

**IMPACT OF PREOPERATIVE CARVEDILOL ON THE OCCURRENCE OF NEW -ONSET ATRIAL FIBRILLATION AFTER CORONARY ARTERY BYPASS GRAFTING**Salla Surya Prakasarao^{*1}, Salla Sweta Ramani², Suma Pusapati³, Srikanth Gummadi⁴, Kartheek Pyla⁵¹Associate Professor, Department of General Medicine, NRI Institute of Medical Sciences, Sangivalasa, Visakhapatnam.²Postgraduate Trainee, Department of Cardiothoracic Surgery, Frontier Lifeline Hospital, Chennai.^{3,4,5}Intern Trainee, Department of General Medicine, NRI Institute of Medical Sciences, Sangivalasa, Visakhapatnam.***Corresponding Author: Salla Surya Prakasarao**

Associate Professor, Department of General Medicine, NRI Institute of Medical Sciences, Sangivalasa, Visakhapatnam.

Article Received on 16/01/2018

Article Revised on 06/02/2018

Article Accepted on 27/02/2018

ABSTRACT

Background: Postoperative Atrial fibrillation (POAF) is the most frequent arrhythmia observed after Coronary artery bypass grafting (CABG). Worldwide incidence is documented to be 20-30% in patients undergoing isolated Coronary artery bypass grafting (CABG). There is no published data for Indian population so far. Hence, the objective of our study is to analyse the occurrence of new-onset POAF in our Indian population and to assess whether the preoperative beta-blocker therapy has any role in its prevention. **Material and Methods:** This is a retrospective and prospective observational study of coronary artery disease patients in NRI Institute of medical sciences, Visakhapatnam, who underwent coronary artery bypass grafting at various institutions between January 2017 and December 2017. The patients with documented AF during the preoperative period and patients undergoing associated cardiac procedures have been excluded from the study. Data has been collected from the patients' medical records and the relative clinical variables were analysed. Chi-square test used for statistical analysis. **Results:** 113 patients with coronary artery disease (followed up at our centre) were found to have undergone CABG during the study period. Among the 113 patients, 95 (84.07%) were males and 18 (16%) were females. The mean age of patients developing AF was 61.9±8.7 and for patients in sinus rhythm was 58.7±7.9 years (range: 37-80 years). 79 patients received preoperative Carvedilol and 34 patients were free from Carvedilol usage. The overall incidence of AF was 6.16%. 3.1% of patients with Carvedilol were noted to have AF while 13.23% of patients with no Carvedilol coverage developed new-onset AF (p<0.05). 14.28% of patients developing AF were with LV function <40%. The mean duration of ICU stay for patients who had POAF was 73.74±39.33 hours and 34.47±19.39 hours for patients in sinus rhythm. **Conclusion:** The incidence of Postoperative Atrial fibrillation in Indian patients is less than the western population. Advanced age and Left ventricular dysfunction increases the risk. The technique of the surgery is not found to be affecting. Postoperative AF remains common with an incidence of 6.14%. The study has shown that preoperative therapy with Carvedilol continuing through the postoperative period significantly reduces the incidence of new-onset postoperative Atrial fibrillation in coronary artery disease patients undergoing coronary bypass grafting.

KEYWORDS: Coronary Artery Disease, Atrial Fibrillation, Coronary Artery Bypass Grafting, Carvedilol.**INTRODUCTION**

Atrial Fibrillation (AF) is a sustained arrhythmia, noticed as a common adverse outcome following cardiac and pulmonary surgeries. Patients are prone to develop haemodynamic instability with an increased risk of thromboembolic events in the postoperative period.

The overall incidence of new-onset postoperative atrial fibrillation (POAF) is documented to be 20-40% after isolated coronary artery bypass grafting (CABG) and nearly 60% after open heart surgeries.^[1-4] Often the AF is of paroxysmal type and self-resolving within 4-6 weeks, but increased morbidity in the immediate postoperative period and prolonged ICU stay warrants

prevention and early management. vide. ref. European heart journal, [http:// dx.doi.org/ 10.1093/ euheart/ehm 308](http://dx.doi.org/10.1093/eurheart/ehm308), pages 2346-2353. There are several western studies recommending prophylactic therapy of beta blockers with or without amiodarone, before the surgery, as a preventive strategy for POAF.^[5-10]

Therefore, we have done this study in our patients with coronary artery disease to determine the occurrence of POAF and the impact of Carvedilol on its prevention.

MATERIAL AND METHODS

The study design is both retrospective as well as prospective observation of patients diagnosed with coronary artery disease and who had subsequently

undergone coronary artery bypass grafting at various hospitals in the city (Some Patients are treated under Aarogyasri Scheme are referred to other Aarogyasri recognized private hospitals for CABG. As per the Aarogyasri Scheme, a free treatment Scheme of the State Government, patients will come in the Post-operative period for free medicines and followup to our Hospital, NRI Institute of medical sciences, Visakhapatnam). These patients were on followup preoperatively as well as postoperatively at our institution, NRIIMS, Visakhapatnam. The following patients were excluded from the study: patients with preoperative rhythm disturbances, patients with prior cardiac surgery or angioplasty and patients with other associated cardiac procedures. The patient details were collected from the medical registry of Department of General Medicine, NRIIMS.

Preoperative variables reviewed were diabetes mellitus (DM), hypertension (HTN), chronic obstructive pulmonary disease (COPD), angina severity, congestive heart failure (CHF), family history of CAD, previous MI, renal insufficiency, peripheral vascular disease (PVD), transient ischaemic attack (TIA), and cerebrovascular disease (CVD). Left ventricle function of all patients based on 2D echocardiographic findings was reviewed. Detailed drug history was taken regarding the usage of beta blocker preoperatively. The Preoperative variables like type of CABG, requirement of intra-aortic balloon pump support, ICU duration, incidence of stroke, acute kidney injury, rhythm disturbances have been collected from patients' discharge summaries. The outcome of the patients (New-onset POAF) at the end of 1 month after surgery has been analysed. The patients have been followed up at our institution at the end of 1 month and 3 months. As per the Aarogyasri Scheme, A free treatment Scheme of the State Government, patients will come in the Post-operative period for free medicines and followup to our Hospital, NRI Institute of medical sciences, Visakhapatnam. The patients' clinical conditions were assessed. ECG assessment for rhythm and echocardiographic assessment for left ventricular function was done.

Definitions: Postoperative AF (POAF) was defined as the documentation of AF of any duration at any time in the ICU and postoperative period on a physician assessment, on the basis of a rhythm strip or 12-lead electrocardiogram recording. AF was defined as non-sustained if lasting between 10 beats and 10 minutes and sustained if persisting for >10 minutes. Angina was defined as per the Canadian Cardiovascular Society Classification and CHF as per the New York Heart Association criteria. Postoperative MI was defined as elevation of troponin/creatinine phosphokinase (CPK) and CPK-MB ≥ 3 times the upper limits of normal, or by new Q waves on follow-up electrocardiograms.

Data was stored electronically and analysed by the use of SPSS version 17.1, for Windows statistical software. All continuous variables were presented as mean \pm standard deviation, minimum and maximum. Fischer's test and Chi square test was used to predict the statistical significance and the p value of <0.05 was considered statistically significant. The study was approved by the Human Ethical Committee at our institution and informed consent was taken from all patients in the study; pharmaceutical companies were not involved in the study. The dosage of Carvedilol was from 3.125 mg to 12.5 mg depending on clinical signs like Tachycardia, Angina, and Dyspnoea and Left Ventricular ejection fraction.

RESULTS

Between January 2017 and December 2017, a total of 113 patients underwent coronary artery bypass grafting. They were followed up at the end of 1st month and 3rd month. The baseline patient variable is as listed in Table 1. The mean age of study population was 58.7 \pm 7.9 years (range: 37 to 80 years). 84% (n=95) were males and 16% (n=18) were females. 19 patients (16.8%) had no comorbidities, 27 patients (23.89%) were hypertensive, and 24 (21.23%) were diabetics. 42 patients (37.1%) had both diabetes and hypertension, and 1 patient (0.88%) had COPD. The preoperative 2D echocardiography assessment of left ventricle function showed 74 patients with EF >60%, 23 with EF of 50-60%, 8 had EF of 40-50% and 8 with severe LV dysfunction with EF <40%. 80 patients underwent CABG under cardiopulmonary bypass while 33 patients had CABG on beating heart without cardiopulmonary bypass.

The overall incidence of POAF among the study population was 6.16% (7/113). 70% of the study population were on carvedilol therapy preoperatively for various indications like hypertension and acute coronary syndrome. 3.14% of the patients on carvedilol coverage developed new-onset POAF while 13.23% of patients with no beta blocker prophylaxis developed new-onset POAF (p<0.05). 5.8% of patients with Off pump CABG developed POAF while 6.28% of patients with On pump CABG were noticed to have POAF (p>0.05). The following treatment strategies (Table 2) were implemented in the management of POAF – 42.85% patients were started on Amiodarone infusions, 28.59% had beta-blocker therapy, 14.28% needed temporary pacing and 14.28% required DC shocks. No other complications were encountered in the study population. None of the patients had any CNS complications. The mean duration of ICU stay for patients who had POAF was 73.74 \pm 39.33 hours while for patients who remained in normal sinus rhythm through the hospital stay was 34.47 \pm 19.39 hours. The mean hospital stays for patients with POAF and for patients in sinus rhythm were 9 \pm 2.3 days and 7 \pm 1.4 days respectively (p value).

These patients with AF were discharged with antiarrhythmic therapy - Tab. Carvedilol 6.25 mg and Tab. amiodarone 200 mg twice daily. 6.25% of patients were affected with POAF when Carvedilol was received in postoperative period alone. We have given Carvedilol in Tachycardia and LVEF, and 16.7% developed POAF, with no Carvedilol coverage either in preoperative period or postoperative (Table 3, 4).

All the patients were followed up at the end of 1 month and 3 months. At the end of 1 month and 3 months, 35.71% and 100% of patients were in normal sinus rhythm. There was no mortality detected in the study population (Relationship between pre-op LVEF and development of POAF if available).

Table 1: Patient Baseline Characteristics.

Variables	AF (%) n=7	NoAF (%) n=106	P value
Age (mean±SD)	61.9±8.7	58.7±7.9	<0.00001*
Male	78.6	84.6	0.9538
Female	21.4	15.4	0.9538
No traditional risk factors	21.4	15.96	0.9500
HTN	50	21.6	0.2770
DM	0	22.06	0.7344
HTN + DM	21.4	37.55	0.8232
COPD	0	0.938	0.7324
LVEF: >60 % 50-60% 40-50% <40%	64.28 14.28 7.14 14.28	64.78 20.6 7.51 7.04	0.6753 0.3017
With Pre-op BB	3.14	96.855	0.0417*
Without pre-op BB	13.23	86.76	
CABG on-pump	6.28	93.71	0.9697
CABG Off-pump	5.82	94.117	
ICU stay (Hours)	73.74±39.33	34.47±19.39	<0.00001*
Hospital stay (Days)	9±2.3	7±1.4	<0.00001*

*indicates statistical significance (p <0.05).

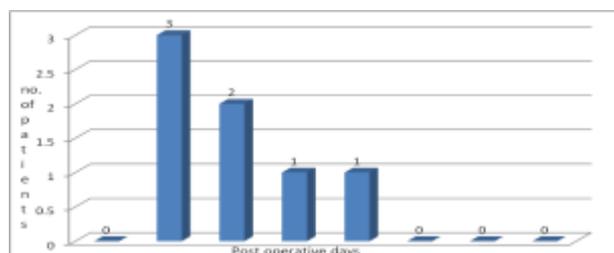


Fig. 1: Post-operative Day of Initial Occurrence for the Post-Operative Atrial Fibrillation

Table 2: Treatment Modalities: POAF.

Therapy	No. of patients (n=7)
Amiodarone	3
Carvedilol	2
Pacing	1
DC Shock	1

Table 3: Comparing Post-Operative Carvedilol Usage in “With Pre-Operative Carvedilol Group”.

	Post-operative Carvedilol use	AF	NSR	Total
Patients with preoperative Carvedilol	Yes	1(1.47%)	67(98.5%)	68 (86.07%)
	No	2(18.18%)	9 (81.82%)	11 (13.92%)
	Total	3	76	79
P = 0.007138 (p<0.05)				

Table 4: Comparing Post-Operative Carvedilol Beta blocker Usage in “Without Pre-Operative Carvedilol Group”.

	Post-operative Carvedilol use	AF	NSR	Total
Without preoperative Carvedilol	Yes	1(6.25%)	15(93.75%)	16
	No	3(16.7%)	15 (83.3%)	18
	Total	4	30	34
P = 0.3467 (p>0.05)				

DISCUSSION

Postoperative atrial fibrillation (POAF) is a frequent complication reported after cardiac surgery. Though not life-threatening, patients are prone to have considerable morbidity. Previous studies have showed a variable incidence in several regions of the world like United States (33.7%), Canada (36.6%), Europe (34.0%), United Kingdom (31.6%), Middle East (41.6%), South America (17.4%) and Asia (15.7%).^[1-10] while in our study, we found an overall incidence of 6.16% of new-onset POAF in our patients. In our study, patients developing AF were found to be of higher age group compared to the ones who remained in sinus rhythm and the result had strong statistical significance. The higher prediction of POAF in elderly age group (≥ 60 years) can be explained by the development of degenerative histological modulations occurring in the atrial myocardium like loss of nodal fibres, increased fibrous and adipose tissue in the sinoatrial node, atrial dilation, focal ventricular fibrosis unrelated to coronary artery disease, and focal interstitial deposits of amyloid in the atria.^[11,12] Ventricular fibrosis affects the ventricular compliance precipitating the atrial dilatation. This in turn results in electrical alterations in the conduction system leading to the fragmentation of the propagating impulse.^[12-16] Goette *et al.*, supported this theory with his histological analysis of right atrial appendage and in determining the relationship between the degree of atrial fibrosis and occurrence of POAF.^[16]

The majority of the initial episodes of atrial fibrillation occurred within the first 3 days after CABG surgery. The presence of preoperative comorbidities and gender had no statistical significance in its occurrence in our study. We have compared the occurrence of POAF between the two techniques adapted to perform CABG, on pump CABG with the use of cardiopulmonary bypass and off pump CABG (without the requirement of cardiopulmonary bypass). The patients who had CABG by on pump technique showed a higher incidence of POAF compared to the ones by off pump, though the value was not statistically significant ($p > 0.05$).

Several studies done by Ascione *et al.*, Tchervenkov *et al.* and Smith *et al.* showed usage of cardiopulmonary bypass as the independent predictor for the development of arrhythmias. The inadequate atrial protection during cardioplegia and the inflammatory responses are believed to trigger the development of arrhythmias.^[17-20] Beta-blockers are the primary therapeutic option in the prevention as well as in the management of POAF.^[21-24] Rate control strategy was implemented with the use of Carvedilol for the management of POAF.^[25-27]

Our study has shown statistical significance in reduction of POAF to 3.14% in the postoperative period. Studies showed that the level of beta-adrenergic receptors in atrial tissues is higher in patients who were on beta blockers. The withdrawal effect of these drugs seems to be an

important risk factor.^[28] Hence, Carvedilol needs to be continued in the postoperative period unless any haemodynamic compromise is noticed. In our study, preoperative Carvedilol therapy when continued in the postoperative period (1.4%) showed a significant reduction ($p < 0.05$) in the prevalence of POAF, while 18.18% of the patients were found to develop POAF when carvedilol was not continued in the postoperative period. Carvedilol when started in postoperative period alone with no preoperative therapy, result though not statistically significant ($p > 0.05$), 6.25% of patients had POAF; while 16.7% developed POAF who had not received carvedilol therapy either in preoperatively or postoperatively. White and his co-workers found a significant increase in the incidence of AF in patients in whom beta blockers were discontinued after CABG.

One patient with POAF developed visual disturbances in the postoperative period which was eventually resolved with conservative management. POAF patients are more prone to develop thromboembolic complications. The meta-analysis studies quoted the incidence of 1.2-1.4%.^[12] The increased duration of ICU and hospital stay was noticed in patients with AF. AF *per se* is not the cause but the conditions like low cardiac output and bronchospasm increases the morbidity and requirement of longer monitoring. In our study, the mean ICU and hospital stay were 73.74 ± 39.33 hours and 9 ± 2.3 days respectively. At the end of 1 month and 3 months, 35.71% and 100% were found to be in normal sinus rhythm, with the postoperative beta blocker and amiodarone therapy. Lower age group of our Indian patients undergoing CABG compared to the Caucasian population might be the reason for the low incidence. Still, postoperative AF remains common with an incidence of 6.14%.

RECOMMENDATION

This study recommends the use of Carvedilol as prophylaxis for CABG patient to prevent postoperative AF and to be continued through the postoperative period as well. For Angina and Tachycardia preoperatively Carvedilol 3.125 to 12.5 mg should be given.

LIMITATION

There can be a possibility of missing the intermittent episodes of atrial fibrillation in the wards due to lack of continuous ECG monitoring. Small sample size and the observational nature of the study prevents us to draw concurrent conclusions. The longer duration followup is needed to rule out late occurrence of arrhythmia or thromboembolic events.

CONCLUSION

Advanced age group increases the propensity for development of atrial fibrillation. As such the incidence of new-onset POAF in Indian patients is lesser than the

western population. The technique of the surgery was not found to be affecting development of POAF. The study has shown that preoperative therapy with Carvedilol continuing through the postoperative period significantly reduces the incidence of new-onset postoperative atrial fibrillation in patients undergoing coronary bypass grafting.

REFERENCES

- Mathew, J.P., Parks, R., Savino, J. S. et al. Atrial fibrillation following coronary artery bypass graft surgery: Predictors, outcomes, and resource utilization. Multicentre study of perioperative Ischemia research group JAMA, 1996; 276: 300-306.
- Amar, D., Shi, W., Hogue, C. W., et al. Clinical prediction rule for atrial fibrillation after coronary artery bypass grafting. J Am Coll Cardiol, 2004; 44(6): 1248-1253.
- Kaw, R., Hernandez, A. V., Masood, I. et al. Short and long term mortality associated with new onset atrial fibrillation after coronary artery bypass grafting; a systemic review and meta-analysis. J Thorac Cardiovasc Surg, 2011; 141: 1305-1312.
- Villareal, P. R., Hariharan, R., Liu, B. C., et al. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. J Am Coll Cardiol, 2004; 43(5): 742-748.
- Hillis, L. D., Smit, P. K., Anderson, J. L. et al. 2011 ACCF/AHA Guidelines for coronary artery bypass graft surgery. A report of American college of cardiology foundation/ American heart association task force on practice guidelines. Circulation, 2011; 124: e652-e735.
- Bradley, D., Creswell, L., Hogue, C.W. Jr., Epstein, A.E., Prystowsky, E.N., Daoud, E.G. Pharmacologic prophylaxis: American college of chest physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest, 2005; 128: 39S-47S.
- Arsenault, K. A., Yusuf, A. M., Crystal, E. et al. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. Cochrane Database Syst Rev, 2013; 1: CD003611.
- Piccini, J. P., Zhao, Y., Steinberg, B. A., et al. Comparative effectiveness of pharmacotherapies for prevention of atrial fibrillation following coronary artery bypass surgery. Am J Cardiol, 2013; 112: 954-960.
- Omae, T., Kanmura, Y. Management of postoperative atrial fibrillation. J Anesth, 2012; 26(3): 429-437.
- Fellahi JL, Fornier W, Fischer MO, Bohadana D, Gerard JL, Hanouz JL. The impact of an algorithm on the optimization of beta-blockers after cardiac surgery. J Cardiothorac Vasc Anesth, 2015; 29(1): 32-37.
- Davies MJ, Pomerance A. Pathology of atrial fibrillation in man Br Heart J, 1972; 34(5): 520-525.
- Creswell LL, Schuessler RB, Rosenbloom M, et al. Hazards of postoperative atrial arrhythmias. Ann Thorac Surg, 1993; 56(3): 539-549.
- Dimmer, C., Tavernier, R., Gjorgov, N., Van Nooten, G., Clement, D. L., Jordaens, L. Variations of autonomic tone preceding onset of atrial fibrillation after coronary artery bypass grafting. Am J Cardiol, 1998; 82: 22-25.
- Kalman, J.M., Munawar, M., Howes, L.G., et al. Atrial fibrillation after coronary artery bypass grafting is associated with sympathetic activation. Ann Thorac Surg 1995; 60(6): 1709-1715.
- Allessie, M. A., Boyden, P. A., Camm, A. J., et al. Pathophysiology and prevention of atrial fibrillation. Circulation. 2001; 103(5): 769-777.
- Goette, A., Juenemann, G., Peters, B., et al. Determinants and consequences of atrial fibrosis in patients undergoing open-heart surgery. Cardiovasc Res, 2002; 54(2): 390-396.
- Ascione R, Caputo M, Calori G, et al. Predictors of atrial fibrillation after conventional and beating heart coronary surgery Circulation, 2000; 102(13): 1530-1535.
- Smith PK, Buhman WC, Levett JM, et al. Supraventricular conduction abnormalities following cardiac operations: a complication of inadequate atrial preservation. J Thorac Cardiovasc Surg, 1983; 85(1): 105-115.
- Abreu, J. E., Reilly, J., Salzano, R. P., et al. Comparison of frequencies of atrial fibrillation after coronary artery bypass grafting with and without the use of cardiopulmonary bypass. Am J Cardiol, 1999; 83(5): 775-776.
- Tchervenkov CI, Wynands JE, Symas JF, et al. Electrical behavior of the heart following high-potassium cardioplegia. Ann Thorac Surg, 1983; 36(3): 314-319.
- Ogawa S, Okawa Y, Goto Y, Aoki M, Baba H Perioperative use of a beta blocker in coronary artery bypass grafting. Asian Cardiovasc Thorac Ann, 2013; 21(3): 265-269.
- Ji T, Feng C, Sun L, Ye X, Bai Y, Chen Q, Qin Y, Zhu J, Zhao X. Are beta-blockers effective for preventing post-coronary artery bypass grafting atrial fibrillation? Direct and network meta-analyses. Ir J Med Sci., 2016; 185(2): 503-11.
- Brinkman, W. T., Herbert, M.A., Prince, S. L. et al. Perioperative beta-blocker usage: Is it really worthy of being a quality indicator? Ann Thorac Surg, 2011; 92: 788-795.
- Bert, A. A., Reinert, S. E., Singh, A. K. A beta-blocker, not magnesium, is effective prophylaxis for atrial tachyarrhythmias after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth, 2001; 15(2): 204-209.
- El-Sheriff, N., Turitto, G. Electrophysiologic effects of Carvedilol: Is Carvedilol an anti-arrhythmic agent? Pacing Clin Electrophysiol, 2005; 28: 985-990.

26. Haghjoo, M., Saravi, M., Hashemi, M.J., et al. Optimal β -blocker for prevention of atrial fibrillation after on-pump coronary artery bypass graft surgery: Carvedilol vs Metoprolol. *Heart Rhythm*, 2007; 4: 1170-1174.
27. Marazzi G, Iellamo F, Volterrani M, Caminiti G, Madonna M, Arisi G, Massaro R, Righi D, Rosano GM. Comparison of effectiveness of carvedilol versus bisoprolol for prevention of postdischarge atrial fibrillation after coronary artery bypass grafting in patients with heart failure. *Am J Cardiol*, 2011; 107(2): 215-219.
28. Kempt FC, Hedberg A, Molinoff P, et al. The effect of pharmacologic therapy on atrial beta-receptor density and postoperative atrial arrhythmias. *Circulation*, 1983; 68(suppl III): 57.