Is amiodarone a safe antiarrhythmic to use in supraventricular tachyarrhythmias after lung cancer surgery?

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Abstract

Background: Supraventricular arrhythmias after thoracotomy for pulmonary resections are well documented. There has been considerable interest in their incidence, nature, predictability from preoperative assessment and treatment. The purpose of this study is to define prevalence, type, risk factors for post-thoracotomy supraventricular arrhythmias and to assess the efficacy of amiodarone as an antiarrhythmic drug.

Methods: The records of 250 patients undergoing pulmonary resection for lung cancer during last two years were followed up in this prospective study with particular attention to possible risk factors (gender, age, extent and side of resection, diabetes mellitus, hypertension, tobacco smoking, beta-blocker ingestion). Patients underwent biopsy only were excluded. Once onset of supraventricular arrhythmia was monitored or documented in the electrocardiogram, intravenous infusion of amiodarone was started with a loading dose of 5 mg/kg in 30 minutes and a maintenance dose of 15 mg/kg until remission of it.

Results: Forty-three episodes (21.6%) of supraventricular arrhythmias were documented with atrial fibrillation being the most common (88.3%). Rhythm disturbances were most likely to develop on the second postoperative day. Pneumonectomy, lobectomy and age >65 years were the statistically significant factors. The overall postoperative mortality was 3.2% and 2.3% for the patients with postoperative supraventricular arrhythmias. In none of the cases did supraventricular arrhythmia cause cardiac failure leading to death. Sinus rhythm was achieved with amiodarone in 37 out of 43 patients (86%). Electrical cardioversion was necessary for 6 patients who were hemodynamically unstable. The most common amiodarone-related complication was bradycardia (13.5%).

Conclusions: Postoperative supraventricular arrhythmias are a common complication in elderly patients undergoing lung resection surgery (especially pneumonectomy or lobectomy). Amiodarone is both safe and effective in establishing sinus rhythm.

Background

Concern about cardiac dysrhythmias was a prominent issue during the early years of thoracic surgery. Since the first actual documentation of cardiac dysrhythmias after pulmonary resections in the early 1940 s, there has been considerable interest in their incidence and nature, their

predictability from preoperative assessment, the ability to prevent their development and their treatment [1].

According to the international literature, most dysrhythmias are supraventricular and by far the most common is atrial fibrillation. The pathophysiologic mechanisms are not well understood and various factors may occur such as hypoxemia, right ventricular dilatation and pulmonary hypertension [2].

Treatment of postoperative supraventricular arrhythmias after lung resection is a controversial topic. Options differ whether supraventricular arrhythmias should be treated with b-blockers, calcium channel blockers or other antiarrhythmic drugs (amiodarone, ibutilide). Digoxin has traditionally been used for the prophylaxis of supraventricular arrhythmias after pneumonectomy but its efficacy remains unproven [3]. Amiodarone (a class III antiarrhythmic drug) has been used after lung resection for cancer in a limited number of studies so far with controversial results due to the implication of the drug in the development of adult respiratory distress syndrome [4].

The purpose of this study was to prospectively evaluate patients who will undergo pulmonary resection, in an effort to determine the incidence and factors related to the development of supraventricular arrhythmias and to assess the effectiveness of treatment with amiodarone.

Methods

This research project was approved by the Ethical Committee of our institution and Aristotle University of Thessaloniki (Institutional Review Board of Research involving Human Subject). Patients undergoing elective thoracotomy for probable pulmonary resection were identified and informed written consent for participation in this study was obtained.

Two hundred and fifty patients were enrolled in this prospective study. All patients in whom pulmonary resection was possible to be performed were considered for the study. Exclusion criteria were a heart rate of less than 50 beats per minute, a systolic blood pressure less than 100 mm Hg, chronic atrial dysrhythmia, heart failure or thyroid dysfunction. Digitalis, b-blockers, calcium antagonists and other antiarrhythmic agents were not allowed for at least 1 week before operation.

Patients who received drugs (macrolide and fluoroquinolone antibiotics, antipsychotic and anidepressant drugs, serotonin agonists of the triptan class, cisapride, dolasetron) that have been reported to be associated with QT interval prolongation were excluded. A baseline cardiac assessment was performed on all patients including cardiac history, physical examination and a 12-lead electrocardiogram (ECG). The exercise tolerance test was indicated in all patients with cardiac symptoms, ECG modifications and in patients who had had a myocardial infarction more than 1 year before the time of hospitalization. If the test was negative, it was followed by surgery. If not, it was followed by coronary artery angiography. Echocardiography was performed in patients who had had a myocardial infarction more than 1 year before and whose exercise tolerance test was negative in order to evaluate the ventricular function. Patients with ejection fraction >25% were eligible for pulmonary surgery.

Each patient's history of hypertension, diabetes mellitus and tobacco smoking was carefully noted.

A thoracic epidural catheter was inserted into all patients before surgery. Postoperative analgesia was maintained with patient-controlled epidural analgesia with an analgesic solution of 0,125% bupivacaine plus fentanyl 2 μg mL^{-1} according to the following program: no initial dose, basal infusion rate 4 mL^{-1}, bolus dose 2 ml and a 10 min lock out interval.

All patients remained in the Intensive Care Unit under continuous electrocardiographic monitoring during the first two postoperative days and later if needed.

The treatment routinely used after thoracic operations was given as usual ie prophylactic antibiotics (cephalosporin), subcutaneous low molecular weight heparin, b$_2$ agonists in aerosol and an H$_2$ antagonist intravenously. Other forms of treatment were given as required. We did not use macrolide or fluoroquinolone antibiotics due to their QT prolonging effects.

Patients with postoperative sinus tachycardia due to pain or intravascular volume depletion were not included. Once onset of supraventricular arrhythmia was monitored or ECG documented, intravenous infusion of amiodarone was started with a loading dose of 5 mg/kg in 30 minutes and a maintenance dose of 15 mg/kg until remission of it.

Supraventricular arrhythmia was considered as ended when sinus rhythm was restored for more than 24 hours and amiodarone was interrupted. Thus, length of amiodarone infusion depended on duration of supraventricular arrhythmia.

Continuous data was analyzed using independent Student's t-test when two sets were compared. Categorical data was analyzed using x^2 analysis or Fisher's exact test (for data sets with one or more cells < or = 5). In all instances, $p < 0.05$ was considered statistically significant.

Table 1: Incidence of supraventricular arrhythmias by type and side of resection.

Resection side	Resection type	n:199	Incidence of supraventricular arrhythmias	
Right	Pneumonectomy	20	10/20	50%
	Bilobectomy	19	4/19	21.1%
	Upper Lobectomy	29	7/29	24.2%
	Lower Lobectomy	20	3/20	15%
	Middle Lobectomy	2	0/2	0%
	Wedge Resection	24	2/24	8.3%
Left	Pneumonectomy	28	11/28	39.2%
	Upper Lobectomy	23	3/23	13%
	Lower Lobectomy	12	2/12	16.6%
	Wedge Resection	22	1/22	4.5%

Results

Two hundred and fifty patients (209 men – 41 women) whose age ranged from 39 to 74 years (mean: 63.1 ± 7.2 years) were included in this study.

Forty eight patients underwent pneumonectomy, 105 a lobectomy, 46 a wedge resection and 51 had an open biopsy. Patients with biopsy were removed from the study. The smaller incision and the little amount of lung removed may have a low impact on development of supraventricular arrhythmias and therefore the inclusion of these patients could decrease the real incidence of post-operative occurence of supraventricular arrhythmias misleading the results.

Forty-three (21.6%) of the 199 patients developed supraventricular tachyarrhythmia with atrial fibrillation being the most common (38/43 patients, 88.3%). Three patients developed atrial flutter and 2 atrial flutter/fibrillation.

The incidence of supraventricular arrhythmias by surgical procedure and side of resection is shown in table 1. Statistical analysis revealed that there is a high incidence of supraventricular arrhythmias in patients undergoing pneumonectomy (p < 0.001) and lobectomy (p < 0.01) versus other type of resections. The side of resection seems to play no role (right side: 26/114 patients 22.8% versus left side: 17/85 patients 20%, p value: 0.383) at least in our material.

Supraventricular arrhythmia occurred in 30 men (18% of the male population) and in 7 women (17% of the female population) (p: 0.416). Twenty-two (33.8%) of the 65 patients aged 65 years or over and 15 (11.1%) out of the 134 younger patients developed supraventricular arrhythmia (p < 0.001). Eleven (17.4%) of the 63 patients with history of hypertension and 5 (17.8%) of the 28 patients with diabetes mellitus developed supraventricular arrhythmia, whereas 26 (19.1%) and 32 (18.7%) of them with no history of hypertension or diabetes mellitus did

Table 2: Risk factors for supraventricular arrhythmias and their statistical significance. SA(+): patients with postoperative supraventricular arrhythmias. SA(-): patients with no postoperative supraventricular arrhythmias. p values less than 0.05 are statistically significant.

Risk factor	SA (+)	SA (-)	p value
Male (n:166)	30/166	136/166	0.416
Female (n:33)	7/33	26/33	
Age > 65 years (n:65)	22/65	43/65	<0.001
Age < 65 years (n:134)	7/134	127/134	
Hypertension (+) (n:63)	11/63	52/63	0.473
Hypertension (-) (n:136)	26/136	110/136	
Diabetes Mellitus (+) (n:28)	5/28	23/28	0.576
Diabetes Mellitus (-) (n:171)	32/171	139/171	
Tobacco (+) (n:165)	31/165	134/165	0.548
Tobacco (-) (n:34)	6/34	28/34	
Beta-blockers preop (+) (n:25)	4/25	21/25	0.513
Beta-blockers preop (-) (n:174)	32/174	142/174	

not (p: 0.473 and p: 0.576 respectively). Thirty-one (18.7%) of the 165 patients who were smokers and 6 (17.6%) out of 34 non-smokers developed supraventricular arrhythmia (p: 0.548). Four (16%) of the 25 patients who received beta-blockers preoperatively and 32 (18.3%) of 174 who did not, developed supraventricular arrhythmia (p: 0.513). The overall incidence of supraventricular arrhythmias according to possible risk factors and its statistical significance is shown in table 2.

The supraventricular arrhythmias lasted from less than 1 day to 6 days with an average of 2.6 days. The peak incidence for the first occurrence of dysrhythmia was on postoperative day 2 and 3 (65.7% and 20.1% respectively). Only 2 patients in this study population experienced the initial onset after 5th postoperative day.

Sinus rhythm was achieved with amiodarone in 37/43 patients (86%). The remaining 6 patients (3 of them underwent pneumonectomy and the other 3 lobectomy) received electrical cardioversion due to the fact that they were hemodynamically unstable. Two of them (both had undergone pneumonectomy) discharged home with persistent atrial fibrillation and per os antiarrhythmic and anticoagulant treatment. The most common side effect because of the use of amiodarone was bradycardia (<50 beats per minute) (5 out of 37 patients – 13.5%). None of the patients receiving amiodarone developed adult respiratory distress syndrome, blurred vision or worsening of the arrhythmia.

The overall postoperative mortality was 3.2% (8/250 patients, 4 had myocardial infarction, 1 pulmonary embolism, 3 respiratory infection) and 2.3% (1/43 patients) for the patients with postoperative supraventricular arrhythmias. This patient had undergone pneumonectomy and developed supraventricular arrhythmia on the 2nd postoperative day. He also developed bronchopleural fistula (15th postoperative day) and died from respiratory insufficiency due to pulmonary infection after major thoracoplasty. In none of the cases supraventricular arrhythmia determined cardiac failure leading to death. All patients were followed up every 2 months for 5–24 months and 3 of them who had experienced supraventricular postoperatively had a new onset again.

Discussion
The observation that thoracotomy performed for non cardiac reasons is often complicated by postoperative supraventricular arrhythmias, dates back more than 50 years. The etiology remains unclear and is almost certainly multifactorial, with the postoperative hyperadrenergic condition and atrial distention as probably most important pathophysiologic factors.

The majority of reports in the literature are retrospective with the incidence of dysrhythmias determined by chart review with its inherent lack of sensitivity. The reported incidence of dysrhythmias after thoracotomy also varies (10–28% in the international literature) [5,6] in part because of definition of dysrhythmias and methods of detection. In this study we purposefully excluded sinus tachycardia often related to presence of pain or intravascular volume depletion. In our material 43 (21.6%) out of 199 patients developed supraventricular arrhythmia with atrial fibrillation being by far the most common (88.3%). This is in agreement with all recently published studies.

Numerous authors [7,8] have suggested that the time of peak onset of development of postoperative dysrhythmias is during the 2nd postoperative day and this also confirmed by our study (65.7% of the patients had the onset of the arrhythmia on the 2nd postoperative day). In contrast Richie and colleagues [9] reported that the most common time for onset of supraventricular arrhythmia is during the first postoperative day.

According to the literature, previously stated risk factors for the development of supraventricular arrhythmias after pulmonary resection include increasing age, sex, side of procedure, extent of resection, history of diabetes mellitus, hypertension, beta-blockers ingestion and previous cardiopulmonary disease, anesthetic agents and preoperative pulmonary functional status. Many authors experienced opposite opinions to these factors [10-12]. In our study increasing age (>65 years) and the extent of pulmonary resection were the only statistically significant factors as we excluded patients with previous history of cardiopulmonary disease.

The extent of pulmonary resection as a risk factor for supraventricular arrhythmias has been a standard for many studies [13,14]. Surgical factors are related to the destruction of cardiac nervous structures. Both sympathetic and parasympathetic cardiac nerves innervate the heart. The vagal and sympathetic fibres emerge, from left to right sides, to form cardiac plexus located between the aortic arch and the tracheal bifurcation. Their filaments accompany the coronary arteries and their branches. The extent of pulmonary resection could determine direct damage to the above mentioned anatomic structures by the dissection of pulmonary hilum during lung resection or hilar and mediastinal node sampling. The significance of these structures was also confirmed by Haissaguerre and colleagues [15] who studied a population of non-surgical patients affected by frequent paroxysms of atrial fibrillation. Electrophysiological study proved that pulmonary veins, especially in their proximal tract, are covered by myocardial tissue, with electrical properties which can generate ectopic beats with consequent atrial

fibrillation. So, surgical knots to the wall of pulmonary veins or other surgical manipulations could probably cause mechanical or ischaemic damage to the zone which is often covered by myocardial excitable tissue. This could generate ectopic beats and atrial fibrillation. No mortality was directly attributed to dysrhythmia. Others have shown mortality associated with dysrhythmia after thoracotomy. Recently, Amar and colleagues [3] have approved that early supraventricular dysrhythmias after resection of non- small cell lung cancer is associated with poor long-term survival, although this finding has to be confirmed by more studies.

Treatment of postoperative supraventricular arrhythmias after pulmonary resection remains a controversial topic. Supraventricular tachyarrhythmias respond well to rate control drugs such as beta-blockers (esmolol, metoprolol) or calcium channel antagonists (diltiazem, verapamil). Class III antiarrhythmic drugs (amiodarone, ibutilide) have been used recently with satisfactory results although there are different opinions [4,16].

Beta-blockers are preferred in patients with ischemic heart disease but may be relatively contraindicated in patients with proven bronchospastic potential, in those with congestive heart failure, severe sinus bradycardia or high degree AV-block [17]. Calcium channel blockers are contraindicated in patients with Wolff-Parkinson-White syndrome since they can accelerate the ventricular rate with atrial fibrillation [11]. Of the class III antiarrhythmic drugs, ibutilide has been used currently with moderate success to convert acute atrial fibrillation in 57% of patients after cardiac surgery, however polymorhic ventricular tachycardia was reported in 1.8% of patients and was attributed primarily to electrolyte imbalance [18].

Amiodarone has been used in recent studies in the management of patients with supraventricular arrhythmia with great success. Ciriaco and colleagues [8] report 90.9% success in establishing sinus rhythm with no side effects. This is in agreement with our study, where amiodarone established sinus rhythm in 86% of the patients with most common side effect bradycardia (<50 beats per minute) in 13.5% of the patients. Only 6 patients required electrical cardioversion due to the fact that they were hemodynamically unstable. In contrast Van Mieghem and colleagues [4] report that amiodarone may be implicated in the development of adult respiratory distress syndrome after lung surgery and especially pneumonectomy.

Because of the greater incidence of supraventricular tachyarrhythmias in the postoperative period most efforts have focused on prevention. A recent review [17] summarized the results of numerous studies examining the effi-

cacy of a variety of drugs to prevent this complication in cardiac surgery patients. It is unclear whether prophylactic treatment against postoperative atrial arrhythmias improves clinical outcomes or shortens hospital stay and whether to employ rate control or rhythm control drugs. But these studies demonstrated also the effectiveness of beta-blockers and class III antiarrhythmics (amiodarone, ibutilide) in reducing the atrial fibrillation incidence after cardiac operations (valvular surgery, coronary artery by pass grafting) [19,20]. Amar and colleagues [21] published the first large, randomized control trial to demonstrate that diltiazem clearly prevents occurence of atrial fibrillation after major thoracic operations. Lanza and colleagues [22] demonstrated that low dose oral amiodarone prophylaxis significantly reduces the incidence of atrial fibrillation after pulmonary resection. Other randomized control trials to test prophylactic effects of the drugs are mandatory to confirm these results in patients after major thoracic non-cardiac operations.

Conclusions
The present study confirms previous data that supraventricular arrhythmias are common in the postoperative period following thoracotomy for lung cancer. The results confirmed the great importance of the extent of surgical resection and increasing age as risk factors. Amiodarone is both safe and effective in establishing and maintaining sinus rhythm.

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