PROTOCOL OF A THESIS FOR PARTIAL FULFILMENT OF M.D. DEGREE IN CARDIOTHORACIC SURGERY

Title of the Protocol:
The impact of pulmonary ligament dissection during lung resection on airway geometry changes: a randomized controlled trial

Postgraduate Student: **Ali Mohamed Warda**
Degree: M.S.C Cardiothoracic surgery - Ain Shams University.

DIRECTOR: **Prof. Dr. Ahmed Anwar Elnory**

Academic Position: **Professor of Cardiothoracic surgery, Faculty of Medicine, Ain Shams University**

Co-DIRECTOR: **Prof. Dr. Hany Hassan El-sayed**

Academic Position: Professor of Cardiothoracic surgery, Faculty of Medicine, Ain Shams University

Co-DIRECTOR: **Prof. Dr. Ahmed Mohamed Osman**

Academic Position: Professor of Diagnostic and intervention radiology and molecular imaging, Faculty of Medicine, Ain Shams University

Co-DIRECTOR: **A. Prof. Dr. Ahmed Mohamed Mostafa**

Academic Position: **Assistant Professor of Cardiothoracic surgery, Faculty of Medicine, Ain Shams University**

Co-DIRECTOR: **Dr. Mohamad Abdel-Gayed Ibrahim**

Academic Position: **Lecturer of Cardiothoracic Surgery, Faculty of Medicine, Ain Shams University**

Faculty of medicine

Ain Shams University

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What is already known on this subject? AND

What does this study add?

Most upper lobectomy procedures are performed due to the high incidence of lung cancer detected in the upper lobe. Previous studies have shown that many thoracic surgeons tend to divide the inferior pulmonary ligament (IPL) during upper lobectomy [1,2]. In theory, a residual cavity is bound to form after the removal of the upper lobe during the operation, and this represents a risk factor for postoperative complications such as pleural effusion and pulmonary infection.

Traditionally, dissecting IPL during surgery is believed to mitigate the postoperative restriction of the lower lobe's range of motion, thus enhancing its expansion and filling the residual cavity, which can reduce postoperative atelectasis and pleural effusion [3,4]. However, IPL may have essential functions beyond lung lobe immobilization, including roles in pleural fluid secretion and reabsorption [8].

There is currently no sufficient evidence to prove that isolating IPL during surgery can improve patient prognosis, and there is still great controversy about whether this step should be performed.

Our study will compare the distinct clinical outcomes of IPL dissection versus preservation in patients with upper lobectomies for various indications, not limited to lung cancer. Our aim is to offer specific evidence to guide clinical decision-making regarding operative techniques.

1.INTRODUCTION/ REVIEW

The inferior pulmonary ligament consists of a double serosal sheath connecting the visceral pleura on the medial surface of the lower lobe of each lung to the parietal pleura covering the mediastinum. It extends downward in a sheet-like manner from the inferior margin of the pulmonary hilus to the diaphragm and loosely attaches the medial surface of the lung to the mediastinum. The ligament forms a barrier between the anterior and posterior parts of the mediastinal portion of the pleural cavity below the root of the lung. When the lung is displaced laterally away from the mediastinum, the pulmonary ligament is stretched and assumes a triangular configuration. It has, therefore, been referred to as the triangular ligament.

The apex of the triangle is situated at the inferior margin of the root of the lung immediately below the inferior pulmonary vein. The lower margin or base of the ligament is usually continuous with the pleura over the diaphragm, leaving a linear bare area on the diaphragm between the two leaves of the ligament. In some cases, the ligament does not reach the diaphragm and terminates in a free falciform border (5).

Histologically, the ligament consists of two serosal layers of pleura with intervening bands of collagenous fibers, reticulum, elastic fibers, and fat. The connective tissue fibers extend medially to merge with fibers around the vagus nerves and esophagus. The ligament is avascular in nature however it may contain an aberrant systemic artery in cases of pulmonary sequestration and nodal tissue.

The function of the pulmonary ligament is not known. It probably provides distensibility to the pleural tube conducting the hilar vessels and bronchi to the lungs so that they are not constricted by vascular engorgement or changes in position during breathing. The ligament also helps the lower lobe to resist torsion, and it limits displacement of the lower lobe by pleural effusion or pneumothorax limiting space problems (5).

With the term “post-operative residual pleural space” we refer to a free volume resulting from a pulmonary resection, which is usually diagnosed in 90% of cases of lobectomy. The residual space depends on both the pre-surgery pulmonary compliance and the pleural lymphatic vessels absorption pressure; it is usually occupied by a shift of the mediastinum and the diaphragm, by an increase in the volume of the remaining lung, and, in part, it is filled by the pleural fluid (8).

The disease that required surgery may play a significant role in the formation of the residual space. It has been demonstrated that patients treated with partial resection because of chronic pleuro-parenchymal inflammatory or infective diseases (tuberculosis, fungal infections, abscess, bronchiectasis and empyema) present a residual air space more often than patients undergoing surgery to treat lung cancers (9).

Another pivotal element which affects the residual lung volume is the persistence of the pre-surgery disease, such as emphysema or fibrosis. In a fibrotic lung, after pulmonary resection, pleural pressure becomes more sub-atmospheric and overcomes the lymphatic draining activity; this leads to an enhanced hydrothorax risk, due to the persistence of the gas bubble (7).

The type of resection can influence the mechanism of persistent air spaces. The air leak tends to be more important and persistent after more complex and invasive operations. Technical and physical obstacles and supplement procedures, during surgery, could increase the risk of air leak. Decortication may be a compelling cause of a persisting space. The incidence of an air leak enduring longer than 5 days is about 3.5% after wedge resection, 6.7% after segmentectomy and 8.6% after lobectomy (7).

Thus, the resulting volume is the consequence of both the new equilibrium between filtration and absorption of the pleural fluid and the new mechanical coupling between the lung and the chest wall.

Post-lobectomy airways complications are associated with significant morbidity and mortality. Lobar torsion, bronchopleural fistula bronchial kinking, stenosis and anastomotic complications pose a challenge to the clinician to secure timely diagnosis and intervention in order to improve outcomes

Lobar torsion is an uncommon but life-threatening complication of pulmonary lobectomy. Axial rotation of the remaining lobar parenchyma on its bronchovascular pedicle results in bronchial occlusion and vascular compromise. The incidence is between 0.09–0.4% (7). Upper lobectomy is responsible for almost 75% of cases with the right middle lobe being most vulnerable particularly following right upper lobectomy (7). Left lower lobe torsion accounts for most of the remainder of cases however torsion has been reported in each lobe following lobectomy (7,8). The degree of rotation in pulmonary torsion is generally 180°, although degrees of rotation between 70° to beyond 360° are reported (9), with two thirds rotating in a clockwise direction.

The devastating clinical effects of torsion are due to simultaneous insults of pulmonary arterial, pulmonary venous and bronchial artery occlusion. Median time to diagnosis is four days, ranging from the day of operation up to three weeks.

A number of factors predispose a lobe to torsion by increasing its mobility, including a long, narrow or skeletonized bronchovascular pedicle, complete oblique fissure, division of the inferior pulmonary ligament, pleural air or fluid, an atelectatic or congested remaining lobe and the absence of adhesions (9).

Upper lobectomy results in upward displacement of the remaining lung and ipsilateral diaphragm. Whilst this movement facilitates obliteration of the pleural space, the displacement and subsequent change in the angle of the remaining bronchus may occur to an extent that kinking of the airway results (5,6). Such kinking of the bronchus is most commonly seen after left upper lobectomy. Sigmoidal distortion of the left main bronchus results in cross sectional narrowing of the left lobar bronchus.

Utilizing CT imaging analysis and computational fluid dynamics Gu *et al*. demonstrated that left upper lobectomy is associated with a significant reduction in the angle between the trachea and left main bronchus. This was associated with increased wall pressure, airflow velocity, sheer stress and turbulent flow at the site of kinking. The authors suggested that these changes may contribute to post-lobectomy negative adaptive remodeling that leads to symptoms of dyspnea and cough in some patients (4).

Change in bronchial angle following upper lobectomy may be associated with reduced postoperative pulmonary function (5). Ueda *et al*. defined bronchial kinking as airway angulation and resultant stenosis exceeding 80%. Postoperative functional lung volume and ventilatory capacity were significantly greater in patients without, than in those with bronchial kinking. Patients with bronchial kinking were more likely to experience intractable cough and shortness of breath (76% *vs.* 21%, respectively, $P<0.01$) (6).

Symptomatic kinking may be difficult to diagnose where patient and clinician expects some breathlessness in the early postoperative phase and where patients differ in their recovery times. Changes in bronchial angle in a patient who is slow to recover may not be causative.

Furthermore, significant radiological kinking may remain subclinical (6). However, symptoms of cough and breathlessness beyond six months may be attributable to kinking (4,9).

The role of preoperative patient factors and technical intraoperative maneuvers in the development of kinking is uncertain. Masuda *et al*. identified that a shorter distance from the carina to the middle lobe may be associated with kinked middle lobar bronchus (9).

The post-lobectomy bronchial angle may be influenced by a number of anatomical and technical factors including the degree of diaphragmatic elevation, extent of mediastinal shift, effect of nodal dissection on hilar release and whether division of the inferior pulmonary ligament is undertaken. Proposed advantages of inferior pulmonary ligament division include reduction in risk of residual space and its consequences of pleural effusion, empyema and prolonged air leak. Whilst some studies have demonstrated that preservation of the inferior pulmonary ligament at upper lobectomy is associated with reduction in change of the bronchial angle and better lung function compared to those who undergo division (9), others have noted no difference in bronchial angle or pulmonary function when comparing division and preservation of the ligament (9).

Differences in findings may be due to the small number of patients in the studies or due to the variation in the modality of imaging utilized to calculate the bronchial angle. In a recent systematic review and meta-analysis of the necessity of inferior pulmonary ligament dissection after an upper lobectomy, the pooled comparison revealed a greater change of the right main bronchial angle (MD 5.00, 95% CI: 1.68 to 8.33, P=0.003) in the group undergoing inferior pulmonary ligament division (10). This collective evidence, together with experience of a case of bronchial kinking in a patient with previous hilar release has influenced a change in the authors practice where lobectomy is performed with preservation of the inferior pulmonary ligament.

2.AIM/ OBJECTIVES

To study the impact of pulmonary ligament dissection and /or preservation after upper pulmonary lobectomies on the change of airway geometry and residual space problems

3.METHODOLOGY:
Patients and Methods/ Subjects and Methods/ Material and Methods

- **Type of Study:** Randomized controlled clinical study (a pilot-exploratory study)
- **Randomization:** Upon obtaining informed consent, patients were enrolled in an electronic data capture system by a research staff member and were given a unique study number prior to randomization. Patients were then randomized in a 1:1 ratio to either Group P or Group D
- **Study Setting:** Ain shams university hospitals
- **Study Population:** Patients attending cardiothoracic surgery department at Ain shams university hospitals.

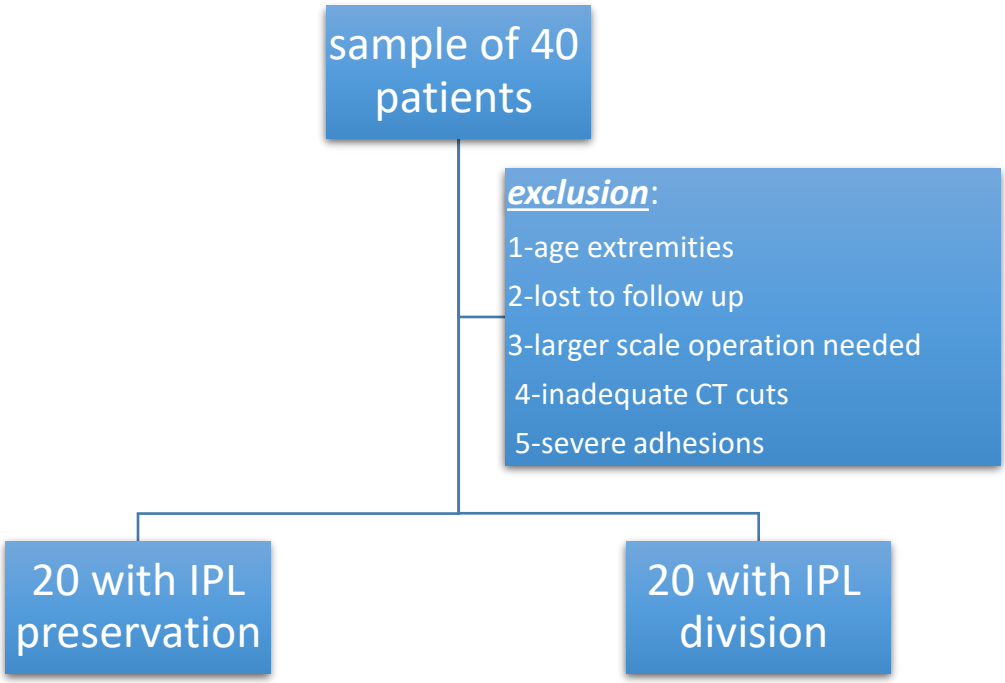
Inclusion Criteria:

1. Age group 18-70 years old
2. Any mass in the upper lobe presented for upper lobectomy
3. Patients presented for bilobectomy for whatever cause
4. Preoperative ECOG score of 0–1, preoperative ASA scores 1–2

Exclusion Criteria:

1. Patients with age extremities <17 and >70 years old
2. Severe thoracic adhesions found during surgery
3. Inadequate CT images (as patients with extensive breathing motion artifacts that hinder proper measurements of the bronchial angles and lung volumetry)
4. Found that a larger-scale operation is required due to multiple lesions
5. Lost to follow-up

- **Sampling Method**: Purposive sampling according to inclusion and exclusion criteria.
- **Sample Size:** By using Power Analysis and Sample Size Software (PASS 15) (Version 15.0.10) for sample size calculation, setting power at 80 %, significance level 0.0**5** and after reviewing previous study results (Moon et.al, 2021) showing that among patients underwent upper lobectomy, the difference between pre- and postoperative left main bronchus curvature index was lower in preservation group (0.03 +/- 0.03) than in group dissection (0.06 +/- 0.03) with statistically significant difference; based on that and after considering 10% dropout rate, **a sample size of at least 40 patients attending cardiothoracic surgery department and fulfil the inclusion and exclusion criteria divided randomly into 2 groups (group P is the preservation and D is the dissection group with 20 patients in each group)** will be needed.



- **Study procedures:**

All participants will be subjected to the following:

- Detailed history taking and sociodemographic data including: age, sex, comorbidities and medications.
- Clinical examination of chest condition.
- CT chest will be done for all the patients pre- and post-operatively using CT machines with at least 16 slice generation.
- No specific preparation will be needed and no contrast will be injected.
- The scanning will be done while the patients in supine position and with breath holding in full inspiration.
- The images will be transferred to a special workstation to be analyzed using a 3D synapse Fuji software.
- The images will be examined in multiplanar reformat (MPR) and after 3D reconstruction.
- The following items will be measured in both pre and postoperative scans in both MPR images and in 3D images:
    - ✓ 1. Lung volume.
    - ✓ 2. Bronchial angle.
- Patients will be operated upon under general anesthesia with double lumen endotracheal tube
    - Posterolateral thoracotomy incision according to the pathological side
    - Patients in both groups will undergo upper lobectomy (either left or right) where in group D the IPL will be dissected and group P will have their IPL preserved.
    - Post-operative analgesia and routine CXR will be done
    - A follow up period of 2 weeks post-operative with chest CT done measuring the bronchial angles and lung volumes at the same setting
    - Symptomatic cough will be identified throughout the follow up period

- **Outcomes:**

  ❖ Primary outcomes:

  1- The change in bronchial angulation pre- and post-operatively

  2- The difference in lung volume pre- and post-operatively using CT 3D reconstructive imaging

  ❖ Secondary outcomes:

  1- The length of hospital stays among patients in both groups

  2- Development of post-operative symptomatic cough (unresponsive to expectorants or mucolytics)

- **Ethical Considerations:**
  - Approval will be obtained from the Scientific Research Ethics Committee at the Faculty of Medicine, Ain Shams University, before starting to work on the study.
  - Data presentation will not be by the patient's name but by diagnosis.
  - All results will be statistically studied using SPSS computer software (SPSS Inc)., tabulated, and discussed.

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