

## CLINICAL STUDIES

# Effect of Right Atrial Pacing, Intravenous Amiodarone and Beta Blockers For Suppression of Atrial Fibrillation After Coronary Artery Bypass Surgery: A Pilot Study

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**Objective.** This pilot study aimed to compare right atrial pacing, intravenous amiodarone and oral beta-blockers in the prevention, time to onset, duration and effect on hospital stay of postoperative atrial fibrillation (AF) after coronary artery bypass graft surgery (CABG) at our center.

**Background.** AF is the most common arrhythmic complication after CABG and is related to increased morbidity, length of hospital stay and costs. Trials with different drugs and other therapeutic modalities including beta-blockers, intravenous amiodarone and override suppression of automatic atrial foci by atrial pacing have shown partial success as preventive measures. However, a comparison between those three interventions has not been reported.

**Methods.** Thirty-six consecutive patients that underwent CABG at our institution were randomly assigned to atrial pacing (18 patients) and intravenous amiodarone (18 patients) after baseline clinical, electrocardiographic and hemodynamic assessment. All patients received concomitant oral metoprolol or atenolol right after extubation. Thirty-three patients who had CABG at our center in the previous two months and that only received beta-blockers during their perioperative period served as a control group.

**Results.** The majority of baseline clinical and hemodynamic characteristics were similar in all groups. Only one patient (5.6%) developed AF in the

atrial pacing group versus five (27.8%) on amiodarone and six (18.2%) who only received beta-blockers. That finding, however, did not attain statistical significance ( $p>0.05$ ). After adjusting for potential confounders, the odds of occurrence of AF was 77% lower in atrial pacing patients (OR = 0.23; 95% CI: 0.02, 2.20;  $p=0.09$ ) and 2.36 times higher in those on amiodarone (95% CI: 0.55, 10.24;  $P=0.053$ ) when compared to patients which only received beta blockers. Since only one patient on right atrial pacing developed atrial fibrillation, the analysis of the median time to onset and median duration of atrial fibrillation was restricted to those assigned to amiodarone and those who only received beta-blockers showing no statistically significant differences ( $p>0.05$ ). Although no statistical significance was achieved, the median hospital stay was one-day shorter in the beta-blockers group. Most of the side effects were minor and resolved without sequelae.

**Conclusion.** This pilot study showed a trend in favor of atrial pacing versus intravenous amiodarone or beta-blockers in the prevention of postoperative AF after CABG in our center. Randomization of a larger patient sample would be required in order to ascertain the true value of the observed trend.

**Key words:** Intravenous amiodarone, Right atrial pacing, Atrial fibrillation, Coronary artery bypass grafting, Puerto Rico

**A**trial fibrillation (AF) is the most common arrhythmic complication after cardiac surgery, with an incidence ranging from 10% to 65% in various studies (1-4). This incidence is reported to be

higher in patients that undergo valvular or combined CABG and valvular interventions, older age, systemic hypertension, male sex, previous episodes of atrial fibrillation and congestive heart failure (5,6). As development of postoperative AF has significant implications in terms of morbidity, increase in length of hospital stay and cost, its prevention has been studied with several pharmacologic agents and other treatment modalities. Among those, the prophylactic use of beta-adrenergic blocking drugs prior to surgery or their continued utilization in the perioperative period has

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consistently shown the greatest effectiveness (7-10). Some studies with low-dose intravenous amiodarone have also demonstrated a reduction of its occurrence in up to 26% of patients (11-15). In contrast, a double-blind study showed that prophylactic oral amiodarone did not significantly reduce the incidence or duration of AF when compared with a placebo (16).

The electrophysiologic mechanisms of postoperative AF remain uncertain, however, it has been postulated that occurrence of frequent atrial ectopy after cardiac surgery relates to AF onset in many patients. Override suppression of automatic foci and reduction of the dispersion of atrial refractoriness through atrial pacing has been suggested as a preventive measure (17). In a study by Greenberg et al., patients assigned to right atrial pacing had a 79% reduction in the incidence of postoperative AF and a 22% reduction in their hospital stay compared with patients who were randomized to a no pacing strategy (18). In a previous study by Gerstenfeld et al., continuous right or biatrial pacing did not significantly reduce postoperative AF but a favorable trend was observed in the subgroup of paced patients who were receiving beta-blockers (19).

The aim of this pilot study was to compare the effect of right atrial pacing, intravenous amiodarone and beta blockers in the prevention of postoperative AF. Secondary end points were to assess the effect of these therapeutic interventions on time to onset and duration of episodes of AF and on length of hospital stay.

## Methods

**Study patients.** Thirty-six consecutive patients with occlusive coronary artery disease and scheduled for CABG were randomly assigned to undergo right atrial pacing or receive an infusion of intravenous amiodarone after their surgical intervention. Thirty-three patients who had undergone CABG at our institution in the previous two months and had just received oral therapy with beta-blockers during their perioperative period were included as a control group.

Patients with a previous history of AF, contraindication for use of beta-blockers, concomitant mitral valve surgery, and use of other anti-arrhythmic agents, including non-dihydropyridine calcium channel blockers (diltiazem or verapamil) were excluded from the study. Patients that developed a heart rate less than 55 beats per minute, bifascicular block, second- or third-degree AV block, clinical signs of congestive heart failure, cardiogenic shock or a cardiac index less than 2.0 L/min/M<sup>2</sup> in the early postoperative period were also excluded. No change in current medications was done prior to surgery.

The study protocol was reviewed and approved by the

Institutional Review Board of the University of Puerto Rico Medical Sciences Campus and the Research Committee of the Cardiovascular Center of Puerto Rico and the Caribbean. Written informed consent was obtained from all patients prior to surgery.

**Study design.** After the random assignment of the first patient to one arm of the protocol, each subsequent consecutive patient was alternatively assigned to each study group. On the day of surgery, the surgeons were informed to which arm of the study the patient belonged, to ensure that right atrial pacing leads were placed to those in the pacing arm. All patients received oral beta-blockers in the postoperative period. Those that were not receiving oral beta blockers before surgery were started on either metoprolol 25 mg every 12 hours or atenolol 50 mg daily right after extubation, with an increase in dose based on patient tolerance. After their initial clinical, electrocardiographic and hemodynamic assessment at the Intensive Care Unit, patients were started on either atrial pacing or intravenous amiodarone. Those assigned to amiodarone received 900 mg of the medication by continuous infusion for 48 hours (37.5 mg/hour). Right atrial pacing was maintained for a period of 48 hours at a pacing rate from 80 to 110 beats per minute in accordance to the heart rate at their initial postoperative clinical evaluation (Table 1).

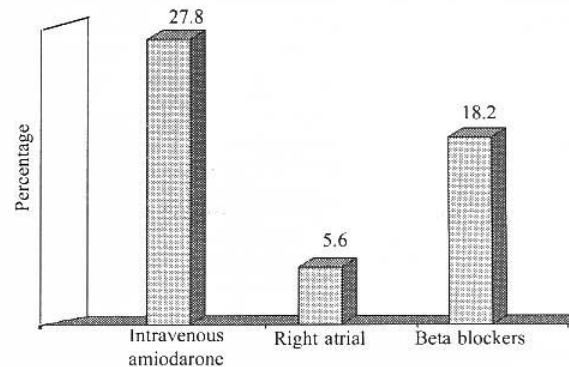
**Table 1.** Right Atrial Pacing Protocol

Native heart rate (beats/min.)	Pacing rate (beats/min.)
<80	100
80-89	105
90-100	110

**Statistical analysis.** Since the distribution of the data in each study group was not normal, median one-way analysis was used to compare continuous data among therapeutic interventions. The chi-square test or Fisher's exact test, when appropriate, was employed to compare the distribution of categorical variables. A logistic regression model was used to evaluate the association between therapeutic intervention and development of AF taking potential confounders into consideration. Baseline patient and operative data that were related to AF in bivariate analysis at  $p < 0.10$  were included as potential confounders. Model parameters were estimated using the method of maximum likelihood and were tested for significance by using the Wald statistic. A two-sided  $p$  value of less than 0.05 was considered to indicate statistical significance. Calculations were performed with the use of SAS software (version 8.0, SAS Institute, Cary, N.C.).

## Results

The data analyzed included 69 patients: 36 randomized to either arm of the study (18 that underwent atrial pacing and 18 that received intravenous amiodarone) versus 33 which comprised the control group (beta-blockers group). Table 2 shows that there was a significantly shorter median pump time (57.5 minutes) in patients randomized to right atrial pacing compared with patients randomized to intravenous amiodarone or those who received beta blockers only ( $p<0.05$ ). In addition, there was a trend towards a lower median pre-operative ejection fraction in patients who received intravenous amiodarone (45%) and a shorter median ischemic time in the right atrial pacing group (34.5 min.) ( $0.05\leq p<0.10$ ).



	Intravenous amiodarone	Right atrial pacing	Beta blockers	P value
Proportion of patients who developed AF	5/18	1/18	6/33	$p>0.05$
Median time to AF onset (hours)	35.3	--	52.7	$p>0.05$
Median duration of AF	16.6	--	10.5	$p>0.05$

**Figure 1.** Percentage of patients who developed postoperative atrial fibrillation according to study intervention

**Table 2.** Baseline and operative characteristics of patients according to study intervention

	Intravenous amiodarone (n=18)	Right atrial pacing (n=18)	Beta blockers only (n=33)	P value
<b>Baseline Characteristics</b>				
Median age (years)	64	64.5	63	$>0.05$
Male sex - n (%)	11 (61.1)	10 (55.6)	16 (48.5)	$>0.05$
Median preoperative ejection fraction (%)	45	55	55	0.08
Myocardial infarction - n (%)	11 (61.1)	6 (33.3)	17 (51.5)	$>0.05$
Hypertension - n (%)	16 (88.9)	16 (88.9)	30 (90.9)	$>0.05$
CHF - n (%)	2 (11.1)	0 (0.0)	3 (9.1)	$>0.05$
Diabetes mellitus - n (%)	9 (50.0)	14 (77.8)	20 (60.6)	$>0.05$
Beta blockers - n (%)	13 (72.2)	13 (72.2)	21 (63.6)	$>0.05$
<b>Operative Characteristics</b>				
Median number of vessels grafted	3	3	3	$>0.05$
Median pump time (min.)	69	57.5	69	0.02
Median ischemic time (min.)	48.5	34.5	44	0.09

With respect to the primary study endpoint, only one patient (5.6%) developed AF in the right atrial pacing group versus five (27.8%) patients in the intravenous amiodarone group and six (18.2%) in the beta blockers group (Figure 1). This difference, however, did not attain statistical significance ( $p>0.05$ ). After adjusting for

preoperative ejection fraction, ischemic time and pump time, the odds of occurrence of AF was 77% (OR=0.23; 95% CI: 0.02, 2.20;  $p=0.09$ ) lower in those on right atrial pacing compared with patients who received beta blockers only (Table 3). In contrast, the odds of occurrence of AF was 2.36 (95% CI: 0.55, 10.24;  $p=0.053$ ) times higher in those on intravenous amiodarone compared with patients who received beta blockers only (Table 3). These findings reached marginal significance ( $0.05\leq p<0.10$ ). Since only one patient on right atrial pacing developed AF, the analysis of the median time to onset of AF was restricted to those assigned to intravenous amiodarone and those who only received beta-blockers (Figure 1). No statistically significant differences in the median time to onset of AF was observed in these two groups ( $p>0.05$ ). In addition, the median duration of atrial fibrillation in both groups was similar ( $p>0.05$ ). The

**Table 3.** Unadjusted and adjusted\* odds ratios and 95% confidence interval for atrial fibrillation in relation to study intervention

Therapeutic intervention	Unadjusted			Adjusted		
	OR†	95% CI†	P value†	OR†	95% CI†	P value†
Right atrial pacing	0.27	0.03-2.39	$>0.05$	0.23	0.02-2.20	0.090
Intravenous amiodarone	1.73	0.45-6.74	$>0.05$	2.36	0.55-10.24	0.053
Beta blockers only	1.00	-	-	1.00	-	-

\*Adjusted for preoperative ejection fraction, pump time and ischemic time.

†OR, odds ratio; 95% CI, 95% confidence interval; P value associated to Wald test statistic.

comparison of the median hospital stay among the three groups did not reveal a statistically significant difference; however, patients who received beta blockers only had a shorter hospital stay (five days) compared with patients on right atrial pacing and intravenous amiodarone (six days) (data not shown).

Most of the side effects were minor and resolved without sequelae (data not shown). Atrial pacing required temporary withholding in 2 patients due to transient hypotension, but it was subsequently restarted without further complications. The overall rate of adverse events in the postoperative period was not significantly different ( $p>0.05$ ) among the three therapeutic interventions.

### Discussion

AF is the most common postoperative arrhythmic complication after CABG, and it is associated with higher morbidity, mortality, length of hospitalization and cost. Its incidence remains high in spite of efforts to identify and control predisposing risk factors and the active search for more effective prophylactic agents and therapeutic interventions.

Review of the medical literature reveals that multiple randomized, controlled studies have shown the beneficial effects of the prophylactic use beta adrenergic blocking agents in patients submitted to CABG (20). The preoperative initiation of those drugs has shown the greatest benefit. Amiodarone has been demonstrated to be the most promising agent in selected groups of patients in various controlled, randomized clinical trials, which have examined the effectiveness of antiarrhythmic agents for prevention of postoperative AF (21). No reports are available comparing amiodarone versus atrial pacing nor the combined effect of amiodarone and beta blockade in the prevention of AF.

The data obtained in the present pilot study, although not conclusive among the prophylactic modalities tried, did show a trend in favor of considering right atrial pacing over intravenous amiodarone or a beta blockers-only intervention, for prevention of AF in patients submitted to CABG. A noteworthy finding was that only one of eighteen patients in the pacing group developed AF. It is recognized that the patient sample size examined was small to completely assess the real statistical validity of that finding. Further confirmation of the observed trend in favor of atrial pacing versus the two other therapeutic regimens could be particularly relevant in the setting of patients with clinical characteristics that entail a high risk for development of postoperative AF. That especially includes patients with contraindications for use of beta adrenergic blocking drugs or other antiarrhythmic

medications and patients in which the treatment of post operative AF with oral anticoagulation alone or rate control alone is anticipated to be complicated.

The utilization of oral beta blockers only showed some effectiveness over that of intravenous amiodarone in the present study and as previously reported by others, remains an alternative therapeutic modality for prophylaxis of AF in the postoperative period in patients with no contraindications for the administration of those medications. Study limitations must be considered when interpreting these results. The relatively small sample size limited our ability to demonstrate whether a more conclusive difference exists among the three interventions. Since only one patient in the atrial pacing group developed AF, we were unable to compare the median time to AF onset and duration among the three groups. A study with a larger sample size would be necessary for a more definitive conclusion regarding this important issue.

### Resumen

La fibrilación atrial (FA) es la arritmia cardíaca más frecuente luego de cirugía de puente aorto-coronario y está asociada a mayor morbilidad, estadía hospitalaria y costo. Estudios previos han demostrado una efectividad parcial en la prevención de esta condición mediante la utilización de bloqueadores beta adrenérgicos, amiodarona intravenosa y estimulación atrial o biatrial. Sin embargo, no se han informado estudios comparativos entre estas tres modalidades de terapia. Este estudio piloto comparó la efectividad de la estimulación con marcapaso en el atrio derecho versus amiodarona intravenosa y beta bloqueadores orales en la prevención, el tiempo para el comienzo y la duración de la FA durante el periodo postoperatorio en pacientes sometidos a esta cirugía. Treinta y seis pacientes consecutivos fueron asignados de forma aleatoria a estimulación atrial derecha o amiodarona intravenosa luego de su operación y de una evaluación clínica y hemodinámica. Todos los pacientes recibieron terapia concomitante con beta bloqueadores (metoprolol o atenolol) luego de su extubación endotraqueal. Treinta y tres pacientes sometidos a la misma cirugía en los pasados dos meses en nuestro Centro y que solamente recibieron beta bloqueadores durante su periodo perioperatorio se utilizaron como grupo control. Tanto la estimulación atrial como la amiodarona intravenosa fueron mantenidas por 48 horas. Sólo un paciente (1/18) en el grupo sometido a estimulación atrial desarrolló FA comparado con cinco (5/18) del grupo de amiodarona y seis (6/33) del grupo de los beta bloqueadores orales. Sin embargo, esta diferencia no fue estadísticamente significativa ( $p>0.05$ ). Luego de ajustar



por variables potenciales de confusión, la posibilidad de desarrollar FA fue 77% (OR=0.23; 95% CI: 0.02-2.20;  $p=0.09$ ) menor en el grupo de estimulación atrial y 2.36 veces mayor en el grupo de amiodarona (95% CI: 0.55, 10.24;  $p=0.053$ ) comparado con el grupo que recibió solamente beta bloqueadores orales. Debido a que sólo un paciente en el grupo de estimulación atrial desarrolló FA, el análisis de la mediana del tiempo para el desarrollo y la duración de la FA se restringió al grupo de amiodarona y beta bloqueadores orales. Dicho análisis reveló que no había diferencias estadísticamente significativas ( $p>0.05$ ). A pesar de que no se observaron diferencias estadísticamente significativas ( $p>0.05$ ), la mediana de la estadía hospitalaria fue un día mas corta en el grupo de beta bloqueadores orales. La mayoría de los efectos secundarios fueron menores y resolvieron sin secuela. En conclusión, la tendencia favorable hacia la estimulación atrial derecha versus las otras alternativas en la prevención de FA en pacientes sometidos a cirugía de puente aorto-coronario observada en este estudio piloto requiere la evaluación prospectiva de una muestra mayor para su eventual corroboración.

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