 0.60, respectively). This suggests, that the alternating current protocol employed in the other study may be more aggressive and results in too many false-positive cases and, therefore, it is not as suitable as the present protocol for the identification of patients with a need of anti-arrhythmic therapy.

The preoperative analysis of signal-averaged P-wave duration gives sensitivity of 0.63-0.86, specificity of 0.39-0.88, positive predictive value 0.34-0.65 and negative predictive value 0.82-0.87 in identifying the patients developing AF after CABG (Table 4). Thus, the result of intraoperative high-rate pacing test (IV), sensitivity 0.61, specificity 0.81, positive predictive value 0.63 and negative predictive value 0.79 are comparable with the predictive value of signal average P-wave duration.
7. SUMMARY AND CONCLUSIONS

AF is the most common arrhythmia CABG. It increases morbidity, resource utilisation, and costs of operative treatment. Prophylactic amiodarone administration and, perhaps, preventive pacing therapy reduce the incidence of AF after CABG. However, the routine use of these therapies for all patients undergoing CABG is not cost effective and may, in addition, cause unwelcome side-effects in some patients. The purpose our study was to find a reliable preoperative method for identifying patients at high risk for AF after CABG.

Data from 3,676 CABG patients were retrospectively analysed to create a logistic regression model to predict the risk of AF after CABG. The model was validated in 1,107 patients. Discrimination power of the model was not good enough for clinical use, since the area under ROC curve was 0.690. The negative and positive predicting value of the model was 0.72 and 0.55, respectively.

Short-term HRV was measured preoperatively in 92 elective CABG patients in standardised physiological conditions. No measured parameters of HRV analysis differed significantly between the patients who developed AF after CABG and those who remained in SR.

Atrial sizes were measured by preoperative echocardiography, and ANP and N-ANP preoperative levels were measured in 88 elective CABG patients in order to analyse their role in predicting the risk of postoperative AF. A large left atrium associated with increased risk of postoperative AF. A high concentration of ANP and of N-ANP correlated with increased risk of postoperative AF, but they were not independent when adjusted for age.

A new intra-operative high rate atrial-pacing test was developed. It was tested in 80 patients undergoing CABG. The positive and negative predictive values of the test (0.63 and 0.79, respectively) for postoperative AF were comparable with the results of other methods. No morbidity was related to the performance of pacing test.
On the basis of the present study following conclusions can be drawn:

1. Old age, large BSA, low ejection fraction, preoperative digoxin use, and IABP or inotropic medication during the first 24 hours after CABG, are independent predictors of postoperative AF. However, a logistic regression model with these parameters is not accurate enough for clinical application. Postoperative AF is associated with an increased risk of postoperative stroke, severe gastrointestinal complications, readmission to ICU, and longer ICU and hospital stays.

2. The patients at high risk of AF after CABG cannot be identified by preoperative short-term HRV analysis performed during standardised physiological conditions.

3. Left atrial enlargement was independent predictor for postoperative AF after CABG. ANP and N-ANP were associated with age and did not independently predict postoperative AF. Furthermore, the wide variation of the peptide levels renders the implementation of this measure in a clinical setting impractical.

4. The intraoperative high-rate atrial pacing test turned out to be simple, safe, and fast way to assess the patients at risk for AF after CABG. The diagnostic accuracy of this test seems to be sufficient to identify a group of patients to whom prophylactic treatment could be proactively targeted.
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