VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2007, Vol. 14, No. 3, pp. 274–280

ISSN 1897–5593

ACE inhibitor therapy: Possible effective prevention of new-onset atrial fibrillation following cardiac surgery

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Abstract

Background: *Atrial fibrillation (AF) is a common complication after coronary artery bypass grafting (CABG). The aims of the study were to assess possible predictors and identify modes of prevention of new-onset AF following coronary surgery.*

Methods: *Retrospective clinical and statistical analysis was made of the medical records of 217 patients who had undergone coronary surgery.*

Results: *AF occurred in 28% (61/217) of the patients. In univariate analysis the age of the patients with AF was higher ($p = 0.0033$), they had a longer history of coronary disease ($p = 0.0417$) and more had > 3 grafts ($p < 0.05$). Low ejection fraction (< 40%) was also a risk factor of arrhythmia ($p < 0.0001$). In multivariate regression analysis two independent predictors of AF were identified: no ACE inhibitor treatment before surgery ($p = 0.0005$) and age > 60 years ($p < 0.01$). Patients with AF had a higher mean heart rate after the procedure: 115 ± 34* vs. *78 ± 21/min ($p < 0.0005$). Patients treated with ACE inhibitors before and after surgery had a lower incidence of AF than non-treated patients: 8%* vs. *48% ($p < 0.0001$) and 4%* vs. *61%, $p < 0.0001$) respectively. Beta-blocker treatment before and after surgery resulted in a lower incidence of AF: at 23%* vs. *75% ($p < 0.001$) and 19%* vs. *96% ($p < 0.0001$), respectively.*

Conclusions: *No ACE inhibitor therapy before surgery, advanced age, low ejection fraction, high post-procedure heart rate, duration of coronary disease and the number of grafts (corresponding to the length of the procedure) were found to be strong probable predictors of AF following cardiac surgery. ACE inhibitor therapy may be effective in the prevention of new-onset AF. Treatment based on individual variables is crucial for proper treatment and to diminish the risk of arrhythmia.* (Cardiol J 2007; 14: 274–280)

Key words: atrial fibrillation, cardiovascular surgery, beta-blockers, angiotensin-converting enzyme inhibitors

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Received: 8.01.2007 Accepted: 3.04.2007

Introduction

Atrial fibrillation (AF) is a common complication after coronary artery bypass grafting (CABG). On the basis of a summary of 40 randomised (2270 patients) and 6 observational (16050 patients) trials this arrhythmia occurs in approximately 5–50% of patients [1, 2]. The consequences of AF are serious. Besides longer hospitalisation, there is a higher risk of cerebrovascular incidents, exacerbation of congestive heart failure, renal complications and a need for pacemaker implantation, all increasing the costs of treatment [2]. Arrhythmia is very common during the first three to five days of intensive care and is commonly treated with beta-blockers and other anti-arrhythmic drugs such as amiodarone, propafenone or verapamil. The precipitating causes of AF are considered to be indirect: volume expansion leading to acute atrial stretch, atrial and/or ventricular ischemia, sympathetic activation that alters atrial refractoriness and increases automatism and metabolic and electrolyte abnormalities [3]. Advanced age, low ejection fraction, male gender, duration of surgery and hypertension are factors that have been proven to increase the risk of AF. There is no significant difference in the prevalence of AF between surgery with or without cardiopulmonary bypass [3, 4]. Controlled studies have revealed that beta-blockers significantly reduce the occurrence and duration of AF attacks and the ventricular rate during these attacks [5, 6]. The still expanding potential of ACE inhibitors as hypotensive, anti-atherosclerotic, hemodynamic and, according to the results of the EUROPA study, anti-ischemic drugs, may have anti-arrhythmic implications [7]. We evaluated different clinical and biochemical predictors as well as pharmacotherapy in patients with late (4 or 5 days or more after surgery) new-onset AF CABG in a retrospective analysis.

Methods

Retrospective analysis was conducted of the medical records of 217 consecutive patients, 156 men and 61 women, with no history of AF who had undergone coronary surgery between January 2000 and December 2002. The patients had been admitted to the Ischemic Heart Disease Department after the 4th postoperative day. Patients who had undergone classical CABG surgery and OPCABG who were on sinus rhythm on the day of admission were included in the analysis. The diagnosis of paroxysmal AF, which took place after admission, was based on standard 12-lead ECG examination. Short transient episodes of AF in the first three days after CABG were not a subject of analysis. The drugs applied were evaluated retrospectively. Database management and statistical analysis were performed using the SAS statistical package (version 8e). For descriptive purposes, all data are presented as mean ± SD (continuous variables) or absolute frequencies and percentages where indicated (discrete variables). The normality of the data distribution was tested by the Shapiro-Wilk test. Differences in continuous variables between groups (AF+ and AF–) were analysed using Student's t-test. The χ^2 test was used for qualitative variables. All test procedures were two-sided with a p value of less than 0.05 indicating statistical significance. Multivariate logistic regression analysis was performed to determine which of these significant univariate predictors of AF provided prognostic information not provided by the others. A model was developed that incorporated only variables of potential statistical significance ($p < 0.05$ required to enter the logistic regression model). The study complies with the Declaration of Helsinki. All patient data was confidential. The research protocol was approved by the Scientific Committee of the Institute of Cardiology, Warsaw, Poland.

Results

The mean age of the patients was: 62.3 years, mean body mass index (BMI) was 27.1 and the mean history of coronary artery disease was 4.9 years since myocardial infarction or the onset of symptoms. The mean duration of hospital stay was 10 days. Paroxysmal AF, confirmed in 12-lead ECG examination, occurred in 28% (61/217) of patients with no previous history of this condition (Table 1). In the univariate analysis the age of patients with AF was higher: 65.2 ± 7.7 (SEM 1.1) *vs*. 61.2 ± 9.4 (SEM 0.8), $p < 0.05$. They had a longer history of coronary artery disease: 6.3 ± 5.7 (0.8) *vs*. 4.6 ± ± 4.9 (0.4), $p = 0.0417$. More of the patients with AF had three-vessel disease: 52% *vs*. 32% ($p < 0.05$), and more had > 3 grafts: 13% *vs*. 2% ($p < 0.005$). Ejection fraction was estimated by echocardiography (acoustic quantification method) or by contrast ventriculogram. Patients with a lower ejection fraction (< 40%) more frequently presented AF in the postoperative course: 51% with AF *vs*. 23% ($p < 0.0001$) (Table 1). Ejection fraction (< 40%) was a significant risk factor in univariate analysis (OR 3.4, 1.8–6.4) (Table 2). Multivariate regression analysis identified two independent predictors of arrhythmia

Table 1. Characteristics of the study group, univariate variables.

	No atrial fibrillation after surgery	Atrial fibrillation after surgery	p
No. of patients	156 (72%)	61 (28%)	
Baseline demographics			
Age [years]	61.2 ± 9.4	65.2 ± 7.7	0.0033
Gender (male/female)	110/46	46/15	NS
Weight [kg]	78.4 ± 12.0	78.9 ± 11.6	NS
Body mass index [kg/cm^2]	27.4 ± 3.5	27.2 ± 3.0	NS
Duration of CAD [years]	4.6 ± 4.9	6.3 ± 5.7	0.0417
Diabetes mellitus	25 (16%)	8 (13%)	NS
Hypertension	115 (74%)	44 (72%)	NS
Hyperlipidemia	128 (82%)	48 (79%)	NS
Smoking history	67 (43%)	21 (34%)	NS
History of myocardial infarction	84 (54%)	39 (64%)	NS
NYHA functional class			
I	33 (21%)	19 (31%)	NS
II	99 (63%)	36 (59%)	NS
III	23 (15%)	5 (8%)	NS
IV	1 (1%)	1 (2%)	NS
CCS functional class: III–IV	103 (66%)	33 (55%)	NS
Ejection fraction < 40%	36 (23%)	31 (51%)	< 0.0001
≥ 3 vessel disease	50 (32%)	32 (52%)	< 0.01
≥ 3 grafts	3 (2%)	8 (13%)	< 0.005
Therapy: before CABG			
Beta-blocker	151 (97%)	46 (75%)	< 0.0001
ACE-inhibitor	100 (64%)	9 (15%)	< 0.0001
Beta-blocker and ACE-inhibitor	98 (63%)	7 (11.5%)	< 0.0001
Therapy: after CABG			
Beta-blocker	155 (99%)	36 (59%)	< 0.0001
ACE-inhibitor	120 (77%)	5 (8%)	< 0.0001
Beta-blocker and ACE-inhibitor	119 (76%)	5 (8%)	< 0.0001

CAD — coronary artery disease, NYHA — New York Heart Association, CCS — the Canadian Cardiovascular Society, CABG — coronary artery bypass grafting, ACE — angiotensin converting enzyme

Table 2. Univariate and multivariate logistic analyses of selected variables.

	Univariate analysis		Multivariate analysis	
	Odds ratio	p	Adjusted odds ratio	p
Age > 60 years	2.31 (1.1–4.82)	< 0.05	8.54 (2.19–57.45)	< 0.01
ACE-inhibitor before	0.10 (0.04–0.21)	< 0.0001	0.15 (0.05–0.42)	0.0005
Ejection fraction < 40%	3.4 (1.8–6.4)	< 0.0001	1.57 (0.63–3.91)	NS
≥ 3-vessel disease	2.3 (1.3–4.3)	< 0.05	1.06 (0.51–1.90)	NS
≥ 3 grafts	7.7 (2.0–30.1)	< 0.005	1.11 (0.05–0.42)	NS

ACE — angiotensin converting enzyme

events: no ACE inhibitor treatment before surgery (p = 0.0005) and age > 60 years (OR 8.54, 2.19––57.45, p < 0.01). Treatment with ACE inhibitors was associated with a significant reduction in the risk of AF (OR 0.15, 0.05–0.42) (Table 2). In the multivariate models neither > 3-vessel disease nor ejection fraction < 40% was a determinant of the incidence of AF after coronary surgery. The area

under a receiver operating characteristic was 0.815 for all significant parameters in multivariate analysis. Patients with AF had a significantly higher mean heart rate (evaluated by 12-lead ECG examination) before incurring the arrhythmia: 101 ± 36 *vs*. 77 ± ± 15 ($p < 0.00001$). Patients with an AF episode had a higher level of leukocytes after surgery (+3700 ± 4300, $p < 0.0001$). There were no significant differences in red blood cell counts, hemoglobin, hematocrit, platelets or biochemical parameters (sodium, potassium, creatinine, BUN, glucose) between groups. Patients treated with beta-blockers before surgery had a lower incidence of AF: 23% *vs*. 75% in patients not treated ($p < 0.0001$). Treatment with beta-blockers introduced (as a continuation or start) after CABG resulted in a significantly lower incidence of AF: 19% *vs*. 96% in those not treated ($p < 0.0001$) (Fig. 1, 2). Patients with AF who were not treated with beta-blockers had a mean heart rate of 115 ± 34 per minute. In contrast, the mean heart rate of the patients treated was 78 ± 21 ($p < < 0.0005$). In multivariate regression analysis treatment with ACE inhibitors before surgery was associated with a lower risk of AF episodes in spite of higher BMI, lower ejection fraction and a smaller number of grafts in patients treated with ACE inhibitors. Administration of ACE inhibitors was associated with a lower incidence of AF before and after surgery: 8% *vs*. 48% of patients not treated ($p < 0.0001$) and 4% vs. 61% ($p<0.0001$) respectively (Fig. 1, 2). Patients treated with ACE inhibitors and beta-blockers before and after CABG had a consistently lower incidence of AF than those not treated: 7% *vs*. 48% ($p < 0.0001$), and 4% *vs*. 60% ($p < 0.0001$) respectively (Fig. 1, 2). No AT1--receptor blockers and amiodarone were used. Treatment with statins did not have any influence on AF occurrence or its course. None of the patients studied left the hospital with persistent AF.

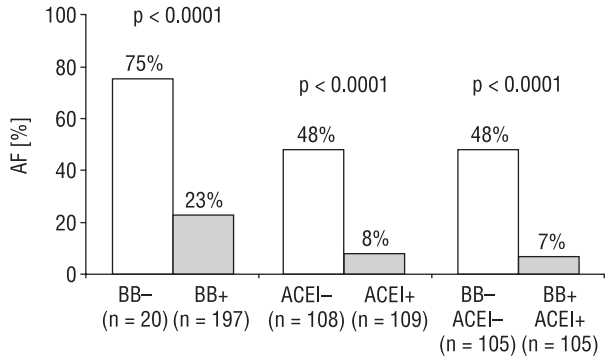

Figure 1. The influence of treatment before surgery on the onset of atrial fibrillation (AF); BB — beta-blockers; ACEI — angiotensin-converting enzyme inhibitors; n — number of patients.

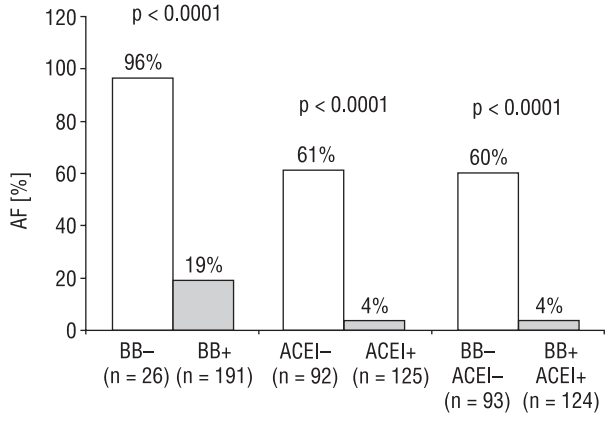

Figure 2. The influence of treatment after surgery on the onset of atrial fibrillation (AF); BB — beta-blockers; ACEI — angiotensin-converting enzyme inhibitors; n — number of patients.

Concurrent analysis of all variables was not possible because of the multi-colinearity of many of them. Statistical fitting of the models including most of the variables was questionable, therefore many parameters were removed for redundancy. Twenty variant models were tested.

Discussion

Although AF after cardiac surgery is quite a common complication, its pathogenesis has not been sufficiently clarified. Most studies report the occurrence of AF between the second and third postoperative days [3]. In our study patients were analysed who, on average, had been admitted to our department after the fourth postoperative day, when the general condition of a patient is considered to be stable. The mean duration of hospitalisation was 10 days. In a meta-analysis of 17 trials (980 patients) the peak incidence of AF was on the second and third day (22–37%). Between the fourth to tenth postoperative days this incidence did not exceed 10% [1]. In our analysis AF occurred in 28.6% of the patients. We did not analyse brief transient self-limited episodes of AF in the intraoperative and early postoperative settings.

One of the most common risk factors confirmed in the majority of studies is advanced age. Sclerotic changes within the atrial myocardium, endocardium, and epicardium result in fragmentation of distinct endocardial layers, infiltration of elastic and collagenous elements, and atrophy of atrial myocytes [8]. In addition to hemodynamic ventricular

and atrial influences, these changes promote intra-atrial conduction disturbances, non-uniform anisotropy and increased dispersion of refractoriness. Goette et al. [9] demonstrated that atrial fibrosis is an important pathophysiological substrate for postoperative AF. In a study from Leitch et al. [10], 17.2% of 5807 patients had AF: in the group below 40 years of age the incidence of AF was 3.7%, while in the group above 70 years it was 27.7%. A longer history of coronary disease correlates with age and the degree of changes in the atrial and ventricular myocardium. The study by Leitch et al. [10] cited above showed that 18% of patients with AF had disease of three more vessels and/or left main vessel disease, in comparison with 15.9% with < 3 vessels involved and without the left-main. The number of grafts corresponds to the degree of preoperative coronary disease and the duration of surgery. In our study 14% of AF patients had > 3 grafts, in comparison with only 2% patients in the non-AF group ($p = 0.0018$). This is in agreement with Leitch's observations, but the results of other smaller studies do not support these reports [11]. There were no significant differences in the mean values of biochemical parameters between groups, but patients treated with ACE inhibitors had a tendency towards higher levels of sodium and potassium.

Patients with a higher postoperative heart rate had a higher risk of AF due to autonomic imbalance. There is still controversy as to whether this is vagal or sympathetic in nature. Amar at al. [12] suggest parasympathetic resurgence competing with increasing sympathetic activity as a triggering mechanism for postoperative AF. Patients with AF had a higher level of white blood cells after surgery ($+3700 \pm 4300$, $p < 0.0001$). The white blood cell count is a marker of inflammation. According to a study by Sajadieh et al. [13], altered autonomic balance (increased heart rate and reduced heart-rate variability) can trigger inflammation and inflammation may, in turn, influence the autonomic balance; these processes can potentiate each other in healthy elderly subjects. These effects can be even more pronounced in patients with coronary artery disease (i.e. atherosclerosis) and can promote arrhythmia. Opinions vary on preventive drug treatment and how it should be administered. Digoxin has been used but, because of its narrow index of therapeutic concentrations, this was unsafe [2]. Class I and III anti-arrhythmic drugs are considered to be as effective in preventing and terminating episodes of AF as beta-blockers and calcium antagonists.

The prophylactic use of beta-blockers in the preoperative and postoperative periods is regarded as safe and beneficial in reducing the risk of AF and other forms of supraventricular arrhythmia. Beta-adrenergic stimulation increases atrial ectopy and shortens refractoriness, providing substrates for AF. It is more common in diseased hearts and is usually preceded by physical stress and an increase in heart rate [14]. In our study patients with AF had a significantly higher heart rate. Aside from pharmacological interventions, catecholamine excess may be due to emotional stress and hemodynamic changes. Patients after cardiac surgery who develop AF have higher norepinephrine levels than controls without arrhythmia [15]. Beta-blockers are safe and valuable drugs that suppress automaticity, prolong refractory periods and slow conduction velocity [2]. There are increasing data to indicate that beta-blocker withdrawal is more pro-arrhythmic, because of the increased beta-adrenergic receptor density in patients treated with these drugs, which makes them more sensitive to catecholamine stimulation in the absence of beta-blockers [16]. In our study 10% fewer patients with AF were treated with beta-blockers after surgery (76% *vs*. 66%). In the group without AF only 2% had beta-blocker treatment discontinued (90% *vs*. 88%).

On the other hand, many postoperative beta-blocker prevention trials have failed to demonstrate their protective effect [17]. There are many studies of preoperative beta-blocker usage with varied results. No clear relationship has been demonstrated between preoperative beta-blockers and a reduction in the incidence of AF. Generally, abrupt cessation of beta-blockers is hazardous because of their obvious indications, namely coronary artery disease and its possible complications: worsening angina, myocardial infarction, risk of sudden death and arrhythmia [18]. The consensus is that non-selective and selective beta-blockers are well tolerated and efficacious in reducing the risk of AF after surgery. This has been demonstrated in many trials and confirmed in two meta-analyses by Kovey et al. [5] (7 trials, 1418 patients, 20.2% *vs*. 9.8% $p < 0.001$) and Andrews et al. [6] (18 trials, 1549 patients, 34% *vs*. 8.7%, $p < 0.0001$). Propranolol was used in most of these. Other beta-blockers include timolol, atenolol, acebutolol, nadolol, and metoprolol. Sotalol was slightly more effective than other beta-blockers, probably thanks to its additional class III action [19]. Overall, beta-blockers can reduce arrhythmia after surgery by 50%. Patients should already be treated before surgery and therapy should be continued after it [18]. In the long term an effective dose of a beta-blocker should keep the heart rate to below 70 per minute, because a higher heart rate is

a significant risk factor of arrhythmia, as confirmed in our study. The widely accepted long-acting beta-blockers, (bisoporolol, betaxolol, metoprolol SR), seem to be more effective because of their pharmacokinetic and pharmacodynamic properties, resulting in continuous blockade of beta-1 receptors.

Angiotensin II promotes activation of fibroblasts and collagen accumulation, which leads to structural remodelling. The development of interstitial changes induced by MAP kinases increases the likelihood of AF. AF itself perpetuates the development of structural atrial alterations by increased expression of ACE and aldosterone [20]. Dipeptidil peptidase IV activity and atrial ACE expression are significantly increased as well, resulting in lower bradikinine levels during AF, which may contribute to degenerative changes [21]. Another mechanism of the deleterious action of angiotensin II is an increase in the calcium influx through L channels by the activation of protein kinase C and the phosphorylation of the channels [22]. Inhibition of the potassium current may influence the voltage of the action potential plateau and affect repolarisation [23]. Angiotensin II also inhibits junctional conduction, which increases the risk of re-entrant ventricular arrhythmia [24]. Nakashima et al. [25] demonstrated in an experimental study that angiotensin II contributes to atrial electrical remodelling.

Angiotensin II increases norepinephrine release from atrial sympathetic nerves by activation of prejunctional AT-1 receptors and can cause a decrease in beta-adrenergic receptor density [26, 27]. Cross-fire, therefore, occurs between the adrenergic and RAA systems. In the present study 100% patients without either ACE inhibitors or beta-blockers before or after surgery, had AF, in comparison with 32% with any kind of pre-surgical or post-surgical treatment ($p = 0.039$). Experimental work by Shi at al. [28] proved that ACE inhibition with enalapril attenuates heart-failure-induced atrial fibrosis and remodelling and reduces the risk of AF. Pedersen et al. [29] have shown in a sub-analysis of the TRACE study that prophylactic ACE inhibitor therapy reduces the risk of AF in patients after myocardial infarction. In hypertension and heart failure AF is a consequence of altered signal transduction [9]. In our study 32% of patients had a low ejection fraction of $< 40\%$, which is an additional argument for possible ACE inhibitor efficacy (Table 2). In addition to their beneficial influence on the electrolyte profile, the potential mechanisms of the deleterious action of angiotensin II mentioned above make treatment with ACE inhibitors logical. Recently many experimental studies on the subject have been published.

Our results, which were first published as an abstract in 2003 [30], are consistent with the results of a multicentre prospective observational study by Mathew et al. [31]. In this study AF occurred in 32.3% of patients after CABG (1503/4657). A reduced risk of AF episodes was associated with the postoperative administration of beta-blockers (OR 0.32, 95% CI 0.22–0.46), ACE inhibitors (OR 0.62; 95% CI 0.48–0.79), potassium supplementation (OR 0.32; 95% CI 0.42–0.68) and non-steroidal anti-inflammatory drugs (OR 0.49; 95% CI 0.40––0.60) Withdrawal of beta-blockers and ACE inhibitors resulted in a significant increase in the odds of developing AF. Further clinical prospective studies are needed to clarify this issue.

Limitations of the study

The study is limited by its method, the retrospective analysis of patients' files. The analysis encompassed consecutive patients transferred to our department following bypass surgery. The other potential limitations are the differences in the kinds of ACE inhibitor and beta-blockers used and the varied doses of these drugs.

Conclusions

ACE inhibitor therapy may be effective in the prophylaxis of new-onset atrial fibrillation Advanced age, duration of coronary artery disease, the number of grafts, reflecting the duration of the procedure, and a low ejection fraction are strong probable predictors for post-discharge atrial fibrillation following cardiac surgery. Therapy based on individual variables is crucial for proper treatment and diminishing the risk of arrhythmia. We believe that optimal pharmacological treatment with beta-blockers and ACE inhibitors with proper dose and drug selection is an effective method of preventing arrhythmia.

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