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Original article

Prevention of postoperative atrial arrhythmias in major broncho-pulmonary cancer surgery: A pilot study of Celiprolol vs. Diltiazem

Sassi Chayma[1], Ouerghi Sonia[1], Fitouhi Nizar[1], Karaborni Rym[1], Ben Zid Ines[1], Ben Amara Kaouther[2], Abdenadher Mahdi[2], Merghli Adel[2], Dridi Amira[1], Mestiri Taher[1]

[1]*Anesthesiology and ICU Department- Abderrahmen Mami University Hospital, Ariana*
[2] *Thoracic cardiovascular surgery Department- Abderrahmen Mami University Hospital, Ariana*

Abstract

Introduction: The incidence of postoperative arrhythmia (POA) after bronchopulmonary cancer (BPC) surgery reaches 50% and is associated with increased morbidity and mortality. The role of pharmacological prevention of POA remains controversial. This study aims to compare the efficacy of the beta-blocker celiprolol versus the calcium channel blocker diltiazem in preventing POA following pneumonectomy and bilobectomy for BPC.

Material and Methods: We conducted a randomized, single-blind, prospective study including patients older than 18 years with preoperative sinus rhythm undergoing major pulmonary resection for BPC. Patients were randomized into two groups: the beta-blocker (BB) group received daily oral celiprolol (Céliprol®) 200 mg and the calcium channel blocker (CCB) group received daily oral diltiazem (Monotildiem® LP) 200 mg postoperatively.

The primary endpoint was the occurrence of early postoperative atrial fibrillation (POAF). Secondary outcomes included the incidence of late POAF, other cardiac arrhythmias, arrhythmia duration, length of intensive care unit (ICU) and hospital stay, drug-related adverse effects, and 30-day mortality. Statistical analysis was performed using SPSS software version 19.0.

Results: Thirty patients were enrolled. The two groups were comparable in demographic characteristics, surgical and anesthetic parameters, and baseline biological data. The overall incidence of POA was 17%. The incidence of POAF was 7%, with no significant difference between groups. All arrhythmias were transient, lasting less than 48 hours, and without recurrence. Supraventricular extrasystoles were the only other observed arrhythmias. Postoperative arrhythmias were significantly associated with bilobectomy, prolonged anesthesia duration, and extended surgical time compared to patients without arrhythmias. The most common postoperative complication was pneumonia. No drug-related adverse effects were observed, and no deaths occurred within 30 days.

Conclusion: Prophylactic treatment reduces the incidence of POAF, but identifying the optimal agent remains challenging. An individualized approach, considering patient comorbidities and surgical factors, is essential for effective prevention.

Keywords: Cardiac arrhythmias, Thoracic surgery, Atrial fibrillation, Pneumonectomy, Celiprolol, Diltiazem

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1. Introduction

Postoperative arrhythmia (POA) is the most common cardiac complication following non-cardiac thoracic surgery, accounting for over 50% of all cardiac complications [1, 2]. Among POA, "de novo" postoperative atrial fibrillation (POAF) is the most prevalent [3]. The American Association for Thoracic Surgery (AATS) defines high-risk procedures as those with a POAF incidence exceeding 15% [4]. Bilobectomy and pneumonectomy are classified as high-risk procedures, with POAF incidence ranging from 10 to 20% after bilobectomy and reaching up to 40% after pneumonectomy [1, 2]. POAF is associated with significant morbidity, including an elevated risk of stroke, prolonged hospitalization, increased healthcare costs and higher long-term mortality [5, 6]. Given its multi-factorial etiology [7], various pharmacological agents have been employed for POAF prevention, though with inconsistent outcomes [8].

Despite extensive research, the optimal pharmacological agent for POAF prevention remains uncertain, particularly in the context of major lung resection surgery [4, 9, 10]. This uncertainty is compounded by the lack of large randomized controlled trials directly comparing the efficacy of different agents.

Beta-blockers (BBs) and calcium channel blockers (CCBs), commonly used in cardiac surgery, are infrequently utilized after lung resection due to their potential adverse effects. These include hemodynamic instability, such as bradycardia and hypotension, and respiratory complications, particularly with non-cardio-selective BBs [4, 11].

***Correspondence:** Dr Sassi Chayma, Abderrahmen Mami Hospital, Ariana, Tunisia. E-mail: d.chayma.sessi@gmail.com

The primary objective of this study is to compare the efficacy of celiprolol (Celiprol®) versus diltiazem (Monotildiem® LP) in preventing atrial arrhythmias in patients undergoing major lung resection.

2. Material and methods

Population and study design

This was a prospective, randomized study conducted at the Department of Anesthesiology and Intensive Care in Thoracic and Cardiovascular Surgery at Abderrahmane Mami University Hospital, Ariana, Tunisia, over 24 months (November 2016–November 2018). After ethics committee approval and informed consent, patients scheduled for elective bilobectomy or pneumonectomy (via thoracotomy or VATS), aged >18 years, and in preoperative sinus rhythm were enrolled.

Exclusion criteria included: a history of paroxysmal arrhythmia or chronic atrial fibrillation, grade II or III atrioventricular block without a pacemaker, current use of CCBs or BBs, hypersensitivity to diltiazem, celiprolol, or their excipients, renal insufficiency (creatinine clearance <40 mL/min), myasthenia, severe COPD (GOLD stages III/IV), intraoperative/postoperative myocardial infarction (per universal definition), or persistent hypotension requiring catecholamine support.

Outcome criteria

The primary endpoint was early post-operative atrial arrhythmias (POAF, atrial extrasystole, or atrial flutter) within 14 days. Secondary endpoints included late atrial arrhythmias (during hospitalization or within 30 days), other arrhythmias (ventricular tachycardia/ extrasystole), ICU/hospital length of stay, 30-day mortality, and drug-related adverse effects.

Patient management

Preoperative assessment: All patients underwent pre-operative evaluation during the anesthesia consultation, including clinical assessment of cardiopulmonary status, echocardiography, and systematic respiratory function tests. Operability and preoperative medications were determined per established guidelines. Patients were informed about the postoperative treatment protocol to reduce arrhythmia incidence, and written informed consent was obtained.

Randomization: Patients were randomized into two groups:
- The beta-blocker (BB) group received celiprolol (Céliprol®) 200 mg once daily, starting six hours post-operatively.
- The calcium channel blocker (CCB) group received diltiazem (Monotildiem® LP) 200 mg once daily, starting six hours postoperatively.

The target heart rate was 70–80 bpm, achieved by titrating doses up to 600 mg celiprolol or 300 mg diltiazem. Treatment was continued for 14 days.

Intraoperative management: A standardized surgical and anesthetic protocol was followed. Patients were monitored in the operating room, and vascular access was established. Antibiotic prophylaxis and epidural catheter placement for postoperative analgesia were performed. General anesthesia was induced, and orotracheal intubation with a double-lumen tube was achieved. Patients were positioned laterally after ensuring hemodynamic and respiratory stability. Intraoperative fluid restriction was maintained at 2 mL/kg/h using isotonic saline. All resections were performed by the same surgical team, with documentation of pericardial involvement and mediastinal lymph node dissection. Two chest tubes were placed post-resection.

Intraoperative bleeding was estimated, and blood products were administered if hemoglobin was <8 g/dL. Intraoperative events were recorded, and all patients were extubated in the operating room.

Postoperative Management: Patients were transferred to the ICU for 48–72 hours with continuous monitoring of ECG, SpO2, NIBP, and respiratory rate. Postoperative analgesia included thoracic epidural infusion (ropivacaine 2 mg/mL with sufentanil 0.5 µg/mL at 5–7 mL/h); supplemented with paracetamol 1 g every 6 hours and morphine titration to maintain a VAS score of ≤3. Fluid intake was restricted to 20 mL/kg/day, and all patients participated in a physiotherapy program.

A complete blood count (CBC) was performed at six hours postoperatively, and serum electrolytes (magnesium, phosphate, calcium) were measured on postoperative day 1, with corrections as needed. Daily chest radiographs assessed for mediastinal deviation (in pneumonectomy cases) and other complications. Fiberoptic bronchoscopy was performed if atelectasis was suspected. Chest drains were removed on postoperative day 2 for pneumonectomy patients or when drainage was <150 mL/24 hours with no air leaks for bilobectomy patients.

Arrhythmia monitoring and definition: Continuous ECG monitoring was maintained for 48–72 hours postoperatively. A 12-lead ECG was obtained at six hours and twice daily or if arrhythmia was suspected. Monitoring continued until discharge.

De novo POAF was defined as atrial fibrillation on a 12-lead ECG performed for clinical or cardioscopic suspicion. In cases of POAF, an etiological workup included:
- Chest X-ray for mediastinal deviation or pleural effusion
- Serum electrolytes (potassium, calcium, magnesium, phosphate) for imbalances
- Troponin and CPK-MB for myocardial ischemia
- CBC for hemoglobin levels
- Drain output for bleeding
- Echocardiography to guide hypovolemia correction

Potential triggers (e.g., bleeding, mediastinal deviation, pneumothorax, pericardial effusion, hypoxia, myocardial ischemia, sepsis, pulmonary embolism) were identified and treated. Persistent POAF was managed per a cardiac rhythm specialist-approved algorithm (Fig. 1).

Statistical study

All data were systematically recorded on the data collection form and analyzed using SPSS (version 19.0). For the descriptive analysis, absolute and relative frequencies were calculated for qualitative variables, while means, medians, standard deviations, and extreme values were determined for quantitative variables. In the analytical analysis, the non-parametric Mann-Whitney test was used to compare two means in independent series. Pearson's Chi-2 test was used

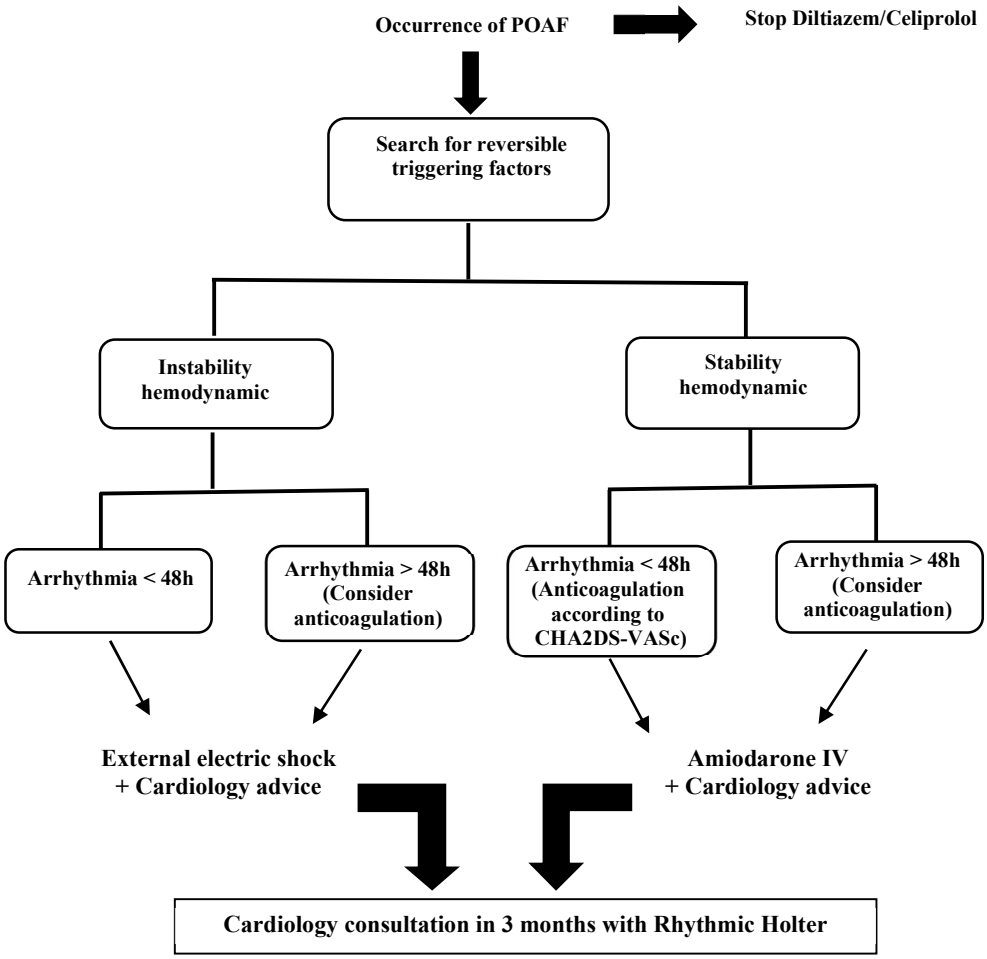

Fig. 1. Algorithm for the management of POAF

to compare proportions between independent series, and the two-tailed Fisher exact test was applied for comparisons of two proportions. A significant level of 0.05 was adopted for all statistical tests, ensuring robust and reliable results.

3. Results

Thirty eligible patients were randomized into two groups: 15 received celiprolol (BB) and 15 received diltiazem (CCB). Both groups demonstrated comparable demographic data, medical history, and severity scores (Table 1). Respiratory function and cardiovascular parameters were similar between groups (Table 2), and operative data are detailed in Table 3.

In the BB group, two cases of transient arterial hypotension occurred. In the CCB group, two incidents were reported: a controlled bleed and a pulmonary artery injury repaired without catecholamines.

Incidence and characteristics of postoperative atrial arrhythmias

Atrial arrhythmias occurred in 17% of patients: 7% POAF and 10% AES (Table 4). These arrhythmias arose between the 2nd and 5th postoperative days, lasted <48 hours, and were well tolerated. One POAF patient experienced recurrence, requiring anticoagulation. Probable causes were identified in three cases: hypovolaemia and postoperative bleeding in the BB group, and hypokalemia in the CCB group. POAF was successfully treated with drug-induced cardioversion, avoiding electrical intervention. AES resolved spontaneously or after addressing the underlying cause.

Post-operative complications and hospital stay

Pneumonia was the most frequent complication, with no agent-related adverse effects observed. Mean ICU and hospital stays were 2.9 and 12.27 days, respectively, with no significant intergroup differences (Table 5).

4. Discussion

In our study, the overall incidence of POA was 17%, with a 7% incidence of POAF and no significant difference between groups. All arrhythmias were well tolerated, lasting less than 48 hours without late recurrence. POA was significantly associated with bilobectomy, prolonged anesthesia, and extensive surgical procedures compared to patients without arrhythmia. No adverse effects related to the prescribed drugs were observed. The incidence of atrial arrhythmias after thoracic surgery varies with the extent of pulmonary resection, ranging from <15% for segmentectomies and wedge resections to >20% for bilobectomies and >40% for pneumonectomies [3, 12]. In our study, the low POAF incidence may be attributed to pharmacological prevention. Despite the high incidence of atrial arrhythmias, mainly *de novo* POAF, few molecules have been studied for primary prevention, likely due to the heterogeneity of pathophysiology. Literature on POAF prevention in thoracic

Table 1. Demographic data, severity scores and history

	BB (n=15)	CCB (n=15)	Total (n=30)	P
Sexe-ratio	14	2.75	5	0.142
Average age (years)	53.87 ± 16.04	50.8 ± 13.55	52.33 ± 14.67	0.299
BMI (kg/m²)	22.68 ± 3.39	24.43 ± 3.3	23.56 ± 3.4	0.125
Thoracoscore (%)	1.47 ± 1.03	2.5 ± 1.77	1.99 ± 1.52	0.187
Classification (ASA):				
ASA 1	6	10	16 (53.3%)	0.143
ASA 2	9	5	14 (46.7%)	
Arterial Hypertension	2	0	2 (6.66%)	0.123
Diabetes	2	1	3 (10%)	0.543
COPD	2	2	4 (13.33%)	1.00
Pre-operative chemotherapy	2	1	3 (10%)	0.543
Pre-operative corticostéroïd therapy	0	1	1 (3.33%)	0.309
Smoking	12	10	22 (73.33%)	0.409

Table 2. Pre-operative respiratory and cardiac investigations

	BB (n=15)	CCB (n=15)	Total (n=30)	p
VEMS (%)	79.54 ± 9.05	82.78 ± 23.01	81.16 ± 17.25	0.617
Tiffeneau report (%)	82.85 ± 15.33	78.86 ± 12.43	80.85± 14.67	0.440
GOLD I	0	1	1	0.309
GOLD II	2	1	3	0.543
PO2 (mmhg)	91.83 ± 10.53	88.2 ± 7.31	89.89 ± 8.74	0.480
PCO2(mmhg)	40.92 ± 13.11	38.84 ± 5.71	39.88 ± 9.78	0.707
FEVG (%)	65.42 ± 6.6	63.23 ± 7.18	64.37 ± 6.85	0.416
Diastolic dysfunction	1	0	1	0.309

Table 3. Type of procedure and operative data

	BB (n=5)	CCB (n=15)	Total (n=30)	p
Type of surgery				
Pneumonectomy	7	11	18 (60%)	0.305
Bi-lobectomy	8	4	12 (40%)	
Pneumonectomy				
Right	2	4	6	0.223
Left	5	7	12	
Lymph node removal	9	10	19 (63.3%)	0.705
Pericardotomy	3	3	6 (20%)	1.00
Duration of surgery (min)	182.33 ± 85.7	192 ± 71.93	187.17 ± 77.9	0.692
Duration of anaesthesia (min)	235 ± 81.78	234.33± 76.55	234.67 ± 77.83	0.967
Intraoperative filling				
Crystalloids (ml)	1133.33 ± 549.89	1100 ± 387.2	1116.67 ± 467.63	0.879
Colloids (ml)	150 ± 227.56	163.33 ± 343.54	156.67 ± 286.39	0.689
Anatomopathology				
Malignant pathology	8	12	20 (66.7%)	0.148
Other lesions or benign tumours	7	3	10 (33.3%)	

Table 4. Type and incidence of postoperative arrhythmias

	BB (n= 4)	IC (n=1)	Total (n=5)	P
Early Atrial arythmias	4	1	5 (17%)	0.361
-POAF	2	0	2 (7%)	0.143
-AES	2	1	3 (10%)	0.543

Table 5. Post-operative complications and hospital stay

	BB (n=15)	CCB (n=15)	Total (n=30)	p
Pneumopathy	2	2	4 (13.3 %)	1.00
Atelectasis	0	1	1 (3.3 %)	0.309
Bleeding	1	0	1 (3.3 %)	0.309
Return to surgery	1	0	1 (3.3 %)	0.309
Noninvasive ventilation	2	0	2 (6.7 %)	0.143
Mediastinal deviation	1	1	2 (6.7 %)	1.00
ICU stay (days)	2.86 (0.83)	3.06 (1.03)	2.96 (0.92)	0.564
Hospital stay (days)	12.06 (7.53)	11.46 (6.79)	11.76 (7.05)	0.820
30-day mortality	0	0	0	

surgery is limited, with few trials comparing pharmacological agents. A 2013 randomized controlled trial by Ciszewski et al. compared acebutolol (BB) and diltiazem (CCB) for POAF prevention after lung resection (lobectomy, bilobectomy, pneumo-nectomy). Among 117 patients divided into three groups (acebutolol, diltiazem, placebo), POAF incidence was 5% in the acebutolol group, 23% in the diltiazem group, and 20% in the placebo group, with no statistically significant difference. However, the acebutolol group had fewer atrial extrasystoles and sinus tachycardias. All arrhythmias occurred on postoperative days 2 or 3 [13].

The overall POAF incidence in prevention studies was 14%, compared to 7% in our study. This lower incidence may be due to factors such as systematic locoregional analgesia and fluid restriction. Most studies compare pharmacological agents to placebo. Diltiazem has demonstrated efficacy and safety in POAF prophylaxis for non-cardiac thoracic surgery. A 2000 randomized double-blind study by Amar et al. involving 330 patients showed statistically significant efficacy of diltiazem in preventing arrhythmias after lobectomy and pneumonectomy [14].

In our study, no side effects were associated with celiprolol, a cardio-selective BB with intrinsic sympathomimetic activity. Its properties limit hypotension and extreme bradycardia at rest, while its beta2 agonist effect avoids respiratory side effects like bronchospasm. Celiprolol has been compared to propranolol, demonstrating bronchodilator properties without worsening respiratory status or bronchial hyperreactivity [15]. Amiodarone has also been shown to significantly reduce POAF incidence and is safe at low doses [16]. Other successful agents include magnesium sulphate [17] and atorvastatin [18], while digitalis [19, 20] and dexmedetomidine [21] have shown no preventive effect.

Prophylaxis reduces POAF incidence after lung resection and is safe when contraindications are respected. However, insufficient data exist to provide clear recommendations for universal POAF prophylaxis. The authors advocate for prophylaxis in high-risk patients using beta-blockers, amiodarone, CCBs, or magnesium, though further studies are needed to evaluate efficacy and safety.

Non-pharmacological prevention methods, such as video-assisted techniques, have not proven effective [24]. Thoracic epidural analgesia has yielded conflicting results, with some studies favoring intravenous analgesia to reduce arrhythmia risk [25, 26].

Our study has limitations, including a small sample size, which reduces statistical power. This is due to declining indications for extensive lung resections and the rise of conservative surgeries like segmentectomy. Only one case of early atrial arrhythmia occurred in the CCB group, compared to four in the BB group, a result requiring cautious interpretation given the sample size.

Future studies should expand to include other surgeries (e.g., lobectomy, pleurectomy), involve multiple thoracic surgery centers, and adopt systematic prophylaxis policies for elderly patients undergoing major lung resections, considering contrain-dications and adverse effects of each drug.

5. Conclusion

Rhythm disorders, mostly postoperative atrial fibrillation (POAF), are the most common cardiac complications after non-cardiac thoracic surgery. Pharmacological prevention has been shown to reduce POAF incidence. Herein, we conducted a single-center, prospective, randomized, single-blind study comparing diltiazem (CCB) and celiprolol (BB) for the prevention of postoperative atrial arrhythmias in patients undergoing lung resection surgery (e.g., pneumonectomy or bilobectomy). The overall incidence of postoperative arrhythmias was 17%, with a 7% incidence of POAF and no significant difference between groups. All arrhythmias were well tolerated, lasting <48 hours. The low POAF incidence in our study aligns with the literature, which associates postoperative atrial arrhythmias with prolonged surgery and anesthesia times. Future studies will expand to other thoracic surgeries and involve multiple centers to achieve a sample size sufficient for statistically significant results in postoperative arrhythmia prevention.

Ethical considerations

Ethical approval was obtained from the Research Ethics Committee of Abderrahmane Mami Hospital, Ariana, Tunisia.

Conflict of interest

The authors declare that there are no conflicts of interest.

Consent of patient

Written informed consent was obtained from all patients to participate in this study.

Consent for publication

Written informed consent was obtained from all patients for publication of this study.

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None.

Authors' contributions

All authors contributed to the article and approved the submitted version.

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