SPECIAL ARTICLE

Postoperative Acute Respiratory Distress Syndrome After Lung Resection

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Introduction

Respiratory complications are the main source of postoperative morbidity and mortality after lung resections. They cover a wide range of clinical situations with different levels of severity, such as atelectasis, bronchopleural fistula, pneumonia, empyema, and acute respiratory insufficiency. Acute respiratory insufficiency is well known and has been widely reported following thoracic surgery. One of its more severe forms involves the appearance of noncardiogenic pulmonary edema, formerly known as postpneumonectomy edema. As knowledge of this clinical manifestation has increased, its clinical and histopathological similarity to acute respiratory distress syndrome (ARDS)—considered to be the most severe form of acute lung injury (ALI)—has become evident.[1,2] The use of theoretically stricter diagnostic criteria has contributed to increasing our knowledge of this syndrome, though there are still many questions and varying results regarding its prevalence, preoperative and perioperative prognostic factors, pathogenesis, and mortality.

Postpneumonectomy Edema

In their 1984 report of 10 cases of postoperative pulmonary edema in patients who had undergone pneumonectomy, Zeldin et al[3] coined the term "postpneumonectomy edema" and indicated that its manifestation, in the absence of left ventricular failure or infection, was due to an excessive fluid perfusion volume that exceeded the drainage capacity of the remaining pulmonary lymphatic tissue. Since then, several studies have contributed to establishing the following clinical characteristics of postpneumonectomy edema: an acute, hypoxemic form of respiratory insufficiency secondary to noncardiogenic pulmonary edema—pulmonary artery occlusion pressure (PAOP) <18 mm Hg—

that manifests as pulmonary infiltrates between 12 hours and 5 days following surgery, accompanied by pulmonary hypertension and increased pulmonary vascular resistance with no evidence of related preoperative predictive factors, an overall incidence of 2.2%-7% (4.7% in pneumonectomy and 1%-7% in lobectomy), and high mortality in the majority of studies (ranging from 50% to 100%).[4-10]

Although the level of evidence was low, pathogenesis of postpneumonectomy edema was considered to be multifactorial and a variety of risk factors related to its development have been described: right pneumonectomy, fluid overload, reduced lymphatic drainage, reduction of the pulmonary capillary bed with edema due to low outflow and the resulting mechanical stress on the capillaries, increased permeability of the alveolocapillary membrane, transfusions of frozen fresh plasma, high intraoperative ventilation pressures, and abnormal lung function.[3-9] In postpneumonectomy edema, measurements of PAOP with a Swan-Ganz catheter may give a false low result that is significantly lower than the pressure in the left atrium.[11] Thus, measurement of effective pulmonary capillary pressure by means of recording PAOP gives a more precise measurement of the true pressure in the pulmonary capillaries. In fact, PAOP may be lower than the pressure in the pulmonary capillaries when there is a high resistance between them and the left atrium (vascular venous bed).[12]

ALI and ARDS

In studies investigating the prevalence, mortality, and pathogenesis of ALI/ARDS after lung resection, the variety of names used to describe the condition have not helped in establishing its frequency, clinical course, and mortality: postperfusion lung syndrome, noncardiogenic pulmonary edema, postpneumonectomy edema, ALI, and ARDS.

In 1994, the American-European Consensus Conference on ARDS provided more objective definitions for diagnosing ALI and ARDS by establishing that both are due to increased alveolocapillary permeability resulting

from a systemic inflammatory syndrome, that they are associated with a number of abnormalities that develop progressively, and that they have different clinical, radiological, and histopathologic stages.[13] Onset is acute and the condition follows a persistent course characterized by severe hypoxemia and bilateral infiltrates in the chest x-ray and PAOP of less than 18 mm Hg (or the absence of clinical evidence for raised pressure in the left atrium). The distinction between ALI and ARDS is really based on the level of hypoxemia: it is considered to be ALI when PaO_2/fraction of inspired oxygen is less than 300 mm Hg and to be ARDS when this ratio is less than 200 mm Hg. ARDS is therefore a deterioration of ALI toward a more severe form. According to the authors, neither mechanical ventilation nor the use of positive end-expiratory pressure (PEEP) are requisites that should be included in the diagnosis of ALI/ARDS.

Until then, neither ALI nor ARDS were cited as complications following lung resection, though it was widely recognized that ARDS was a devastating clinical manifestation (first described in critical patients by Asbaugh in 1967) that caused severe acute respiratory insufficiency in different medical and surgical situations. The high protein content observed in postpneumonectomy edema suggests that the increase in alveolocapillary permeability is the cause of the clinical symptoms and its similarity to the changes in the lung that occur in ARDS show that both conditions follow an identical clinical, radiological, and histologic course. Major lung resections have come to be considered one of the various causes of ALI/ARDS,[14-16] despite the fact that diffuse pulmonary infiltration can obviously only be unilateral in the case of pneumonectomy.

The overall combined frequency of ALI/ARDS after thoracic surgery and lung resection is 2.2% to 5.1%. Results are variable regarding mortality, which ranges from 26% to 43% for acute lung injury and from 53% to 88% for ARDS; both conditions are responsible for 72.5% of total postoperative mortality.[2,4,17-20] In a multicenter study of 1113 cases of ALI in heterogeneous patients, Rubenfeld et at[21] established that hospital mortality was 38.5% for ALI and 41.1% for ARDS.

In most studies, the clinical manifestation is directly related to the extent of the surgery, such that both incidence and mortality are related to the amount of lung tissue resected. In pneumonectomy, the reported frequency of ALI/ARDS is 4% to 7.9% (higher incidence in right pneumonectomy) and mortality is 59%, whereas in lobectomy the reported frequency is 2% to 5% and mortality is 44%. Nevertheless, these results cannot be considered uniform or generally applicable as ALI/ARDS has been reported following small sublobar resections,[19] sometimes with a higher frequency (3.2%) than that found following left pneumonectomy (3%), bilobectomy (2.4%), and lobectomy (2%).[2] Other authors have also found (with no satisfactory explanation) a higher incidence of ARDS after lobectomy (5.6%) than after pneumonectomy (3.9%), with no difference in frequency with respect to the side on which surgery was performed.[14] In an attempt to explain this diversity of results, the possibility has been put forward of different levels of lung involvement,

ranging from mild to moderate ALI to the most severe form of ARDS, which is associated with a less favorable prognosis, and a clinical spectrum has been described that would range from mild, reversible edema to more severe and possibly irreversible edema.[22] This diversity of results is presumably related to the different and characteristic pathogenic mechanisms that can cause ARDS after thoracic surgery.

The mean presentation time following surgery is 3.5 to 5.2 days (range, 1-10 days) for ALI and 4.2 to 6 days (range, 1-13 days) for ARDS.[2,14,17,19] Licker et al,[18] however, described an interesting 2-stage distribution pattern for ALI after lung resection due to cancer. Those authors stated that, in most cases (3.1%), the condition would be a primary form of lung injury that appears in the first 3 days after surgery and would be associated with chronic alcohol abuse, pneumonectomy, fluid overload, and ventilatory mechanical stress due to barotrauma. In a minority of cases (1.1%), the presence of gastric aspiration, pneumonia, or bronchopleural fistula would lead to secondary ALI between 3 and 12 days after surgery. Secondary ALI would be associated with higher mortality than primary ALI (60% compared to 26%; $P<.05$).

Diagnosing ALI and ARDS

In general, the figures for frequency and mortality of ALI/ARDS after thoracic surgery are highly variable and this may be related to both the limited diagnostic accuracy of the criteria for ARDS and the particular and different pathogenetic mechanisms that doubtless have a highly variable influence on the severity of clinical course.

The diagnostic criteria for ALI and ARDS described by the American-European Consensus Conference on ARDS establish and differentiate both clinical situations based exclusively on the level of hypoxemia and do not take into consideration respiratory support, PEEP, the origin of the respiratory disorder (pulmonary or extrapulmonary), or the possible failure of other organs (ARDS is the manifestation in the lungs of a systemic inflammatory response). The exclusion of PEEP in the definition of ARDS has led some authors to conclude that this definition does not reflect the true severity of the lung damage or the patient´s chances of surviving, and they have suggested the need for more specific methods for evaluating the state of gas exchange, including a specific PEEP value, since this can substantially alter the level of hypoxemia.[23]

When the clinical criteria for ARDS have been compared with autopsy findings, the diagnostic accuracy of the definition established by the consensus conference is merely moderate, with sensitivity ranging from 75% to 83% and a specificity of between 51% and 84%.[24,25] Pathology findings in patients who met the criteria for ARDS but had no diffuse alveolar damage were the following: pneumonia (74%), pulmonary hemorrhage (10%), pulmonary edema (7%), pulmonary embolism (7%), and interstitial fibrosis (2%). However, patients who were not diagnosed with ARDS but who were shown to have diffuse alveolar damage in the autopsy

had been diagnosed with pneumonia (45%) and pulmonary edema (45%); lung disease had not been diagnosed in 10% of those patients.[24] The definition of ARDS was more accurate for patients with extrapulmonary risk factors than for patients with a primarily pulmonary cause. These findings may have important clinical implications, particularly for the difficulty of distinguishing severe diffuse pneumonia from ARDS in patients with pulmonary risk factors using the existing clinical definition, especially in cases of late-onset pneumonia.

ARDS and Postoperative Pneumonia

Postoperative infections are one of the main factors associated with morbidity following thoracic surgery. Hospital-acquired pneumonia is a relatively frequent complication of lung resections and it is associated with a high percentage of postoperative morbidity and mortality. There are clear differences regarding its prevalence. The different frequencies reported are related to the diagnostic criteria used, type of surgery, use of different prophylactic antibiotic regimes, and postoperative management. The criteria for defining postoperative pneumonia and the methods used to identify it are generally highly variable. Most authors report an incidence of 5% to 26%, and 35% to 50% of cases include microbiological evidence. This disease is a common, severe, and early-onset pneumonia that presents in the first week after surgery. It has a reported mortality of between 19% and 60% (severe pneumonia or empyema) and leads to longer stays both in intensive care and in hospital.[1,26,27]

The most commonly isolated pathogenic bacteria are those typically associated with early-onset hospital-acquired pneumonia: *Haemophilus influenzae*, *Streptococcus pneumoniae*, and other streptococci. *Enterobacter* and *Pseudomonas* species are less common and etiology is polymicrobial in 33% of these pneumonias.[27] In other cases where different results are reported, the predominant bacterial flora may be clearly influenced by the type and duration of preoperative prophylaxis.[28] Several risk factors related to postoperative pneumonia have been reported: advanced age, male sex, underlying disease, deficient nutritional state, smoking, neoplastic disease, chronic obstructive pulmonary disease, forced expiratory volume in the first second of less than 1500 mL, anemia, transfusions, prior radiotherapy, prior chemotherapy, preoperative colonization of the airways, antibiotic prophylaxis, prolonged surgery, extent of the resection, admission to the intensive care unit, and poor postoperative analgesia.[26,27,29,30]

In this context, it may be difficult to establish a differential diagnosis between ARDS and severe postoperative pneumonia, particularly if the pneumonia is not early-onset. Radiologic changes in ARDS occur after clinical deterioration and may vary from signs of diffuse interstitial infiltration to a pattern of clear alveolar edema. Routine bacterial cultures would make it possible to identify pneumonia if the results are positive, though both diseases may coexist.[31]

Pathogenesis of ALI/ARDS After Lung Resection

Ischemia-reperfusion injury certainly occurs in thoracic surgery involving single-lung ventilation. In anesthesia with single-lung mechanical ventilation, ischemia in the ipsilateral lung is followed by reexpansion and reperfusion of the remaining lung tissue after a lobectomy and by hyperperfusion and hyperinflation of the contralateral lung in the case of pneumonectomy. A lung subject to single-lung ventilation is exposed to the risk of the combined action of hyperoxia, volutrauma, hyperinflation, barotrauma, and hyperperfusion with endothelial mechanical stress. As a result, the cumulative or synergistic effect of pulmonary hyperinflation, surgical trauma, and ischemia-reperfusion leads to the release of inflammatory mediators that, together with a combination of injuries to the alveolar-endothelial barrier, results in a low-pressure pulmonary edema (ARDS) and, finally, multiorgan failure.[15,18,31]

ARDS is usually triggered or precipitated by one or more recognizable predisposing factors. In the case of lung resections, however, different specific factors have been implicated that are especially related to different clinical situations and surgical or perioperative factors. The table shows the pathogenetic factors related to this particular form of postoperative ARDS.[3-9,14-18,22,31,32]

Conclusions

ARDS after lung resection was initially known as postpneumonectomy edema and is a rare clinical condition with a devastating clinical course and high mortality. Its appearance involves a large number of perioperative pathogenetic mechanisms that, either in isolation or together, alter the inflammatory response and the permeability of the alveolocapillary membrane after surgery. This multifactorial etiology that is so characteristic of this type of surgery would appear to be the reason for the different frequencies described in relation to both the amount of tissue resected and the severity of the clinical course, which would presumably have different levels of histopathologic severity, leading to the varying percentages of associated mortality found by different studies. For example, if the main cause of ARDS is reduced outflow and the inadequacy of the capillaries of the remaining lung, prognosis will presumably be worse and mortality higher than if the pulmonary edema is exclusively the result of perioperative fluid excess.

Furthermore, the limited sensitivity and specificity of the diagnostic criteria for ALI/ARDS that are currently used in clinical practice make it impossible to affirm the exact prevalence of the condition and the evident possibility of postoperative pneumonia not only makes the differential diagnosis difficult (especially in the case of late-onset pneumonia) but also makes it necessary to consider the coexistence of both diseases, where the infection may be the cause of the ALI/ARDS or a severe added complication in ARDS following lung resection, especially in patients who have been admitted to intensive care units.

**Etiologic Factors for Acute
Lung Injury/Acute Respiratory Distress Syndrome
After Lung Resection**

Predisposing factors
    Advanced age
    Alcohol abuse
    Lung cancer
    Fluid overload
    Prior radiotherapy and chemotherapy
    Level of prior lung and heart disease
    Amount of lung tissue resected
    Pneumonectomy, right pneumonectomy
    Transfusion of frozen fresh plasma
    Mechanical ventilation: volutrauma, barotrauma
    Duration of relative hypoxemia and repercussion
    Bronchial aspiration
    Early-onset sepsis

Mechanical factors
    Ipsilateral injury of lymph vessels and insufficient drainage
    Reduction of the pulmonary capillary bed and reduced
       outflow
    Endothelial injury due to mechanical stress
       (shearing and rupture)
    Distension of intercellular junctions
    Increased permeability of the alveolocapillary membrane
    Loss of hypoxic pulmonary vasoconstriction
    Injury due to surgical manipulation
    Single-lung ventilation, hyperinflation
    High oxygen concentrations

Ischemia-reperfusion
    Metabolic acidosis
    Adenosine triphosphate depletion, failure of the
       transmembrane gradient
    Release of toxic oxygen radicals, oxidation damage
    Release of cytokines, activation of leukocytes
    Reperfusion: toxic metabolites into the microcirculation
    Peroxidation of cell-membrane lipids
    Neutrophils, release of endothelial factors, nitric oxide
    Endothelial damage, epithelial damage, or both

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