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Original Article

Predictors of Postoperative Atrial Fibrillation after On-Pump Coronary Artery Bypass Grafting: Is Duration of Mechanical Ventilation Time a Risk Factor?

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Purpose: This study aimed to establish the role of risk factors in the etiology of postoperative atrial fibrillation (AF) after coronary artery bypass grafting (CABG).

Methods: Between September 2001 and March 2008, 1040 patients underwent isolated CABG at our clinic. Nine hundred and eleven of these patients did not have any AF (Non-AF Group) and the other one hundred and twenty-nine had AF (AF Group). A retrospective study was performed for patient, disease and treatment related factors and multivariate analysis was used to identify independent clinical predictors of postoperative AF.

Results: Postoperative AF was identified in 129 (12.4%) of the patients, and those were significantly older and had significantly higher additive EuroSCORE score as compared with patients without AF. During the postoperative course, patients with postoperative AF also had significantly higher and prolonged (≥6 hours) mechanical ventilation time, longer and prolonged intensive care unit stay and longer hospital stay. Logistic regression analysis revealed that postoperative AF development ratio was 1.690 times higher when the ventilation time was over 6 hours (OR 1.690, 95% CI 1.092–2.615, p = 0.018); 1.240 times higher in the presence of elevated additive EuroSCORE score (OR 1.240, 95% CI 1.109–1.385, p = 0.0001); 1.052 times higher in the presence of advanced age (OR 1.052, 95% CI 1.031–1.0741, p = 0.0001).

Conclusion: Analysis of our data reveals that, patient's age, additive EuroSCORE score, and prolonged ventilation are predictors of postoperative AF. Identification of risk factors might lead to better prevention of this problem and its potential consequences. However, to support our investigation and obtain more reliable evidence, prospective randomized controlled trials are needed.

Keywords: cardiopulmonary bypass, coronary artery bypass grafting, atrial fibrillation, ventilation

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Introduction

Atrial fibrillation (AF) is the most common complication which affects approximately 10% to 65% of the patients undergoing coronary artery bypass graft surgery (CABG).[1] The presence of AF following CABG is associated with a two-fold increase in cardiovascular morbidity and mortality.[2] There is a higher occurrence of heart failure and stroke, both related to longer hospital stay, and consequently, with very high surgery costs.[3]

The underlying mechanisms that lead to onset and persistence of arrhythmia have been difficult to elucidate. Recent studies suggest that a multifactorial mechanism is involved which includes oxidative stress, inflammation, atrial fibrosis, excessive production of cathecolamines, changes in autonomic tonus and in the expression of connexins that lead to the formation of a pro-arrhythmic substrate.[4]

Some risk factors are related to an increase in the occurrence of postoperative AF, such as old age, gender, obesity, systemic arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease, history of paroxistic AF, previous myocardial infarction, left ventricular dysfunction, discontinuation of beta adrenergic drugs prior to surgery, aortic cross-clamp time, use of extracorporeal circulation, postoperative ischemia and use of vasoactive amines.[5,6]

A clinically useful prediction model for postoperative AF in CABG patients is still lacking. The prediction of AF may reduce postoperative complications and hospitalization time. In this study, we aimed to identify predictors of postoperative AF through preoperative and surgical variables. We further wanted to evaluate the predictive quality of the final model by multivariate analysis.

Materials and Methods

Study design

A retrospective study was performed on 1040 consecutive patients who underwent isolated CABG surgery at our institution between September 2001 and March 2008 in our clinic. Of these patients, 911 did not present AF postoperatively (Non-AF Group), whereas 129 did (AF Group). The exclusion criteria were previous atrial arrhythmia, need for additional procedures, emergency operation, left ventricle dysfunction, renal dysfunction, chronic obstructive pulmonary disease, re-operation and beating heart surgery.

Outcome parameters

A retrospective study was performed for relevant preoperative, intraoperative and postoperative data of the study group. The specific pre- and intraoperative data obtained for each case were age and gender; history of hypertension, diabetes, smoking, obesity, hyperlipidemia, body surface area and body mass index, family history of coronary artery disease, previous cerebrovascular accident or myocardial infarction (MI), presence of unstable angina, prior percutaneous transluminal coronary angioplasty, presence of carotid artery disease, presence of peripheral artery disease, left ventricular ejection fraction, presence of left main coronary artery disease, additive EuroSCORE (European System for Cardiac Operative Risk Evaluation) score and extent of coronary disease. The postoperative data collected were number of grafts per operation and graft types used (i.e., left internal mammary artery, radial artery or saphenous vein grafts), cardiopulmonary bypass time and aortic cross-clamp time, mechanical ventilation time, need for inotropic or intraaortic balloon pump support, perioperative MI (immediate postoperative period), infective, pulmonary, neurologic, or gastrointestinal complications, renal dysfunction, sternal dehiscence, re-exploration for bleeding or cardiac tamponade, prolonged ventilation time, length of stay in the intensive care unit (ICU), overall hospital stay, and hospital mortality (defined as death in the first 30 days after CABG). As noted, we also applied the additive EuroSCORE risk stratification model, which is widely used in cardiac surgery.[7]

Surgical management and postoperative care

In each case, the patient was placed under general anaesthesia and conventional median sternotomy was performed. All patients underwent on-pump CABG, and cardiopulmonary bypass was established by cannulating the ascending aorta and right atrium. Anticoagulation was achieved with heparin (3 mg/kg) such that activated clotting time was maintained at longer than 450 seconds and a roller pump and non-pulsatile flow (2.4 L/m^2/min) were used. The body was cooled to a core temperature of 32°C to 34°C when distal anastomosis was being performed, and was warmed to 36°C before weaning from cardiopulmonary bypass. Cold blood cardioplegia was delivered via antegrade and retrograde routes intermittently throughout the procedure. A final dose of "hot-shot" cardioplegia was administered just before the aorta was unclamped. An epicardial temporary pacemaker lead (FLEXON 3–0 temporary cardiac pacing

lead, Syneture, Covidien, Mansfield, Massachusetts, USA*)* was placed on right ventricle. None of our patients required pacing. All patients received β-blocker (metoprolol, nebivolol) pre and postoperatively until discharge. Metoprolol 50 mg twice a day was administered preoperatively to all patients and dosage was adjusted according to hemodynamic responses of patients. If radial artery graft was chosen, postoperative calcium channel blockers (diltiazem or nifedipine) were the drugs of choice. Nebivolol was preferred as an additional drug when nifedipine was used. All patients received once-daily subcutaneous low-molecular-weight heparin postoperatively until discharge. As a routine protocol, all postoperative patients received atorvastatin, acetylsalisilic acid and nitrate. angiotension receptor blockers were chosen for hypertensive patients if additional antihypertensive therapy is required. Criteria for extubation included an alert and hemodynamically stable patient with no excessive bleeding, ability of the patient to breathe through a T-tube for at least 30 minutes with a fraction of inspired oxygen of less than 0.40, a respiratory rate less than 25 breaths/min, an arterial blood PO_2 greater than 70 mmHg, a PCO_2 less than 40 mmHg, and a pH greater than 7.35, with no metabolic acidosis. Other criteria were a tidal volume of 6 mL/kg, a peak negative inspiratory pressure of less than 20 cmH_2O, and a mandatory chest radiograph before extubation to rule out pneumothorax, pleural effusion, and atelectasis. All postoperative patients are administered to ICU unit. Continuous electrocardiogram (ECG) monitoring is used for assessing cardiac rhythm and ECG changes for at least 48 hours. After discharge from the ICU, each individual was evaluated for radial pulse rate at least 4 times daily and for symptoms that suggest arrhythmia at each pulse check by residents and nurses, and the data were recorded. A 12-lead ECG was obtained immediately after each operation, on postoperative days 1, 2, and 4, and just before hospital discharge. A 12-lead ECG trace was also recorded immediately if a patient showed clinical signs of arrhythmia. All postoperative AF episodes required appropriate anti-arrhythmic treatment for their termination. To prevent stroke, any patient who developed AF was treated with standard heparin via intravenous injection instead of the low-molecular-weight heparin.

Definitions

AF was diagnosed if 12-lead ECG showed rapid oscillations or fibrillatory P waves that vary in size, shape, and timing, associated with irregular QRS complexes. For this study, postoperative AF was defined as AF of any duration in the postoperative period, with AF diagnosis based on physician assessment and 12-lead ECG findings. Patients who developed AF were treated with a standard protocol of anticoagulation and amiodarone. None of the 129 patients who developed AF required electrical cardioversion. All of these individuals were discharged home after conversion to sinus rhythm. A patient was considered to have perioperative MI if new Q waves appeared or there was significant loss of R-wave amplitude (>25% loss) in at least 2 leads on ECG. As noted, hospital mortality was defined as death in the first 30 days after CABG. Preoperative renal insufficiency was defined as serum creatinine level ≥1.5 mg/dL prior to CABG.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Relationships between post-CABG AF and preoperative, intraoperative, and postoperative factors were analyzed using different methods: the independent samples t-test for normally distributed continuous variables (expressed as mean ± SD), and chi-square and Fisher's exact tests for categorical variables, as appropriate. Each variable that yielded a result of $p \leq 0.2$ in univariate analysis was further analyzed in a multivariate logistic regression equation. We also performed regression analysis on certain variables that univariate analysis did not identify as independently associated with post-CABG AF but that the literature had previously identified as predictors. The results were assessed within a 95% reliance and at a level of $p < 0.05$ significance.

Results

This study was comprised of 911 patients (218 female, 693 males) without postoperative AF and 129 patients (34 female, 95 males) with postoperative AF. Postoperative AF incidence in this study was 12.4% (129/1040). Operative mortality was similar in both groups (1.6% vs. 1.8%, respectively; $p = 0.891$).

Non-AF group and AF group were compared in terms of patient, disease, and treatment related factors predisposing to postoperative AF after CABG surgery in **Table 1** and **Table 2**. Patients with postoperative AF were significantly older than those without AF. The mean age of the Non-AF group was 59.6 ± 9.7 years, as opposed to 64.1 ± 9.4 years for the AF group. The difference between the two groups was statistically significant

Table 1 Patient, and disease related factors predisposing to postoperative AF after CABG surgery

	Non-AF group (n = 911)	AF group (n = 129)	p Value
Age (years)	59.6 ± 9.7	64.1 ± 9.4	**0.0001**
Female gender	218 (23.9%)	34 (26.4%)	0.547
Diabetes mellitus	195 (21.4%)	17 (13.2%)	**0.030**
Hypertension	322 (35.5%)	54 (41.9)	0.157
Obesity	163 (17.9%)	20 (15.5%)	0.505
Body surface area (m^2)	1.78 ± 0.21	1.75 ± 0.17	0.468
Body mass index (kg/m^2)	26.2 ± 3.7	25.6 ± 3.9	0.086
History of smoking	545 (60%)	72 (55.8%)	0.362
Family history of CAD	294 (32.3%)	37 (28.7%)	0.408
Prior stroke	13 (1.6%)	2 (1.8%)	0.894
Hyperlipidemia	338 (37.9%)	49 (38.9%)	0.836
Unstable angina	148 (16.2%)	23 (17.8%)	0.650
Peripheral vascular disease	23 (2.5%)	3 (2.3%)	1.000
Carotid artery disease	96 (10.6%)	21 (16.3%)	0.073
Prior myocardial infarction	554 (60.9%)	81 (62.8%)	0.677
Prior PTCA	61 (6.7%)	5 (7.6%)	0.218
One-vessel disease	70 (7.7%)	9 (7%)	0.777
Two-vessel disease	316 (34.7%)	42 (32.6%)	0.634
Three-vessel disease	525 (57.6%)	78 (60.5%)	0.541
LMCA disease	25 (2.7%)	4 (3.1%)	0.820
LV ejection fraction (%)	51.3 ± 9.6	50.6 ± 9.2	0.676
EuroSCORE	3.2 ± 2.1	4.2 ± 2.2	**0.0001**
RCA-vessel disease	637 (71.4%)	90 (70.9%)	0.899

Data expressed as mean ± SD or n(%). AF: atrial fibrillation; CABG: coronary artery bypass grafting; CAD: coronary artery disease; PTCA: percutaneous transluminal coronary angioplasty; LMCA: left main coronary artery; LV: left ventricle; RCA: right coronary artery

(p = 0.0001). A significant negative correlation between diabetes mellitus and postoperative AF was detected. Patients with postoperative AF had significantly lower diagnosed diabetes mellitus than the Non-AF group (13.2% vs. 21.4%, p = 0.03). Patients with postoperative AF had significantly higher additive EuroSCORE score (4.2 ± 2.2 vs. 3.2 ± 2.1, p = 0.0001). There was a significant difference in mechanical ventilation duration and prolonged ventilation time between the groups (7.9 ± 5.2 vs. 10.6 ± 21.6, p = 0.002 and 66.9% vs. 77.3%, p = 0.017; respectively). In the AF group, ICU stay was longer (3.1 ± 1.6 days versus 2.3 ± 1.5 days, p = 0.0001; respectively). Length of hospital stay was also longer in the AF group 7.3 ± 1.9 days versus 6.6 ± 1.6 days, p = 0.0001; respectively). There were no statistical differences between patients with and without postoperative AF with respect to sex, presence of hypertension, hyperlipidemia, obesity or peripheral vascular disease, body surface area, body mass index, history of smoking, stroke, myocardial infarction or history of percutaneous transluminal coronary angioplasty, family history of coronary artery disease, included vessels, type of procedure, operating time, cross-clamp time, need for inotropic support, and postoperative complications.

When time frames of less than 6 hours, between 6 and 12 hours, between 12 and 24 hours and more than 25 hours are considered there was not any significant difference between AF and non-AF groups (**Table 3**).

After the significant risk factors were determined, assessment of the relative importance of the independent variables was established by using logistic regression analysis on these risk factors yielded the following data: postoperative AF development ratio was 1.690 times higher when the ventilation time was over 6 hours (OR 1.690, 95% CI 1.092–2.615, p = 0.018); 1.240 times higher in the presence of elevated additive EuroSCORE score (OR 1.240, 95% CI 1.109–1.385, p = 0.0001); 1.052 times higher in the presence of advanced age (OR 1.052, 95% CI 1.031–1.0741, p = 0.0001) (**Table 4**).

Table 2 Treatment related factors predisposing to postoperative AF after CABG surgery

	Non-AF group (n = 911)	AF group (n = 129)	p Value
LIMA used	902 (99%)	128 (99,2%)	0.817
Radial artery used	365 (40.1%)	54 (41,9%)	0.697
No. of grafts per operation	3.01 ± 0.89	3.12 ± 0.99	0.199
Cross-clamp time (min)	69.9 ± 18.4	73.1 ± 21.9	0.095
Cardiopulmonary bypass time (min)	88.9 ± 24.4	92.8 ± 25.6	0.078
Inotropic Support	51 (5.6%)	9 (1.7%)	0.530
Intraaortic balloon pump	13 (1.4%)	4 (1.3%)	0.161
Total arterial revascularization	297 (32.6%)	40 (31%)	0.870
Mechanical ventilation duration (hours)	7.9 ± 5.2	10.6 ± 21.6	**0.002**
Prolonged ventilation time (≥6 h)	606 (66.9%)	99 (77.3%)	**0.017**
Length of ICU stay (days)	2.3 ± 1.5	3.1 ± 1.6	**0.0001**
Prolonged ICU stay (≥6 days)	17 (10.9%)	6 (4,7%)	**0.044**
Length of hospital stay (days)	6.6 ± 1.6	7.3 ± 1.9	**0.0001**
Hospital mortality (first 30 days)	13 (1.6%)	2 (1.8%)	0.891
Re-exploration for bleeding or tamponade	18 (2.1%)	1 (0.8%)	0.497
Significant pleural effusion	16 (1.8%)	3 (2.3%)	0.655
Pneumonia	2 (0.2%)	1 (0.8%)	1.000
Perioperative myocardial infarction	4 (0.4%)	1 (0.8%)	1.000
Gastrointestinal system complications	3 (0.5%)	-	0.675
Superficial wound infection	8 (0.9%)	2 (1.6%)	0.358
Deep wound infection	2 (0.2%)	1 (0.8%)	0.328
Sternal dehiscence	3 (0.5%)	-	0.513
Renal dysfunction	1 (0.2%)	-	0.708

Data expressed as mean ± SD or n(%). AF: atrial fibrillation; CABG: coronary artery bypass grafting; LIMA: left internal mammarian artery; CPB: cardiopulmonary bypass; ICU: intensive care unit; TIA: transient ischemic attack

Table 3 Relationship between AF and ventilation time (p = 0.80)

Ventilation Time (h)	AF group (n,%)	Non-AF group (n,%)	Mean (hours)
0–6	29 (22.5%)	302 (33.1%)	5.16 ± 0.91
6–12	86 (66.6%)	556 (61%)	8.42 ± 1.41
12–24	11 (8.5%)	47 (5.2%)	15.40 ± 2.46
>25	3 (2.3%)	6 (0.6%)	27 ± 2.74

AF: atrial fibrillation

Discussion

There are many defined clinical risk factors for AF following cardiac surgery. This study aimed to establish the role of risk factors in the etiology of postoperative AF after CABG. A significant relationship was found between postoperative AF development and presence of advanced age, elevated additive EuroSCORE score, and ventilation time over 6 hours.

Currently, the most robust risk factor for postoperative AF is advanced age.[8,9] In the general population, the frequency of postoperative AF increases 24% for every 5-year increase in age and plateaus after the age of 80 years.[10] The cause of this relationship is the degenerating ultrastructural changes that occur in cardiac muscle during aging. The atrial myocite loss and the increase of areas of age related, fibrotic infiltrates may create multiple pathways for re-entry that induce atrial arrhythmias including AF.[11] Different events occurring during the surgical procedures have also been proposed as contributing to the development of postoperative AF including ischemic myocardial damage and oxidative stress due to hypotension, elevation of atrial pressure due to post anaesthesia and postoperative left ventricular dysfunction, sympathetic nervous system activation caused by volume loss or pain or from use of adrenergic drugs, from increased vagal tone, and electrolyte and metabolic imbalances. These may explain significantly higher mean age at AF Group.

Additive EuroSCORE is a risk stratification system, which is created to predict hospital mortality and assess

Table 4 Results of multivariate analysis for prediction of independent risk factors

	p Value	Odds Ratio (95% CI)
Age (years)	**0.0001**	1.052 (1.031–1.0741)
Hypertension	0.158	0.763 (0.524–1.111)
Body Mass index (kg/m^2)	0.086	0.955 (0.906–1.007)
Carotid Artery Disease	0.058	0.609 (0.364–1.017)
EuroSCORE	**0.0001**	1.240 (1.109–1.385)
No. of grafts per operation	0.199	1.141 (0.933–1.395)
Cross-clamp time (min)	0.079	1.009 (0.999–1.019)
Cardiopulmonary bypass time (min)	0.102	1.006 (0.999–1.013)
Intraaortic balloon pump	0.171	0.452 (0.145–1.409)
Mechanical ventilation duration (hours)	0.072	1.022 (1.008–1.047)
Prolonged ventilation time (≥6 hours)	**0.018**	1.690 (1.092–2.615)

Data expressed as mean ± SD or n(%). CI: confidence interval

the quality of care. It takes into account general patient information, preoperative general and cardiac risk factors, and operative information.[12] Analysis of the data revealed that AF Group had a significantly higher mean additive EuroSCORE score than Non-AF Group. Applying this risk-scoring model might make it possible to administer appropriate pharmacologic and non-pharmacologic prophylaxis before or after CABG, and thus reduce postoperative AF and its consequences.

AF usually begins postoperative 2–4 days. In our study there was no difference at AF onset time.

Prolonged ventilation time was the strongest predictor of postoperative AF in the present study. Mechanical or spontaneous ventilation may cause changes in intrapleural or intrathoracic pressure and lung volume. These may affect preload, afterload, heart rate and myocardial contractility. Changes in intrathoracic pressure have direct effect on the heart and pericardium, the great arteries, and the veins. Spontaneous inspiration creates negative pressure and decreases pressure in the right atrium. On the contrary, intermittent positive pressure ventilation increases intrathoracic pressure and right atrium pressure. If positive end expiratory pressure is added, pressure will remain higher than atmospheric pressure all over the respiratory cycle.[13] Because of the relationship between atrial arrhythmia and increased right atrium pressure, we believe that mechanical ventilation increases AF. Increased sympathic activity is another cause of increased arrhythmia incidence postoperatively. Mechanical ventilation increases this sympathetic activity. Prolonged ventilation may be an additive mechanism of new-onset AF via sympathic activity. Edgerton, et al. found that immediate extubation reduces AF independent from comorbidities.[14] Straka, et al. found an incidence of 21% AF in early extubation group, but they did not use a control group.[15] Ascion, et al. could not show any relationship between AF onset and mean mechanical ventilation time, but they did not check for early extubation in particular.[16] Cheng, et al. could not find any significant differences between 1–6 hour extubation group and 6–24 hour extubation group; indeed, AF incidence peaks on the second day, and we believe that the authors must have missed many new-onset AFs.[17] Analysis of our data has shown that late extubation of patients after CABG surgery increases the incidence of postoperative AF to 14% from 8.8% in patients maintained on a mechanical ventilator. This comparison shows us that late extubation is an independent risk factor for new-onset postoperative AF.

In the present study, the mean hospital length of stay and postoperative ICU length of stay were significantly longer in AF Group than subjects in Non-AF Group. Borzak, et al. noted that subjects with AF had a longer length of stay in the ICU and on the ward.[18] Almassi, et al. reported a longer stay in the hospital: 3 days more in the ICU for patients with AF versus 2 days for patients without AF.[19] Thus, the reported length of stay varies widely between centers. This variance may be due to time (more recent trend to rapid discharge), and variations in ICU admission criteria. However, all reports agree that patients with AF stay in the ICU and on the ward longer, and our results subscribed to those of others. Determining the reason for the lengthened stay is difficult. To some degree, the difference might be explained by more hospitalization time required to execute interventions to convert to sinus rhythm, check out stabilization of the therapy, or institute and monitor use of anticoagulants for subjects who do not convert.

Although postoperative AF (POAF) is associated with higher early mortality rates in a number of studies, ranging from 2.4 to 7.4% after cardiac surgery, this was not supported in the present study, as in-hospital mortality was low in the postoperative AF group at 1.8%.[20,21]

The present study has several limitations. A major limitation was the retrospective nature of this work. Second, the samples could not be considered representative of the general patient population, because the subject population was only obtained from one center, resulting in possible sampling bias. Third, we established each patient's cardiac rhythm status based on preoperative ECG findings and relied on the history in medical charts to determine whether there had been any prior episodes of atrial arrhythmia. As a result, we might have missed individuals with paroxysmal atrial arrhythmia who were unaware of their conditions and showed normal sinus rhythm on the preoperative ECG. A fourth limitation is that continuous Holter ECG monitoring was not continued after ICU discharge. Further, 12-lead ECG was performed on postoperative days 1, 2, and 4, just prior to hospital discharge, and whenever a patient showed clinical signs of arrhythmia. It is possible that short episodes of asymptomatic AF might have been overlooked, but radial pulses and symptoms were assessed at least 4 times daily, and it is unlikely that any sustained episodes of AF were missed.

Conclusions

AF is the most common complication and a very popular subject in coronary artery surgery. Identification of risk factors might lead to better prevention of this problem and its potential consequences. Analysis of our data reveals that, patient's age, additive EuroSCORE score, and prolonged ventilation are predictors of postoperative AF. Using anti-arrhythmic agents for patients with advanced age and with high additive EuroSCORE score before POAF occurs could decrease the risk of postoperative complications. However, to support our investigation and obtain more reliable evidence, prospective randomized controlled trials are needed.

Disclosure Statement

None.

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