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Risk Factors and Clinical Management of Cardiac Arrhythmias Arising After Lung Cancer Surgery

George D. Bablekos[1]* and Stylianos A. Michaelides[2]

[1]*University of Applied Sciences / Technological Educational Institute (T.E.I.) of Athens, Faculty of Health and Caring Professions, Agiou Spyridonos, Egaleo, Athens, Greece*

[2]*Department of Occupational Lung Diseases and Tuberculosis, Sismanogleio –Amalia Fleming General Hospital, Maroussi, Athens, Greece*

Abstract

In the present short review it is attempted to analyze and discuss, along with the appropriate clinical management, the risk factors promoting the emergence of supraventricular cardiac dysrhythmias (SVDs) after lung cancer surgery that may negatively influence the postoperative clinical outcome of these patients. By searching the relevant international literature of the last three decades (from January 1st 1990 to November 30th 2017) 30 out of 101 eligible articles were finally selected on the basis of their title and abstract. The key words which had been used are as follows: Arrhythmias, Cardiac (Mesh), Lung Neoplasms/Surgery (Mesh), Postoperative Complications (Mesh), Postoperative Period (Mesh). The impact of the autonomous nervous system tone, being influenced by the extent of thoracic surgical trauma, on the atria, is of paramount importance regarding the triggering of SVDs. Moreover, it seems that amiodarone constitutes a safe and efficient agent to either protect or restore disturbances of the sinus rhythm resulting from lung cancer surgery. Other medicines such as digitalis, verapamil, diltiazem and beta-blockers, with the exception of amiodarone, should not be administered after thoracic surgery in patients presenting Wolf-Parkinson-White syndrome. Verapamil and diltiazem is contraindicated in patients intravenously receiving beta-blockers or presenting congestive heart failure. The role of cardioversion to restore cardiac arrhythmias after thoracic surgery is also discussed along with the role of anti-coagulation treatment.

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Introduction

A frequently reported and discussed issue in the relevant literature is the impact of lung cancer (LC) surgery on the occurrence of cardiac arrhythmias and myocardial ischemia during the first postoperative days [1-8], thus increasing both postoperative morbidity and mortality in these patients.

To the best of our knowledge the precise mechanisms leading to the emergence of cardiac arrhythmias after-LC surgery remain still unclear. The aim of this short review is by searching the relevant literature from January 1st 1990 to November 30th 2017, to outline the risk factors contributing to heart rate disturbances after LC-surgery, along with the appropriate clinical management for improving the clinical condition and outcome of these patients.

Materials and Methods

The search of the literature was conducted covering the last three decades, from January 1st 1990 till November 30th 2017, by using the Pubmed data base. The items Arrhythmias, Cardiac (Mesh) were combined with AND with the items Lung Neoplasms/surgery (Mesh), arising in the first group of results with a number of 151 published articles. Also, the items Arrhythmias, Cardiac (Mesh) were simultaneously combined with AND with the items Lung Neoplasms (Mesh) as well as with AND with the items Postoperative Complications (Mesh) OR Postoperative Period, thus ensuring the second group of results with 84 articles. The aforementioned first and second group of results were combined with OR and a total number of 90 published articles were detected as more appropriate for our topic. An additional search of the literature from Google covering from January 1st 2000 to November 30th 2017 was also conducted by using the items Preoperative Cardiac Evaluation, Anesthesia, Cancer, Chemotherapy and eleven articles were located as more appropriate for our topic. From 101 articles finally found, 30 articles were selected and used for the writing of this review because of their title, abstract and whole content. Seventy-one articles were excluded as irrelevant to the topic of this review.

The literature search and the selection of the articles which had been used for the writing of the present work are presented on Figure 1.

Discussion

In this work it is attempted to present concentrated knowledge and discuss what has already been published in the relevant literature on the topic of cardiac arrhythmias after LC surgery, focusing on the following items:

1. Pathogenesis
2. Prevention
3. Clinical Management

Concerning the Pathogenesis of the supraventricular dysrhythmias (SVDs) they represent the most frequent postoperative complication after thoracic surgery, being associated with prolonged hospital stay [9] and decreased long-term survival [3]. Atrial flutter and atrial fibrillation (AF) are both attributed to re-entry circuits located in the atrial tissue [10,11]. Particularly, the atrial flutter seems to be dependent upon only one re-entry circuit while AF, being a more complex type of cardiac arrhythmia depends on multiple re-entry

***Corresponding Author:** Dr. George D. Bablekos, Thoracic Surgeon, Androu 16B str, Melissia 15127, Athens, Attiki, Greece; E-mail: gbableko@otenet.gr

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circuits [9]. It is reported that the maintenance of the AF is based on the depolarization of a number of ancillary nerve circuits entering the atrial tissue independently of each other [11]. The occurrence of SVDs after LC surgery is associated with the boost of the tone of either the vagus nerve or of the sympathetic neural plexus as well as to postoperative haemodynamic disturbances [9]. The role of the tone of the autonomous nervous system concerning the sensitivity of the atrial tissue in the emergence of an imminent AF is extremely important [9]. Furthermore, patients with AF and/or atrial flutter present a delay of the stimulus particularly through the tissue of the right atrium (short right refractory periods) [12]. The aforementioned delay is attributed to the following [9]: (i) hypertrophic myocardial cells, (ii) distension of the atrial tissue along with the presence of interstitial fibrosis, (iii) hypertension in the left atrium, (iv) myocardial infarction located in the atrial tissue, (v) pericarditis, (vi) previous cardiothoracic surgery, (vii) injury of the atrial tissue. Regarding the influence of cardiothoracic surgery in the emergence of postoperative SVDs, the role of coronary artery bypass grafting (CABG) is underlined in the relevant literature: SVDs usually occur during the first four postoperative days [13,14]. It is important to note that age over 70 years, stenosis of the right coronary artery and reduced administration of beta-blockers, all can lead to AF after CABG [15]. Also, for patients older than 75 years only 10% of the cells of the sinus remain still operational [16,17]. Moreover, although the prolonged signal averaged P-wave duration (SAPWD) is considered to be the single independent prognostic factor for the emergence of the AF after cardiac surgery [18], this is not in effect in other types of thoracic surgery except for CABG [19]. Also, according to the relevant literature, there is no release of SVDs during sleep [20, 21], a fact that is indicative of the contribution of the sympathetic autonomous nervous system in the onset of SVDs. It has been further reported that the vast thoracic surgical trauma influences postoperatively the endogenous regulation of the autonomous nervous system thus boosting the adrenergic activity due to increase of the release of catecholamines from the atrial cells, resulting in the occurrence of SVDs [9].

In the context of Prevention of cardiac arrhythmias after thoracic surgery, the rate of occurrence of AF is one out of five patients who underwent LC-surgery and particularly on the second [5,22] or on the third postoperative day [22]. The administration of the digitalis to prevent SVDs following thoracic surgery was found to be accompanied with side-effects [23, 24]. Additionally, digitalis presents a lack of activity during the early postoperative period because this is secondly activated via the central nervous system, while the tone of the vagus nerve is also boosted [25]. Another study focuses on the intravenous administration of verapamil to inhibit SVDs after operations in the thorax [26]. The surgical resection of the lung parenchyma results in an increase of the pressure in the right heart compartment as a consequence either of a reactive constriction of the remaining pulmonary capillaries or of the anatomical post-surgery decrease of the pulmonary hilum [27,28]. The augmentation of the pressure in the right heart generates a mechanical dilation of the atrial tissue leading to shortening of the refractory period [20]. The aforementioned shortening of the refractory period provokes the adrenergic activities which are involved in the release of SVDs [20].

Moreover, according to the relevant literature, the prophylactic daily dose of intravenous verapamil, (bolus infusion), to prevent the onset of AF after lung operations was 10mg with a maintenance for at least three days, while bradycardia and hypotension occurred in 9% and 14% respectively of patients [22]. The same study showed that the administration of verapamil immediately after lobectomy orpneumonectomy reduced the postoperative occurence of AF by 50%

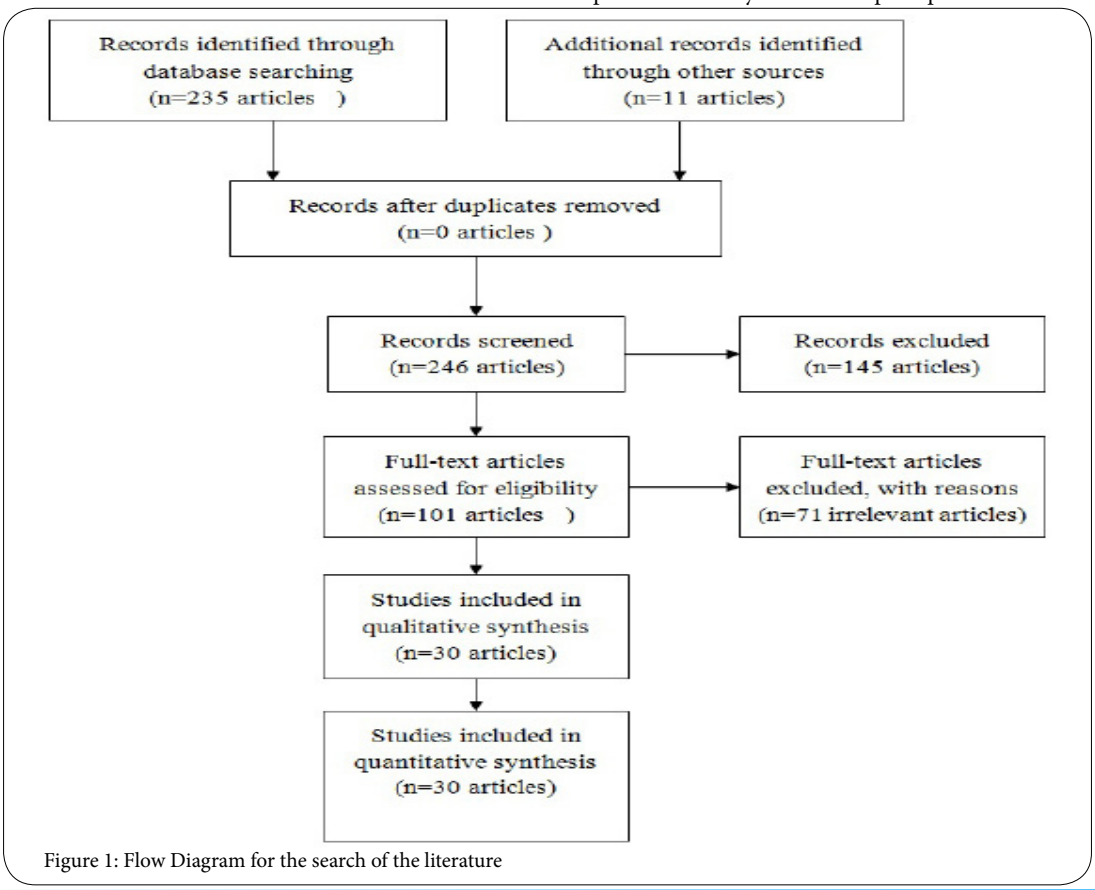

Figure 1: Flow Diagram for the search of the literature

[22]. Concerning the prevention of SVDs after thoracic surgery, beta-blockers and calcium-channel blockers can also be administered. It is known that beta-blockers moderate the adrenergic response, while calcium-channel blockers decrease pulmonary pressure that rises after LC-surgery in order to improve the postoperative clinical outcome [9]. It has been further reported that in candidates for thoracic surgery, it is of paramount importance to reduce preoperatively the after-load values in the right heart compartment [9]. Moreover, the role of diltiazem (calcium-channel blockers) has been extensively studied in fighting SVDs detected after thoracic surgery [29-33]. According to Borgeat et al., diltiazem presents a lower inhibitory effect on the activity of the smooth muscles which encircle vessels thus respectively resulting in a less dilation of the wall vessels [29]. Also, diltiazem has fewer complications and side-effects when administered to treat SVDs [30-33]. In addition, a previous comparative study concerning the effects of diltiazem and digitalis administered during the first three postoperative days in order to prevent cardiac arrhythmias after pneumonectomy, showed that diltiazem was more efficient and safer compared with digitalis [33]. Age greater than 70 years and a hospital stay exceeding nine days were also both considered as risk factors leading to occurrence of SVDs after pneumonectomy [33]. Another two medicines which can be used to inhibit release of cardiac arrhythmias after the surgical resection of the lung parenchyma, are flecainide [29] and amiodarone [34]. Flecainide, despite its efficacy to inhibit cardiac arrhythmias particularly after non-cardiac thoracic surgery, it is suggested to be implicated in ventricular arrhythmias [29]. Also, amiodarone is associated with the emergence of acquired respiratory distress syndrome (ARDS) [34] and bradycardia [35]. Nevertheless, although bradycardia is the most common complication developed in 13.5% of the patients receiving amiodarone to either prevent or treat SVDs after LC-surgery, it seems that amiodarone is a safe and efficient medicine to protect and restore disturbances of the sinus rhythm after thoracic surgery [35-38]. Besides, the administration of Dexmedetomidine (DEX) during LC-surgery seems to decrease the eventuality for emergence of postoperative AF [39]. It is also reported that for patients who underwent chest surgery b-adrenergics and theophylline can be postoperatively used in order to prevent deterioration of lung function, given that the concentrations in plasma of the aforementioned medicines along with the administered doses will be monitored [9].

The role of chemotherapy and radiotherapy influencing cardiac function in the context of LC-surgery is also discussed. Myocardial ischemia, arrhythmias, pericarditis, myocarditis and changes in blood pressure may result from chemotherapy-induced cardiotoxicity [40, 41], while supraventricular tachycardias attributed to androgen deprivation therapy administered for prostate cancer treatment have also been recorded [42,43]. Therefore, the effect of cardiotoxicity in heart rate as a consequence of the neo-adjuvant treatment before pulmonary parenchyma resection [44] should be taken into account. It is further reported that candidates for LC-surgery having previously received neck and/or chest radiotherapy are considered to be as high risk patients for the emergence of perioperative cardiac arrhythmias [44]. The early diagnosis of the left ventricular dysfunction (LVD) due to cardiotoxicity, should be treated with angiotensin-converting enzyme inhibitors and b-blockers, thus contributing to the recovery of the cardiac function by simultaneously decreasing the possibility for perioperative occurrence of cardiac arrhythmias [44,45].

The maintenance of normothermia throughout the operation of the LC resection in association with the management of the postoperative pain, are both important to avoid postoperative cardiac dysfunction [46], including heart rate disturbances.

Concerning the Clinical Management of the SVDs emerging as a the sequel of thoracic surgery there is a number of risk factors that should be taken into account, since they frequently contribute to the occurrence of these events after lobectomy or pneumonectomy [4, 9, 47-62]. These risk factors are as follows: (i) disturbances of acid-base balance and ventilation [9], (ii) tissues oxygenation status [9], (iii) electrolyte disturbances, (iv) influence of bronchodilators on cardiac function [9], (v) history of ischemic heart disease, congestive heart failure, intra-operative cardiac arrest and rethoracotomy [4], (vi) age, history of hypertension and lymph node resection [47], (vii) concomitant cardiopulmonary diseases, lower P_aO_2 and P_aCO_2, extent of thoracic surgery [48], (viii) history of chronic obstructive pulmonary disease (COPD) [49], (ix) serum concentration of Mg [50], (x) autonomic denervation and stress-mediated neurohumoral mechanisms [51], (xi) elevation of preoperative and perioperative NT-proBNP [52,53], (xii) lack of control of postoperative pain (patient-controlled analgesia with opioids such as fentanyl and tramadol than patient-controlled epidural analgesia with ropivacaine) [54], (xiii) increasing age, increasing extent of operation, male sex, nonblack race and stage II or greater tumors [55], (xiv) medical history of pre-existing left ventricular diastolic dysfunction [56], (xv) preoperative size of the left atrium [57], (xvi) preoperative fluctuation of heart rate variability (HRV) [58], (xvii) left lobectomy [59] and (xviii) preoperative levels of B-type natriuretic peptide [60,61]. Also, according to Iwata T et al [7] it seems that factors such as the male gender, the extent of the surgically removed lung parenchyma, the preoperative level of the brain natriuretic peptide (BNP) as well as the left ventricular early transmitral velocity/mitral annular early diastolic velocity (E/e') calculated by echocardiography, all should be considered as predictive factors for postoperative AF despite the fact that predictive values of each individual parameter were not high. Another recent study confirmed the role of the mediastinal lymph node resection in the occurrence of postoperative AF after LC-surgery [62].

To treat atrial flutter and or AF occurring after LC-surgery, verapamil, diltiazem or beta-blocker, all leading to decrease of the ventricular response, are considered as medicines of choice [9,63]. Digitalis, also leading to decrease of the ventricular response, or medications such as quinidine, flecainide, disopyramide, procainamide, propafenone and sotalol, contributing to a long-term inhibition of SVDs following LC-surgery, can be alternatively administered as well [9,63]. Digitalis, verapamil, diltiazem and beta-blockers, with the exception of amiodarone, should not be postoperatively administered in patients with Wolf-Parkinson-White syndrome candidates for thoracic surgery, even if AF or atrial flutter will emerge after surgery [9,63]. Concerning atrial arrhythmias other than AF or atrial flutter, the relevant literature reports that adenosine, verapamil and diltiazem are considered as the treatment of choice [9,63], while, esmolol (beta-blocker), digitalis and ablation can also be used [9,63]. It is additionally reported that for types of atrial arrhythmias other than atrial flutter and AF, procainamide, quinidine, disopyramide, beta-blockers, diltiazem, verapamil, flecainide, propafenone and digitalis are medicines adequately efficient for the long-term inhibition of these arrhythmias [9,63]. Furthermore, verapamil and diltiazem should be cautiously administered to patients simultaneously receiving quinidine per os [9,63]. Also verapamil and diltiazem are not indicated for patients intravenously treated with beta-blockers or presenting congestive heart failure [9,63].

It is useful, either for the general or the specialized physician involved in the clinical management of SVDs after LC-surgery, to concisely quote a few points from the relevant literature [9] as

Pathogenesis	Pathogenesis is attributed to the following: i) re-entry circuits located in the atrial tissue, ii) boost of the tone of the vagus nerve or of the sympathetic neural plexus, iii) postoperative haemodynamic disturbances.
Prevention	Preventive medication for maintenance of sinus rhythm after thoracic surgery are dialtiazem and amiodarone.
Clinical Management	Atrial flutter and fibrillation can be treated with verapamil, diltiazem or β-blockers
	Cardiac arrhythmias other than atrial flutter or fibrillation after surgery can be treated with procainamide, quinidine, disopyramide, beta-blockers, diltiazem, verapamil, flecainide, propafenone or digitalis.
	Prevention and treatment of thromboembolic episodes amenable to SVDs occurring in the first postoperative days is of paramount importance.

Table 1: Main messages for the management of cardiac arrhythmias recorded after lung cancer surgery

follows: (i) digitalis is considered to be the medication of choice only in patients with congestive heart failure, (ii) beta-blockers should not be administered in case of pre-existing bronchospasm or congestive heart failure, (iii) for patients with pre-existing thyrotoxicosis or myocardial ischemia, beta-blockers are considered as the treatment of choice and (iv) diltiazem and verapamil are considered as the treatment of choice for patients presenting high concentrations of adrenergic substances in the plasma or in those with congestive heart failure or bronchospasm.

Moreover, in order to prevent SVDs after LC-surgery, it is suggested to postoperatively administer low-dose landiolol which is an ultrashort-acting b-blocker [64], or to intraoperatively continuously infuse low-dose human atrial natriuretic peptide which exerts a prophylactic effect against the postoperative emergence of AF [65]. Another study showed that the continuous intraoperative infusion of olprinone during LC-surgery in patients having elevated preoperative B-type natriuretic peptide (BNP) levels (≥ 30 pg/mL) significantly reduces the incidence of postoperative AF [66]. Also, for patients with chronic obstructive pulmonary disease (COPD) candidates for LC-surgery, it has been found that the administration of long-acting β2-adrenoceptor agonists does not postoperatively promote the occurrence of atrial arrhythmias [67]. An issue that it should be reported as well is the emergence of thromboembolic incidents attributed to SVDs after LC-surgery, something which requires immediate treatment [68]. Thromboembolism usually occurs between 24h and 72h after the occurrence of AF [69]. The sinus rhythm should have been restored 48h after the onset of SVDs (AF) [69]. If cardiac arrhythmia remains for more than two days, then anticoagulation treatment in spite of postoperative bleeding is indicated [9,69]. The existence of postoperative AF for three or four weeks, despite administration of antiarrhythmics and anticoagulants, then cardioversion is the treatment of choice [9,69]. If, after cardioversion of the AF, no recurrence of the arrhythmia appears, antiarrhythmic medication should be further administered during four or eight weeks and then stopped [69]. In case of recurrence of the arrhythmia, along with the continuously administered antiarrhythmic medication simultaneous cardioversion will be performed, while, even if under total restoration of the sinus rhythm, antiarrhythmic medication will be administered for twelve weeks [69]. Moreover, since, despite the second attempt of cardioversion of the AF, cardiac arrhythmia still remains, in that case warfarin per os is administered while a third cardioversion is attempted between six or twelve weeks after the second one [69]. The 5-year overall survival and disease-free survival (DFS) were also examined between two groups of patients who underwent LC-surgery [70]. The one group presented AF as a preoperative co-morbidity and the other one was without AF [70]. Although no statistically significant differences were found between the two groups for all studied parameters (p=0.30 for the 5-year overall survival and p=0.31 for DFS), it has been concluded that these patients should be monitored after-surgery, in order to prevent thromboembolic events [70].

The main messages, for decision making in clinical practice, are concluded on Table 1.

The extent of thoracic surgical trauma contributes to cardiac dysrhythmias after LC-surgery. Medications usually administered to prevent and restore disturbances of the sinus rhythm following thoracic surgery, are diltiazem and amiodarone. Also, atrial flutter or AF occurring after LC-surgery can be treated with verapamil, diltiazem or beta-blocker. For cardiac dysrhythmias other than AF or atrial flutter occurring after thoracic surgery, medications usually administered are procainamide, quinidine, disopyramide, beta-blockers, diltiazem, verapamil, flecainide, propafenone or digitalis. The prevention and treatment of thromboembolic episodes due to SVDs emerging in the first three days after LC-surgery are also of paramount importance for the postoperative outcome of these patients.

Competing Interests

The authors declare that no competing interests exist.

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