Supraventricular arrhythmia following lung resection for non-small cell lung cancer and its treatment with amiodarone

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Abstract

Objective: From January 1998 to February 1999, 160 patients undergoing lung resection for non-small cell lung cancer were studied to define factors that increase the risk of postoperative supraventricular arrhythmia (SA) and to assess the effectiveness of amiodarone as an antiarrhythmic drug.

Methods: All patients were monitored intraoperatively and postoperatively up to day 3. Onset of SA was documented with ECG. Amiodarone was administered to those who developed SA with a loading dose of 5 mg/kg in 30 min and a maintenance dose of 15 mg/kg in 24 h.

Results: Mean age was 64 years (range 27–83 years). There were nine wedge resections, six segmentectomies, 127 lobectomies and 18 pneumonectomies. Twenty-two patients (13%) had SA, all of which were atrial fibrillations. The incidence of supraventricular arrhythmia with pneumonectomy and lobectomy was 33 and 12%, respectively (P < 0.02). None of the patients who had a minor resection developed SA. The peak incidence of onset of SA occurred on postoperative day 2 and lasted from 1 to 12 days (average 3.4 days). Sinus rhythm was achieved with amiodarone in 20 patients (90.9%) with no side effects. Two patients received electrical cardioversion because hemodynamically unstable. Mean preoperative pO2 and pCO2 were lower in patients with SA: pO2 80.8 vs. 85 mmHg (P = 0.04); pCO2 35.5 vs. 38 mmHg (P = 0.01). Patients with concomitant cardiopulmonary diseases presented an odds ratio for postoperative arrhythmia of 12.4 (confidence interval 4.5–34.1) (P < 0.0001).

Conclusion: Concomitant cardiopulmonary diseases, lower pO2, pCO2 and extent of surgery increase the risk of postoperative SA after lung resection for non-small cell lung cancer. Cardiac monitoring in patients at risk is recommended. Amiodarone was both safe and effective in establishing and maintaining sinus rhythm.

Keywords: Lung cancer; Supraventricular arrhythmia; Amiodarone; Thoracotomy

1. Introduction

Supraventricular arrhythmias (SA) following pulmonary resection are well documented with a reported incidence ranging between 10 and 28% [1–4]. The mechanisms of SA are not well understood and various factors may co-occur such as hypoxemia, right ventricular dilatation, pulmonary hypertension and increased right-heart pressure [3,4]. Reported risk factors are extent of resection, age, lung cancer and intrapericardial dissection [2,3]. There is no standardized treatment for SA. While digoxin has been routinely used in the majority of the studies reported in the literature [5], a decrease in the incidence of postoperative SA has been also reported with preoperative infusion of magnesium sulfate [6] or administration of calcium-channel blockers [7].

Amiodarone, a class III antiarrhythmic drug, has been used in studies on ventricular tachycardia or ventricular fibrillation [8] in the United States although its use for SA is not approved by the Food and Drug Administration. The few European papers which report the use of amiodarone for SA following pulmonary resection present contrasting results due to the implication of the drug in the development of adult respiratory distress syndrome after lung surgery [9,10]. The aim of the present study was retrospectively to evaluate the risk factors for onset of SA after lung resection for non-small cell lung cancer (NSCLC) and the effectiveness of treatment with amiodarone.

2. Materials and methods

From January 1998 to February 1999, 173 patients underwent lung resection in elective thoracotomy at our Institution. Patients who had undergone explorative thoracotomy, lung resection for benign disease or open lung biopsy and...
those with a history of paroxysmal or chronic SA were excluded from the study.

Overall, 160 patients, (134 men and 26 women) who had undergone lung resection for NSCLC entered the study. Preoperative staging included total body computed tomography scan, bone scan, fibrobronchoscopy, pulmonary function tests (PFTs) and arterial blood gas. A baseline cardiac assessment was performed on all patients including cardiac history, physical examination and a 12-lead electrocardiogram (ECG). The same cardiologist (P.M.) evaluated all patients with a history of myocardial disease and/or abnormal ECG and planned additional examinations when required. All patients were intraoperatively and postoperatively monitored by means of continuous ECG until day 3. Monitors had automatic tachycardia detection and diagnosis of SA was made by a cardiologist alerted by the physician in the postoperative ward. Patients received heparin 15 000 IU subcutaneously per day from postoperative day 1 until discharge. Analgesia consisted in epidural catheter or continuous infusion of morphine intravenously when the catheter could not be placed. No pharmacological antiarrhythmic prophylaxis was undertaken. Once onset of SA was ECG documented, pharmacological therapy was promptly started with amiodarone with a loading dose of 5 mg/kg in 30 min and a maintenance dose of 15 mg/kg in 24 h until remission of SA. Electrical cardioversion was given only to hemodynamically unstable patients. SA was considered as ended when sinus rhythm was restored for more than 24 h and amiodarone infusion was interrupted. Thus, length of amiodarone infusion depended on duration of SA. Biochemical and physiologic parameters analyzed during the onset of SA included blood pressure, pO2, pCO2, serum potassium, magnesium and calcium levels.

2.1. Statistical analysis

Data are presented as mean ± standard deviation, unless otherwise indicated. Continuous data were analyzed using unpaired t-test when two sets where compared. The Wilcoxon rank sum test was used when continuous variables were not normal. Categorical variables were analyzed using the chi-squared test or Fisher’s exact test when expected cell frequencies were smaller than 5. Multivariate analysis was performed by logistic regression with stepwise selection to identify independent risk factors for onset of postoperative SA. P-Values less than 0.05 were considered statistically significant.

3. Results

One hundred and sixty patients whose age ranged from 27 to 83 years (mean 64 ± 9.7 years) were included in the study. Forty-four patients (27%) were 70 years old or over. There were 134 men and 26 women. Seven patients (4.7%) required additional preoperative cardiac exams other than ECG. Of these, five had an echocardiography because of previous myocardial infarction (MI) (two patients), cardiomyopathy (one patient), mitral insufficiency (one patient) and prior aortic valve replacement (one patient), while two patients had coronary angiography because of suspected left main disease not confirmed after angiography. Twenty-four patients (15%) had concomitant cardiopulmonary diseases which included chronic obstructive bronchopulmonary disease (ten patients), previous cardiac surgery (six patients), hypertension (four patients) and previous MI (four patients, one of whom had had a MI less than 6 months before). Eighteen patients underwent pneumonectomy, 127 a lobectomy, six a segmentectomy, and nine patients had a wedge resection.

Twenty-two (13%) of the 160 patients developed postoperative SA, all of which were atrial fibrillations. SA occurred in 21 men (15% of the male population) and in one woman (3.8% of the female population) (P = 0.13). Eight (18%) of the 44 patients aged 70 years or over and 14 (12%) out of the 116 younger patients developed SA (P = 0.31). Postoperative complications other than SA included one early bronchopleural fistula, three minithoracostomies for secretions (complication rate 3.1%) and one postoperative pneumonia-related death (mortality rate 0.6%). None of these patients developed postoperative SA.

The incidence of SA in patients who had undergone lobectomy or pneumonectomy was 12 and 33%, respectively (P = 0.02). None of the patients who underwent wedge resection or segmentectomy developed SA (Table 1). Ten patients (41%) out of the 24 with concomitant cardiopulmonary diseases developed postoperative SA with an odds ratio for postoperative arrhythmia of 12.4 (confidence interval 4.5–34.1) (P < 0.0001). None of the patients experienced SA on the day of operation. The peak incidence of onset of SA occurred on postoperative day 2 (45% of 22 patients) and lasted from 1 to 12 days (average 3.4 days). Three of the 22 patients (13%) experienced the initial onset of SA after postoperative day 6. In nine patients out of 22 (40%), SA lasted more than 48 h. The day of onset of SA is indicated in Fig. 1. Sinus rhythm was achieved with amiodarone in 20 of the 22 patients (90.9%) with no side effects. The remaining two patients received electrical cardioversion on days 4 and 6 after onset of SA, since they failed to respond to the amiodarone therapy and were hemodynamically unstable.

Preoperative mean FEV1 was 2.55 ± 0.65 l (range 1.13–4.06) with a mean FVC of 3.39 ± 0.52 l (range 2.13–5.11).

Table 1

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Total no. of patients</th>
<th>Patients with SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonectomy</td>
<td>18</td>
<td>6 (33%)</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>127</td>
<td>16 (12%)</td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>6</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Wedge resection</td>
<td>9</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* Pneumonectomy vs. lobectomy, P = 0.02
Pulmonary function tests were not predictive of onset of postoperative SA. Mean $pO_2$ and $pCO_2$ at the time of admission were 84.4 ± 9.1 mmHg (range 63–99) and 37.7 ± 2.9 mmHg (range 28–45.5) and were significantly lower in patients who developed postoperative SA: $pO_2$ 80.8 ± 8 vs. 85 ± 9 mmHg ($P = 0.04$), $pCO_2$ 35.5 ± 4 vs. 38 ± 2 mmHg ($P = 0.01$). At the onset of SA there were no significant changes in $pO_2$ and $pCO_2$ values. Serum magnesium, calcium and potassium levels were within the normal range at the time of surgery and in the postoperative period. No differences in onset of SA were found between patients receiving epidural analgesia and intravenous morphine. All the variables considered are described in Table 2. Table 3 shows the subset of risk factors independently associated with postoperative SA selected by multivariate logistic regression analysis.

Postoperative length of stay was not significantly increased when SA occurred (7 ± 2 days vs. 9 ± 1 days). Four patients were discharged on a regimen of amiodarone per os for 30 days because they experienced more than one episode of SA during the postoperative period before achieving sinus rhythm; no patient was discharged with SA. Patients were seen within 4 weeks after being discharged from the hospital. None of them had symptoms correlated with onset of SA during this period and SA was not diagnosed in any of the patients at the time of follow-up. All patients were followed up every 3 months for 7–21 months and none experienced SA or pulmonary distress syndrome.

### 4. Discussion

Supraventricular arrhythmia after thoracotomy for pulmonary resections is well documented, with atrial fibrillation acknowledged to be the most common occurrence [1,2]. However, the incidence of SA reported in the literature varies from 10 to 28% and this is due partly to the lack of uniformity in defining SA and partly to the inclusion of non homogeneous populations undergoing lung resections not only for cancer but also for benign disease [3,6,7].

In our study we only considered patients who had had resections for NSCLC. Thus the incidence of postoperative SA was relatively low (13%) compared with that of other authors [1–3,6]. We did not include patients with sinus and atrial tachycardia often related to the presence of pain or intravascular volume depletion and chronic atrial fibrillation.

Lung cancer is considered one of the risk factors for onset of postoperative SA, not for the disease per se, but because history of smoking and COPD, often associated in these patients, cause a decrease in cardiopulmonary function. Moreover, lung cancer requires a more extensive lung resection than a benign disease, and the incidence of SA is higher following pneumonectomy or lobectomy as compared with smaller resections [1,2,7].

In our series 24 patients (15%) had concomitant cardiopulmonary diseases and 41% of them developed postoperative SA. In most of these patients mean $pO_2$ and $pCO_2$ were lower than in the rest of the group, although at the time of onset of SA we did not find a condition of severe hypoxemia. Preoperative PFTs did not represent a risk factor for onset of postoperative SA in our study. This is in agreement with some authors [4,11] who did not find a correlation between pre- and postoperative arterial blood gas values and PFTs with the development of SA [1]. At the time of surgery none of our 160 patients presented cardiac diseases such as subcritical valvular stenoses nor did they have prior histories of supraventricular tachyarrhythmias which could increase the risk of postoperative SA.

We found a higher incidence of SA in patients who underwent a pneumonectomy compared with patients who had a minor resection (33 vs. 12% for lobectomy, $P = 0.02$). Several other studies that examined the correlation between postoperative complications and SA report an increased rate of dysrhythmias after pneumonectomy as compared with lobectomy [1,2]. Curtis and colleagues showed an incidence of postoperative SA in 46.1% of the patients who underwent a pneumonectomy as compared with 14.3% of those who had a lobectomy ($P < 0.005$) [1]. Loss of one lung increases the cardiac workload with ventricular dilatation, increased right-heart pressure and pulmonary hypertension. These are

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$SA(+) (n = 22)$</th>
<th>$SA(-) (n = 138)$</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$pO_2$ (mmHg)</td>
<td>80.8 ± 8</td>
<td>85 ± 9</td>
<td>0.04</td>
</tr>
<tr>
<td>$pCO_2$ (mmHg)</td>
<td>35.5 ± 4</td>
<td>38 ± 2</td>
<td>0.01</td>
</tr>
<tr>
<td>FEV$_1$ (l)</td>
<td>2.6 ± 0.6</td>
<td>2.5 ± 0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>3.4 ± 0.7</td>
<td>3.3 ± 0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Men</td>
<td>21</td>
<td>113</td>
<td>0.13</td>
</tr>
<tr>
<td>Women</td>
<td>1</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Age &gt; 70 years</td>
<td>8</td>
<td>36</td>
<td>0.31</td>
</tr>
<tr>
<td>Age &lt; 70 years</td>
<td>14</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>Concomitant cardiopulmonary diseases</td>
<td>10</td>
<td>14</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
reported as co-factors for onset of postoperative SA [3,4]. Postoperative arrhythmias are also reported after lung transplantation with an incidence of 10–15%. Huddleston has proposed an anatomical explanation on the basis of a laboratory model of lung transplantation. He found that cutting across the base of the pulmonary veins creates a line of conduction block due to the transection of the atrial fibers that come out on the pulmonary veins. The disruption of the atrial fibers caused by the process of ligating the pulmonary veins proximally in pneumonectomy may account for the increased incidence of SA reported with these procedures (see discussion in Ref. [1]).

Extrapleural pneumonectomy and side of pneumonectomy have also been correlated with higher incidence of SA development [7,12,13]. Side of pneumonectomy did not seem to influence onset of postoperative SA in our data.

Previously stated risk factors for the development of SA after pulmonary resection also include sex and age [7,14]. Women in our series had a lower incidence of concomitant cardiopulmonary diseases and a lower incidence of postoperative SA development [7,12,13]. Side of pneumonectomy did not seem to influence onset of postoperative SA in our data.

Previously stated risk factors for the development of SA after pulmonary resection also include sex and age [7,14]. Women in our series had a lower incidence of concomitant cardiopulmonary diseases and a lower incidence of postoperative SA (3.8%) compared with men (15%, $P = 0.13$) although it did not reach statistical difference. Male patients more frequently had associated COPD or cardiomyopathy. Older age is often correlated with a longer smoking history and thus with a higher probability of impaired oxygenation and cardiac function. Moreover, by 75 years of age only approximately 10% of normal sinus node pacemaker cells remain viable leading to a higher probability of developing SA in stress conditions [15].

We found continuous ECG monitoring sufficient to detect postoperative SA. Curtis and colleagues evaluated the use of additional exams, such as Holter monitoring, to detect preoperative abnormalities of the rhythm that could be correlated with onset of postoperative SA but concluded that this was not a helpful modality to select patients for prophylaxis against SA after thoracotomy [1].

Richie and colleagues [5] reported that the most common time for onset of SA is during the initial 24 h after thoracotomy. Only 18% of our patients with postoperative SA experienced SA during the initial 24 h with a peak incidence on postoperative day 2 (45%). Seven patients developed SA after day 3 (31%), suggesting that ECG monitoring is also advisable after day 3 in patients considered at risk. Three patients (13%) had SA after day 6. This information is of relevance to developing clinical pathways and hospital dismissal strategies for patients undergoing thoracotomy. The occurrence of SA did not influence length of hospitalization in our study (9 ± 1 days) since patients who undergo major resection for lung cancer in our Division are not discharged before day 10 for pneumonectomy and day 7 for lobectomy, even in the absence of complications. Our global mean hospitalization for both procedures is 7 ± 2 days.

Treatment of postoperative SA after lung resection is still a controversial topic [2,6,7,10]. Opinions differ whether SA should be treated with drugs that attenuate the adrenergic response to operation (i.e. b-blockers) or with those that may attenuate the pulmonary hypertensive response (i.e. calcium-channel blockers) [7]. b-Blockers are frequently contraindicated in patients undergoing pulmonary resection because of associated bronchoreactive states. Digoxin has traditionally been used for the prophylaxis of SA after pneumonectomy [7], but its efficacy remains unproven since the action of the drug on the atrioventricular node is mediated by an increase in the vagal tone that does not occur after thoracic operations when the adrenergic output is high. Amiodarone, a class III antiarrhythmic drug, has been used after lung resection in a limited number of studies so far [9], although it is currently used for the treatment of atrial fibrillation in the cardiac clinic [16]. The drug exerts a non-competitive antisynaptic action against a- and b-receptors. Its vasodilator action can decrease cardiac workload and consequently myocardial oxygen consumption. Amiodarone has a decreased inotropic effect compared with other antiarrhythmic drugs and can also be administered in patients with cardiac insufficiency and/or a poor general condition [17]. Moreover, although amiodarone is slower in converting arrhythmia, it is more effective in maintaining sinus rhythm. In our series, sinus rhythm was maintained even after the drug was discontinued; only four patients who had achieved sinus rhythm after more than one episode of SA were discharged on amiodarone per os as a prophylactic treatment. There where no recurrences of SA at the 4-week follow-up and none of the patients who were symptomatic when SA occurred in the postoperative period reported relapse of symptoms. We do not prescribe Holter monitoring after discharge since it has not been found to be predictive of increased incidence of SA [1], despite its higher accuracy as compared with ECG, in detecting premature atrial contractions, and it does not therefore add any ulterior information for the diagnosis of SA.

Amiodarone may be implicated in the development of ARDS after lung surgery [9,10] especially after pneumonectomy. Short-term administration of the drug in our study did not cause complications, or side effects such as liver injury, loss of vision or worsening of the arrhythmia. Nevertheless we recommend strict ECG monitoring to

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**Table 3**

Risk factors independently associated with postoperative supraventricular arrhythmia

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Parameter</th>
<th>$P$-value</th>
<th>Odds ratio</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant disease</td>
<td>2.88</td>
<td>0.0001</td>
<td>17.8</td>
<td>5 – 62.7</td>
</tr>
<tr>
<td>pCO$_2$</td>
<td>$-0.27$</td>
<td>0.0045</td>
<td>0.76</td>
<td>0.6 – 0.9</td>
</tr>
<tr>
<td>Extent of surgery</td>
<td>1.65</td>
<td>0.014</td>
<td>5.2</td>
<td>1.4 – 19.7</td>
</tr>
</tbody>
</table>

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$P < 0.05$.
verify the effects on cardiac frequency and on atrioventricular conduction. Pharmacological treatment with amiodarone was effective in 90.9% of our patients and only two patients required electrical cardioversion as they were hemodynamically unstable. It is not our policy to use prophylactic antiarrhythmic treatment since in our series, postoperative SA does not seem to be correlated with major morbidity and/or mortality; moreover prophylactic protocols reported in the literature differ in efficacy and side effects [6,7,12,13]. We adopt low-dose heparin prophylaxis for the prevention of pulmonary embolism throughout the postoperative stay.

We conclude that concomitant cardiopulmonary diseases, lower pO2, pCO2 and extent of surgery increase the risk of postoperative SA after resection for NSCLC cancer. Cardiac monitoring in patients at risk is recommended before discharge in order to detect SA occurring after day 3. Amiodarone is both safe and effective in establishing and maintaining sinus rhythm. Short-term administration is also recommended in order to avoid dangerous side effects.

Acknowledgements

The authors wish to thank Dr Fabrizio Veglia for his statistical analysis.

References


Appendix A. Conference discussion

Dr P. Van Schil (Antwerp, Belgium): I noticed from your series that there were more than 100 lobectomies but only 18 pneumonectomies. Our intensive care physicians refuse to use amiodarone after pneumonectomy, as there was a higher incidence of ARDS or post-pneumonectomy pulmonary edema in some reports. Did you see this complication?

Dr Ciriaco: We never experienced this kind of complication. I know there are papers in the literature that report this. Probably the short-term administration and the relatively low dose administered avoided the problem for us.

Dr Van Schil: Did you use any prophylactic treatment?

Dr Ciriaco: No, we didn’t.

Dr R. Jashari (Leuven, Belgium): Do you use digitalis postoperatively? And a second question is, in cases that don’t convert to sinus arrhythmia, do you give anticoagulation postoperatively over the long term to prevent thromboembolism?

Dr Ciriaco: Well, we do not use digitalis as a prophylaxis. We don’t think we need to use prophylaxis for these kinds of patients. And, yes, we use a mild anticoagulation on a regular basis for all patients that undergo lung resection. We use heparin calcium, 15 000 IU per day.

Dr Jashari: But in cases if they remain in supraventricular arrhythmias, do you use long-term anticoagulation?

Dr Ciriaco: No, no.

Dr T. Rice (Cleveland, OH, USA): Amiodarone is a very effective drug, but its cost is prohibitive in the United States, $2000 per intravenous administration. Can you tell us about the cost in Italy?

Dr Ciriaco: I don’t know exactly the cost in Italy, but it is not that expensive because it is the kind of drug that is used on a regular basis by the cardiologists here. The cost is about $50 per intravenous administration.

Dr Rice: Our cardiologists use it regularly too, but we try to treat our patients preoperatively and postoperatively with oral medication to avoid the prohibitive intravenous costs. What side effects did your patients experience with the medication?

Dr Ciriaco: None at all.

Dr Rice: No pulmonary problems?

Dr Ciriaco: No.