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Incidence and Predictors of New-Onset Atrial Fibrillation in the Early Postoperative Period after On-pump Coronary Artery Bypass Graft Surgery: A Prospective Observational Study

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ABSTRACT

INTRODUCTION

Postoperative atrial fibrillation (POAF) is the most common complication after coronary artery bypass grafting (CABG), with an incidence range between 10% to 40%. The aim of the study was to determine the incidence and predictors of new onset atrial fibrillation (NOAF) in an era of advancement in myocardial protection for patients undergoing on-pump CABG surgery.

METHOD

In this prospective study, we evaluated 121 patients who underwent elective on-pump CABG with or without valve replacement. If NOAF persisted more than 15 minutes, an attempt to pharmacological cardioversion was performed using intravenous administration of amiodarone. Direct current (DC) cardioversion was planned in case of NOAF persisting despite 24 hours of i.e. amiodarone or if the patient had a hemodynamically unstable NOAF.

RESULT

A total of 121 patients were enrolled in the study. A total of 11 patients (9%) developed NOAF in the postoperative period in intensive care unit (ICU). The multivariate analysis identified four independent predictor associated with the NOAF which includes age (OR = 1.32; CI, 1.03 to 1.70; P = 0.024), left atrial volume index (OR = 1.09; CI, 1.02 to 1.16; P = 0.01), diastolic dysfunction (OR = 6.78; CI, 2.78 to 16.54; P = 0.033), mechanical ventilation duration (OR = 1.27; CI, 1.12 to 1.31; P = 0.001).

CONCLUSION

Advanced age, enlarged LA volume, diastolic dysfunction ≥ Grade 2 and the prolonged mechanical ventilation were found to be independent predictors of NOAF after on pump CABG surgery. In future, development of a validated risk stratification model would be the priority to appropriately target protocols for prevention of NOAF.

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KEYWORDS

Postoperative atrial fibrillation; Coronary artery bypass grafting; Congestive heart failure

INTRODUCTION

Postoperative atrial fibrillation (POAF) is the most common complication after coronary artery bypass grafting (CABG), with an incidence range between 10% to 40% [1-3]. It usually manifested on the second to fourth postoperative days and is often considered as a transient, self-limiting and benign [4]. However, occasionally it can be life-threatening and may increase postoperative complications such as congestive heart failure, renal insufficiency, thromboembolic events, prolongation of hospital stay, repeat re hospitalization and overall has a major impact on the cost of treatment [5].

Therefore, it is necessary to identify the factors predicting POAF and effective preventive measures can be implemented to avoid the deleterious effects of POAF. Unfortunately, we still lack an accurate scoring tool to predict POAF. Age is considered the only risk factor that has been systematically proven in the literature to have a positive association with POAF. And, literature supporting role of other possible preoperative risk factors such as obesity, male gender, hypertension, hypercholesterolemia, cardiac failure, renal failure, diabetes mellitus, chronic obstructive pulmonary disease, tobacco addiction, myocardial infarction history, peripheral artery disease, and echocardiographic factors such as left ventricular (LV) systolic dysfunction, LV diastolic dysfunction and left atrial disease are inconclusive [6-8]. Myocardial ischemia and inadequate cardioplegic protection of the atria are other associated risk factors causing increased incidence of POAF [9].

Over the years, several pharmacologic agents such as digoxin, beta-blockers, calcium channel blockers, quinidine, magnesium, and sotalol have been proposed to prevent or treat POAF [10-13]. But, none of them has been uniformly accepted as a drug of choice. Amiodarone has been reported to be effective in converting AF to sinus rhythm [14]. Electrical cardioversion delivers a direct current (DC) synchronized with the R wave in case the patient is hemodynamically unstable. So far there has been no evidence regarding the efficacy of stepwise escalation of therapy using amiodarone and DC cardioversion after cardiac surgery.

The aim of the study was to determine the incidence and predictors of new onset atrial fibrillation (NOAF) in an era of advancement in myocardial protection for patients undergoing on-pump CABG surgery.

METHODS

In this prospective study, we evaluated 121 patients who underwent elective on-pump CABG with or without valve replacement at our institute between August 2018 and December 2019 after obtaining approval from the institutional ethical committee (NK/4862/3394). The inclusion criteria were: Age more than 18 years, elective on-pump CABG with or without valve replacement. All of the patients were in sinus rhythm and had a baseline corrected QT interval of 0.44 seconds or less. The exclusion criteria were: Paroxysmal or persistent AF in preoperative period, patients on a temporary or permanent pacemaker, redo cardiac surgery and off-pump CABG. Written informed consent was obtained from all the patients one day prior to surgery.

Anaesthesia Technique

A standard anesthesia technique was used for all the patients. Inside the operation room (OR), standard American society of anesthesiologists (ASA) monitoring including five lead electrocardiography (ECG), pulse oximetry, and non-invasive blood pressure (NIBP) were

applied. Anaesthesia was induced with intravenous administration of fentanyl, propofol and endotracheal intubation was facilitated with vecuronium. Invasive arterial pressure monitoring access and central venous access were secured after induction of general anaesthesia. After induction of general anaesthesia, an adult transesophageal echocardiography (TEE) probe was introduced. Anaesthesia was maintained by isoflurane, intravenous fentanyl 2 µg/kg/hr, and intermittent vecuronium boluses. A standard anticoagulation technique was used for all the patients before cannulation. Heparin 4 mg/kg was given for achieving activated clotting time (ACT) more than 480 seconds. During bypass, ACT was maintained more than 480 seconds by giving intermittent boluses of heparin.

Operative Technique and CPB Management

All the procedures were accomplished through a median sternotomy. Cardiopulmonary bypass (CPB) was established after attaining an ACT of more than 480 seconds via standard aortocaval cannulation at mild hypothermia (32°C to 34°C). Myocardial protection was achieved by intermittent cold blood cardioplegic solution delivered antegrade via aortic root and retrograde via the coronary sinus. While on CPB the hematocrit value was maintained more than 21%. Distal graft anastomoses were performed during a period of aortic cross-clamping and proximal anastomoses were performed with the use of side biting clamp during rewarming. However, when CABG was combined with valve replacement surgery, distal anastomosis was performed first followed by valve replacement than proximal anastomosis. According to our institute standard operating procedure (SOP), all procedures used left internal mammary artery (LIMA) as a graft for the left anterior descending coronary (LAD) artery and the saphenous vein was used for grafting remaining culprit vessels. No case received total arterial revascularization. Proximal anastomoses were performed with the use of a side-biting clamp.

Echocardiography Data

After induction of GA and achieving hemodynamic stability, a comprehensive TTE was performed by two experienced persons using M5S transducer (Vivid 7; GE Medical Systems, Horten, Norway). Echocardiographic parameters measured were LA maximum volume index (four chamber and two chamber view), LV ejection fraction (Simpson's rule), LV global longitudinal strain (GLS), LV diastolic function (mitral E/A ratio, annular e' velocity, average E/e' ratio, LA maximum volume index and peak tricuspid regurgitation velocity). An average of three consecutive readings of echocardiographic parameters were taken for statistical analysis.

Study Protocol

After surgery, all patients were shifted to the surgical intensive care unit (ICU) and monitored continuously with electrocardiography (ECG), arterial oxygen saturation and invasive blood pressure (BP) monitoring. The presence of NOAF was evaluated in the immediate postoperative period until the discharge from ICU, using a continuous monitoring ECG system. Twelve-lead ECG was performed once in 24 hours and additionally when clinical suspicion of arrhythmia was detected.

All patients with arrhythmia detected on the monitor were subjected to a 12 lead ECG for confirmation of diagnosis. Once confirmed as NOAF, close monitoring was performed and the duration of NOAF was noted. If NOAF persisted more than 15 minutes, an attempt to pharmacological cardioversion was performed using intravenous administration of amiodarone 300 mg over 10 minutes - 15 minutes and followed by 1mg/kg/hr amiodarone for 6 hours, and 0.5 mg/kg/hr amiodarone for next 18 hours in hemodynamically stable patients. This complete protocol was followed for 24 hours or till reversion to normal sinus rhythm whichever is earlier. Direct current (DC) cardioversion with an initial energy of 50 joules biphasic non-synchronized, was planned

under sedation with injection ketamine 0.5 mg/kg, in case of NOAF persisting despite 24 hours of i.e. amiodarone or if the patient had a hemodynamically unstable NOAF. The decision regarding the inotrope tapering, mechanical ventilation, and ICU discharge was left at the discretion of attending intensivist.

Furthermore, all the patients were divided into two groups: Patients who developed NOAF and patients who did not develop NOAF; and remains in sinus rhythm (SR) during the ICU course. Both groups were compared regarding the patient's baseline demographic, intraoperative, and postoperative characteristics.

Outcome Measures

1. Our primary objective was to determine the incidence and predictors of NOAF in patients undergoing on pump CABG +/- valve replacement.
2. Secondary objective is to determine the effect of NAOF on outcome such as vasoactive inotropic score, duration of ICU stay, duration of mechanical ventilation, renal failure, and in-hospital mortality.

Statistical Analysis

Data were analyzed using SPSS, Version 21. Data were checked for normality using Kolmogorov-Smirnov test. Continuous variables with a normal distribution were expressed as means (standard deviation) and were compared using the Student t-test. Variables whose distribution was not normal were expressed as medians and quartiles; these were compared using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and were compared using Fisher's exact test or the $\chi 2$ test as required. The potential predictors of NOAF were analyzed using univariate logistic regression. Multivariate logistic regression included those factors that were significant ($P<0.05$) in univariate analysis. Significance was set at $P<0.05$.

RESULTS

A total of 121 patients were enrolled in the study. 110 patients underwent isolated CABG, and 11 patients underwent CABG combined with valve replacement. A total of 11 patients (9%) developed NOAF in the postoperative period in ICU. The incidence of NOAF peaked at a median of 2 days (range 0 to 5) after CABG surgery. Table 1 shows the demographic parameters of the patients with or without NOAF. Patients who developed NOAF were older; mean age (65.82 ± 3.8164 *vs.* 59.18 ± 9.27 years; $P<0.05$) and had higher prevalence of diabetes mellitus [30(27.27%) *vs.* 6 (54.54%); $p<0.05$]. None of the other parameters such as serum protein, serum albumin, serum creatinine and medications like a beta blocker, statins, ACEI, and diuretic were significantly difference in NOAF compared to those with no AF.

	SR Group	AF Group	P Value
	N = 110 (91%)	N = 11 (9%)	
Age (mean + SD)	59.18 ± 9.27	65.82 ± 3.81	0.005*
Male Sex (%)	87 (79.09%)	9 (81.81%)	0.691
Diabetes	30 (27.27%)	6 (54.54%)	0.03*
Beta Blocker	101 (91.81%)	9 (81.81%)	0.745
Statins	86 (78.18%)	6 (54.54%)	0.129
ACEI	22 (20%)	2 (18.18%)	0.999
Metformin	32 (29.09%)	3 (27.27%)	0.987
Diuretics	14 (12.72%)	2 (18.18%)	0.492
Creatinine mg/dl	1.25 ± 0.32	1.31 ± 0.42	0.653
Total Protein g/dl	7.1 ± 0.56	6.9 ± 0.24	0.37
Albumin g/dl	4.2 ± 0.39	4.025 ± 0.39	0.215
Diagnosis			
TVD	104 (94.54%)	6 (54.54%)	0.02*
TVD ± MVD/AVD	6 (5.45%)	5 (45.45%)	

Table 1: Preoperative characteristics.
SR: Sinus Rhythm; AF: Atrial Fibrillation; ACEI: Angiotensin Converting Enzyme Inhibitors; TVD: Triple Vessel Disease; MVD: Mitral Valve Disease; AVD: Aortic Valve Disease.

Baseline echocardiographic data shown in Table 2: Patients with ejection fraction less than 35% prior to

surgery were more in NOAF group compared to no NOAF (36.36 *vs.* 10.90%; p<0.05). Furthermore, diastolic dysfunction of ≥ Grade 2 (82.27 *vs.* 12.72%; p<0.05) and larger left atrial volume index (37.38 ± 14.23 *vs.* 25.32 ± 7.26; p<0.05) parameters were shown to be associated with NOAF. However, no such association was observed with GLS (-10.67 ± 2.03 *vs*. -12.23 ± 1.34%; p >0.05).

	SR Group	AF Group	P Value
	N = 110	N = 11	
LAVI	25.32 ± 7.26	36.38 ± 10.23	0.012*
LV GLS (%)	-12.23 ± 1.34	-10.67 ± 2.03	0.119*
LV EF			
>35%	98 (89.09%)	7 (63.63%)	**0.02***
<35%	12 (10.90%)	4 (36.36%)	
LV Diastolic Function			
Grade 0	56 (50.90%)	0 (0%)	
Grade 1			
≥ Grade 2			0.002*

Table 2: Preoperative echocardiographic parameters.
SR: Sinus Rhythm; AF: Atrial Fibrillation; LAVI: Left Atrial Volume Index; LV GLS: Left Ventricle Global Longitudinal Strain; LV EF: Left Ventricle Ejection Fraction; LV: Left Ventricle.

The only intraoperative factor which showed a significant association with NOAF was CABG combined with valve replacement surgery (45.45 *vs.* 5.45%; p<0.05). However; the CPB time, AXC time, temperature during surgery, and total grafts performed showed no significant difference between the groups (Table 3).

	SR Group	AF Group	P Value
	N = 110	N = 11	
CPB (Time)	137.8 ± 30.4	132.4 ± 34.3	0.562
Aortic Cross Clamp Time (Minutes)	118.5 ± 26.7	116.8 ± 41.2	0.298
Lower Temperature	34.2 ± 3.21	34.6 ± 2.03	0.657
Surgery	104 (94.54%)	6 (54.54%)	
CABG			0.02*
CABG + MVR/AVR	6 (5.45%)	5 (45.45%)	
Total Graft	3.32 ± 0.99	3.30 ± 1.33	0.664
VIS Score	12.01 ± 7.6	8.02 ± 5.9	0.03*
MV (Hours)	23.76 ± 5.65	30.32 ± 6.43	0.001*
ICU Stay	5.97 ± 3.21	7.01 ± 4.26	0.113
Post Blood Transfusion	1.80 ± 1.13	1.29 ± 0.83	0.085
AKI (%)	29 (26.36%)	7 (63.63%)	0.005*
Protein POD 1	5.56 ± 0.73	5.70 ± 1.09	0.704
Albumin POD 1	3.54 ± 0.607	3.34 ± 0.344	0.465

Table 3: Intraoperative and postoperative characteristics.

Postoperative data revealed that patients who developed NOAF had more VIS score (12.01 ± 7.6 *vs.* 8.02 ± 5.9; p<0.05), required prolonged mechanical ventilation (23 ± 5.65 *vs*. 30.32 ± 6.43 hrs; p<0.05) and were more likely to develop AKI (63.63 *vs.* 26.36%; p<0.05) compared to those who did not develop NOAF. However, the length of ICU stay, number of blood transfusion, serum protein, and serum albumin level were comparable between the groups (Table 3).

Multivariate analysis (odds ratio, 95% CI, P value) was performed to detect independent predictor which are associated with NOAF. The variables studied were age, diabetes mellitus, ejection fraction, left atrial volume index, diastolic function, type of surgery, vasoactive inotropic score, mechanical ventilation duration, and acute kidney injury. The analysis identified four independent predictor of the NOAF which includes age (OR = 1.32; CI, 1.03 to 1.70; P = 0.024), left atrial volume index (OR = 1.09; CI, 1.02 to 1.16; P = 0.01), diastolic dysfunction (OR = 6.78; CI, 2.78 to 16.54; P = 0.033), mechanical ventilation duration (OR = 1.27; CI, 1.12 to 1.31; P = 0.001) (Table 4).

	Odds Ratio	95% CI		P Value
		Upper	Lower	
Age (Years)	1.32	1.7	1.03	0.024*
MV Duration (Hours)	1.27	1.31	1.12	0.001*
LAVI	1.09	1.16	1.02	0.01*
Diastolic Dysfunction	6.78	16.54	2.78	0.033*
≥ Grade 2				

Table 4: Multivariate analysis of predictors of NOAF after OPCABG surgery.
SR: Sinus Rhythm; AF: Atrial Fibrillation; LAVI: Left Atrial Volume Index

In this study, only one ICU mortality was found from the SR group due to low cardiac output in the postoperative period. All patients who developed NOAF in the postoperative period were pharmacologically converted to sinus rhythm within 24 hours. No patient required DC cardioversion (Table 5).

	SR Group	AF Group	P Value
	N = 110	N = 11	
Stroke	5 (4.54%)	1 (9.09%)	0.403
Delirium	9 (8.18%)	2 (18.18%)	0.100
Mortality	1 (0.90%)	0	0.822

Table 5: Postoperative complications.

DISCUSSION

In this study, we found increasing age, LAVI, diastolic dysfunction ≥ Grade 2, and prolonged mechanical ventilation as independent perioperative risk factors which can predict the NOAF in patients undergoing on-pump CABG surgery. Despite advancements in surgical technique, anaesthesia technique, and myocardial protection, the incidence of AF have not decreased after cardiac surgery [14,15]. The incidence of NOAF in our study was 9.0% (n = 11) which is lesser than the previous study by Mariscalco et al. where they found an incidence of POAF between 10 to 40% [3]. Also, we found the incidence of NOAF peaked at a median of 2 days (range 0 to 5 days) after on pump CABG surgery which corresponded to time to maximum inflammation and the shift of third space volume into intravascular space. This is similar to findings of Funk et al. where they showed NOAF commonly manifesting within the first 3 days with peak incidence on the postoperative day two [16].

Prior studies has shown advanced age as the only consistent predictor of NOAF after cardiac surgery [17,18]. In a study done by Mathew et al. [19], for every 10-years increase in age, there is a 75% increase in the odds of developing AF. Thus, based on age, those who are older than 70 years are considered to be at high risk for developing AF [19]. In our study mean age of patients who developed NOAF (65.82 ± 3.81 *vs*. 59.18 ± 9.27 years) was significantly higher than in patients who did not develop NOAF. With advancing age, atria undergo structural changes in the form of dilatation, focal fibrosis, and muscle atrophy [20,21]. These factors create changes in local atrial refractory periods, delays SA and AV node conduction times [22]. This lack of uniformity, in the presence of triggering factors, may develop arrhythmia in the form of AF [23].

Increasing LA pressure leads to LA dilation which invariably causes thinning and fibrosis of myocardial tissue and conducting fibers resulting in disordered electrical activation and contractility. Enlarged atria also lead to increased wall tension because of intermittent or chronic elevation of ventricular filling pressures [24,25]. Increased LAV is the best measurable indicator that reflects the burden of cardiovascular disease, and the remodeled cardiovascular system can be expected to be more susceptible to increased adrenergic stress and dynamic volume changes associated with surgery [26]. Osranek and co-authors have found that LAV >32 ml/m^2 was the strongest predictor of POAF, with an almost five-fold increased risk of POAF independent of age and other clinical and surgical parameters [27]. In our study, we found that elevated LAVI with a mean of >36 ml/m^2 is an independent predictor of NOAF after CABG surgery.

To our knowledge, there is only one previous study which has been conducted by Melduni et al. [28] which has evaluated the association between diastolic function and POAF in patients undergoing isolated CABG and/or valve repair/replacement. This study concluded that diastolic dysfunction as an important predisposing factor for the initiation of new-onset POAF after cardiac surgery. Similar to the study of Melduni et al. [28] our study reported a significant association between NOAF and the diastolic dysfunction ≥ Grade 2 in patients undergoing CABG surgery. Conduction abnormality due to fibrosis of the cardiac chambers associated with aging leads to increased susceptibility to POAF in the setting of surgical insult [29-31]. When extended ventilation was needed in the postoperative period, in our patients, it was associated with an increased incidence of NOAF. Our results also

agree with those of Dave et al. with respect to prolonged mechanical ventilation as a predictor of NOAF [32]. However, in our study those who developed NOAF had a mean duration of mechanical ventilation of 33 hours which corresponds to the peaked incidence of NOAF at a median of 2 days, thus NOAF may be responsible for the prolonged mechanical ventilation.

Previous study has demonstrated treatment with beta blockers and statins prior to surgery reduces the risk of developing NOAF [33,34]. However, we did not find any such association between NOAF and intake of beta blockers and statins. NOAF is often considered a transient, self-limiting and benign complication [4]. However, it can be life-threatening and is associated with an increased rate of postoperative complications such as congestive heart failure, renal insufficiency, thromboembolic events, prolong the length of hospital stay, increase risk of re hospitalization and the overall impact on the cost of treatment [35]. Therefore, the utmost importance is to develop a validated risk-stratification model and appropriately target protocols for the prevention of NOAF.

LIMITATIONS

The main limitations of this study are its small sample size and its non-randomized nature. The incidence of NOAF in this study was 9%, but this incidence may have been underestimated due to limited period of ICU stay. The sample size was not calculated and arbitrarily chosen based on our workload. Transthoracic echocardiograms are not routinely repeated in the postoperative period in ICU. We did not perform a long term follow up to determine long term outcome of these patients and compare the outcome.

CONCLUSION

New onset atrial fibrillation remains a common complication after on pump cardiac surgery. In our study, advanced age, enlarged LA volume, diastolic dysfunction ≥ Grade 2 and the prolonged mechanical ventilation were found to be independent predictors of NOAF after on pump CABG surgery. For NOAF treatment, amiodarone is still an effective pharmacological agent of choice without any major complications. In future, development of a validated risk stratification model would be the priority to appropriately target protocols for prevention of NOAF.

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