Frequency and mortality of acute lung injury and acute respiratory distress syndrome after pulmonary resection for bronchogenic carcinoma

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Abstract

Objective: We reviewed the frequency and mortality of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) in our population of patients submitted to pulmonary resection for primary bronchogenic carcinoma. Methods: From January 1993 to December 1999, a total of 1221 patients received pulmonary resection for primary bronchogenic carcinoma. Of these, 27 met the criteria of post-operative ALI/ARDS. There were 24 men and three women with a mean age of 64 years (range 45–79). Pre-operatively, predicted mean of PaO₂, PaCO₂ and %FEV₁ were 72 mmHg (57–86), 37 mmHg (33–42) and 80% (37–114), respectively. Associated cardiac risk factors were present in eight patients. Three patients (11%) had pre-operative radiotherapy. Surgical–pathologic staging included 14 patients at Stage I, 8 patients at Stage II, four patients at Stage IIIa and one patient at Stage IIIb.

Results: ALI/ARDS occurred in 2.2% of our operated lung cancer patients. ALI was diagnosed in 10 patients and ARDS in 17 patients. The mean time of presentation following surgery was 4 days (range 1–10) and 6 days (1–13) for ALI and ARDS, respectively. According to the type of operation, the frequency was highest following right pneumonectomy (4.5%), followed by sublobar resection (3.2%), left pneumonectomy (3%), bilobectomy (2.4%), and lobectomy (2%). The frequency following extended operations was 4%. No differences were found between the ALI/ARDS group and the total population of resected lung cancer patients. ALI was diagnosed in 10 patients and ARDS in 17 patients. The mean time of presentation following surgery was 4 days (range 1–10) and 6 days (1–13) for ALI and ARDS, respectively. According to the type of operation, the frequency was highest following right pneumonectomy (4.5%), followed by sublobar resection (3.2%), left pneumonectomy (3%), bilobectomy (2.4%), and lobectomy (2%). The frequency following extended operations was 4%. No differences were found between the ALI/ARDS group and the total population of resected lung cancer patients (control group) with respect to sex, mean age, pre-operative lung function, staging and pre-operative radiotherapy. Four patients with ALI (40%) and 10 patients with ARDS (59%) died. Mortality was highest following right pneumonectomy, extended operations and sublobar resections. Hospital mortality of the total population of operated lung cancer patients in the same period was 2.8% (34 patients). ALI/ARDS accounted for 41% of our hospital mortality. Conclusions: (1) ALI/ARDS is a severe complication following resection for primary bronchogenic carcinoma. (2) We did not detect any significant difference between the ALI/ARDS group and the control group regarding age, pre-operative lung function, staging and pre-operative radiotherapy. (3) ALI/ARDS is associated with high mortality, the highest mortality rates having been observed following right pneumonectomy and extended operation; it currently represents our leading cause of death following pulmonary resection for lung carcinoma. (4) ALI/ARDS may also occur after sublobar resections with an associated high mortality rate. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Lung carcinoma; Acute lung injury; Acute respiratory distress syndrome; Surgical therapy

1. Introduction

Pulmonary resection is the most effective procedure to control the progression of bronchogenic carcinoma. Major developments in thoracic surgery have occurred over the past 30 years, which have resulted in a dramatic reduction of post-operative mortality and morbidity. Currently, the reported mortality rates following lung resection range from 4 to 9% after pneumonectomy and from 1 to 3% after lobectomy. Sublobar resections are associated with even lower mortality rates. Morbidity rates range from 20 to 40% depending on the reported series [1–3]. As surgical and anaesthetic techniques improved, a number of high-risk groups of patients have progressively been considered for surgery, including patients older than 70 years, those submitted to neoadjuvant therapy, those with previous cardiac diseases or with reduced pulmonary reserve [4–6]. As expected, complication rates in these high-risk patients have been reported to be almost double [4–9].

The causes of both mortality and morbidity following lung resection for bronchogenic carcinoma are classified
as cardiac (arrhythmias and myocardial infarction), pulmonary embolic and respiratory [10,11].

Respiratory complications include a wide spectrum of conditions with different degrees of severity, including retained secretions, atelectasis, prolonged air leak, pneumonia and bronchopleural fistula. Among respiratory complications, the occurrence of acute respiratory failure has long been reported in the past and has been variously named as non-cardiogenic pulmonary oedema, post-perfusion lung, adult respiratory distress syndrome, and post-pneumonectomy pulmonary oedema [12,13]. As the number of reports describing the syndrome increased, it became evident that most of the clinical and radiologic characteristics of the condition were similar if not identical to those of the acute respiratory distress syndrome (ARDS), which in turn is considered the most severe form of acute lung injury (ALI) [14]. It was therefore agreed that the term ALI/ARDS should be employed to indicate any form of acute respiratory failure occurring after lung resection associated with radiologic pulmonary infiltrates in the absence of left cardiac failure. Despite its reported frequency and severity, very few studies have been published investigating prevalence, predictive factors and mortality of the condition.

Our study was undertaken to retrospectively analyse our population of patients submitted to lung resection for primary bronchogenic carcinoma in the last 7 years in order to (1) assess prevalence and mortality of post-operative ALI/ARDS and (2) identify any pre-operative or peri-operative causative factor.

2. Materials and methods

From January 1993 to December 1999, a total of 1221 patients received pulmonary resection as curative treatment of primary bronchogenic carcinoma. There were 1038 men and 183 women in the age range from 24 to 82 years with a mean age of 63 years with 71% of the patients being 60 years or older.

2.1. Pre-operative assessment

Our routine pre-operative evaluation includes a complete history and physical examination, biochemical profile with blood cell count, electrocardiogram (EKG), chest radiograph, computed tomography (CT) of the chest and upper abdomen, fibre optic bronchoscopy with cytological, histologic (if appropriate) and microbiological specimens, pulmonary function tests (PFTs) with arterial blood gas analysis.

Cardiac consultation with additional cardiac investigations was required when routine EKG was abnormal or a history of cardiac diseases was recorded.

In case of reduced lung function, a split lung perfusion scan using microaggregated albumin labelled with 99m Technetium or exercise testing to determine oxygen consumption were employed to assess the feasibility of pulmonary resection.

Brain CT scan and total body bone scan were performed selectively.

Pre-operative mediastinal lymph nodal sampling by means of mediastinoscopy or anterior parasternal mediastinotomy were employed selectively in the case of enlarged (>1.5 cm) mediastinal lymph nodes at CT scan.

FEV1% (of predicted), PaO2 and PaCO2 of 200 randomly selected patients out of the total population of patients submitted to lung resection for primary bronchogenic carcinoma were recorded and used as control for comparison with corresponding data in the ALI/ARDS group.

2.2. Operation and peri-operative management

The types of operations performed were 188 pneumonectomies (88 right and 100 left), 41 bilobectomies, 820 lobectomies, 93 sublobar resections (wedge resections and segmentectomies), 79 exploratory thoracotomies (6.4%). These operations included 101 extended operations in which major lung resection was associated with either resection of intrathoracic structures (chest wall resection or resection of Pancoast’s tumor) or technical procedures in which a significant increase of operative time and one-lung anaesthesia might be anticipated (mostly carinal, bronchial or arterial sleeve procedures).

Before surgery, all patients had a central venous catheter and a radial arterial catheter for the monitoring of central venous pressure (CVP) and arterial blood pressure (ABP). A bladder catheter was inserted for monitoring the urine output.

Patients were intubated using either a left- or right-sided double-lumen endotracheal tube. The affected lung was deflated as soon as the pleural space was opened and deflation was maintained through most of the operative time. The lung was definitely reinflated at the end of the resection for check of the air leaks and closure. The fraction of inspired oxygen (FiO2) during surgery ranged from 0.8 to 1.0 according to intra-operative blood gas analysis evaluation.

Most operations were performed through a posterolateral thoracotomy. Since 1996, muscle-sparing incisions were routinely employed. A complete hilar and mediastinal lymph node dissection or sampling was carried out in all patients for staging.

In general, patients were extubated at the end of the procedure and they were transferred to the ward after a brief stay in the recovery area.

Intra-operative fluid management greatly depends upon the operative time, the extent of the operation, and the intra-operative blood losses and was therefore difficult to report. Standard post-operative fluid management included 1500 ml of crystalloids for 48 h.

Post-operative analgesia was obtained using intravenous buprenorphine converted as oral codeine–paracetamol after 48 h.
2.3. ALI/ARDS population group

The definitions of ALI and ARDS adopted in the present study were those proposed by the American–European Consensus Conference in 1994 and are indicated in Table 1.

Twenty-seven patients developed ALI or ARDS following pulmonary resection for primary bronchogenic carcinoma. There were 24 men and three women in the age range from 45 to 79 years with a mean age of 64 years. Twenty patients were 60 years of age or older. Eight patients were 70 years or older.

Lung function performed pre-operatively using PFTs and arterial blood gas analysis revealed a mean PaO\textsubscript{2} of 72 mmHg (range 57–86), mean PaCO\textsubscript{2} of 37 mmHg (range 33–48) and mean PaO\textsubscript{2}/FiO\textsubscript{2} expressed as percentage of predicted of 80% (range 37–114). Associated cardiac risk factors were present in eight patients (coronary artery disease (CAD) in two patients and rhythm disorders in six). Three patients had pre-operative radiotherapy (dose 25–30 Gy). No patient received amiodarone post-operatively as prophylaxis or treatment of supraventricular tachyarrhythmias.

The types of operations performed included seven pneumonectomies (three left and four right; mean age 62 years), one bilobectomy, 16 lobectomies (seven on the left and nine on the right; mean age 65 years), and three sublobar (wedge or segmentectomy) resections (all on the left; mean age 67 years). In four of the aforementioned patients, an extended operation was undertaken including one right sleeve pneumonectomy, two right sleeve lobectomies and one right pneumonectomy and chest wall resection (three ribs). For all patients who developed ALI/ARDS, the operative time (as index of time of one-lung ventilation) and the intra-operative fluid intake was recorded.

Surgical–pathologic staging according to the New International System of Staging for Lung Cancer included 14 patients at Stage I, eight patients at Stage II (of whom 2 T3N0 parietal), four patients at Stage IIIa and one patient at Stage IIIb (T4 carinal).

Any patient who developed ALI/ARDS post-operatively was transferred to the intensive care unit (ICU) where arterial blood gas analysis, haemodynamic data (supplemented in selected cases by the data obtained by insertion of a pulmonary artery catheter), microbiological specimens on blood and tracheobronchial secretions, and radiological evaluation were all performed as appropriate.

Therapeutic management of patients who developed ALI/ARDS in our series varied according to the severity of the disease. No patient in our series could be managed with non-invasive ventilatory support. The mainstay of the treatment is an appropriate mechanical ventilation associated with optimal patient positioning.

Most of our patients were treated using the so-called ‘lung protective strategies’, which basically consist of a reduced-V\textsubscript{I} (tidal volume) (\(<10\text{ ml kg}^{-1}\)), pressure-controlled ventilation and PEEP to limit peak alveolar pressures while maximising alveolar recruitment. A permissive hypercapnia was usually tolerated. As for the use of PEEP, we tend to adopt a technique of periodic volume recruitment manoeuvres (VRMs) in which temporary increases of PEEP are used to generate a transpulmonary pressure sufficient to exceed airway opening pressure in dorsal lung regions.

Steroids were generally employed in moderate doses (methylprednisolone, 125 mg day\textsuperscript{-1}) on an empirical basis.

2.4. Statistics

Post-operative mortality and morbidity were defined as any event (death or major complication) occurring from the time of operation before hospital discharge. Differences between frequencies when all expected cell frequencies are greater than or equal to 5 were tested using the chi-square statistics; otherwise, Fisher’s exact test was used. Continuous data were compared using the Mann–Whitney test. A P-value equal to or less than 0.05 was considered statistically significant. Logistic regression analysis was employed to measure the correlation for binary dependent variables. Statistical analysis was undertaken using SPSS Base 9.0 (SPSS Inc., Chicago, IL, US).

| Table 1 | Recommended criteria for the diagnosis of ALI and ARDS |
|---|---|---|---|
| **Timing** | **Oxygenation (PaO\textsubscript{2}/FiO\textsubscript{2})\textsuperscript{a}** | **Chest X-ray** | **Pulmonary artery wedge pressure** |
| ALI | Acute | \(\leq 300\) | Bilateral infiltrates | \(<18\text{ mmHg}\textsuperscript{b}$$) |
| ARDS | Acute | \(\leq 200\) | Bilateral infiltrates | \(<18\text{ mmHg}\textsuperscript{b}$$) |

\textsuperscript{a} Regardless of PEEP level.

\textsuperscript{b} Or no clinical evidence of left atrial hypertension.
3. Results

3.1. ALI/ARDS frequencies

Twenty-seven out of 1221 patients (2.2%) submitted to lung resection for primary bronchogenic carcinoma met the criteria of post-operative ALI/ARDS. Clinical manifestations generally included a rapidly evolving respiratory impairment with profound hypoxemia requiring increasing O₂ supply associated with the development of pulmonary infiltrates at chest radiograph. Other causes of post-operative hypoxemia should be ruled out including retained secretions, pulmonary infection and pulmonary embolism.

ALI was diagnosed in 10 patients and ARDS in 17 patients. The prevalence of the two complications was 0.8 and 1.4%, respectively, out of the total population of resected carcinomas.

The mean time of presentation after surgery was 4 days (range 1–10) for patients developing ALI and 6 days (range 1–13) for patients developing ARDS.

We analysed frequencies of ALI/ARDS according to sex and age and we found no differences in male versus female patients or in patients younger or older than 60 years (P = 0.6 and P = 0.7, respectively).

We further analysed frequencies of ALI/ARDS according to the type of operation (Table 2). Frequencies were 4% after extended operations (4/101), 3.8% after pneumonectomies (7/188), 2.4% after bilobectomies (1/41), 2% after lobectomies (16/820) and 3.2% after sublobar resections (3/93). No patient developed ALI/ARDS after exploratory thoracotomy.

Finally, we analysed frequencies of ALI/ARDS according to the side of the operation without identifying any significant difference. ALI/ARDS developed in 14 patients following operation on the right side (2.1%) and in 13 patients following operation on the left side (2.6%) (P = 0.5). In particular, the observed frequencies were 4.5% following right pneumonectomy (4/88), 3% following left pneumonectomy (3/100), 1.9% following right lobectomies (9/475), 2% following left lobectomies (7/345), 0% following right sublobar resections (0/51) and 7.1% following left sublobar resections (3/42).

3.2. Pre-operative and peri-operative predictive factors for ALI/ARDS

The mean operative time, as an index of time of one-lung ventilation, was 200 min (range 65–365); mean intra-operative fluid intake was 2100 ml (range 1550–3200). Both figures were similar to those observed in the total population of resected carcinomas.

In order to identify possible risk factors for the occurrence of ALI/ARDS, we compared the group of patients who developed ALI/ARDS and the total group of patients resected for bronchogenic carcinoma (control group) with respect to surgical pathologic staging, use of pre-operative radiotherapy and mean pre-operative PaO₂, PaCO₂ and %FEV₁ (Table 3). No differences were detected in the ALI/ARDS group and in the control group for all the considered variables.

3.3. ALI/ARDS mortality

Fourteen patients with ALI/ARDS died, that is the 52% of the patients who developed the syndrome. Of these, there were 4 patients with ALI (40%) and 10 patients with ARDS (59%). Our hospital mortality for ALI/ARDS out of the total population of resected bronchogenic carcinoma is 1.2% (14/1221). During the study period, our total hospital mortality was 2.8% (34 patients out of 1221). ALI/ARDS therefore accounts for 41% of our hospital mortality and represents our current main cause of death. Other causes of deaths included pneumonia (three patients), pulmonary embolism (four patients), myocardial infarction (three patients), dysrhythmias (three patients), bronchopleural fistula (two patients) and miscellaneous (five patients).

We analysed mortality rates for ALI/ARDS according to the extent of the resection: four out of seven patients died following right sublobar resections (0/51) and 7.1% following left sublobar resections (3/42).

Table 2

<table>
<thead>
<tr>
<th>Frequency of ALI/ARDS by the extent of operation</th>
<th>ALI/ARDS</th>
<th>Control group</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended operationb</td>
<td>4</td>
<td>101</td>
<td>4</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>7</td>
<td>188</td>
<td>3.8</td>
</tr>
<tr>
<td>Bilobectomy</td>
<td>1</td>
<td>41</td>
<td>2.4</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>16</td>
<td>820</td>
<td>2</td>
</tr>
<tr>
<td>Sublobar resection</td>
<td>3</td>
<td>93</td>
<td>3.2</td>
</tr>
<tr>
<td>Exploratory thoracotomy</td>
<td>0</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>1221</td>
<td></td>
</tr>
</tbody>
</table>

a P = 0.3.
b Extended operations include patients from other groups and are therefore excluded from the total count.

Table 3

<table>
<thead>
<tr>
<th>Comparison of surgical pathological staging, pre-operative radiotherapy and pre-operative lung function between ALI/ARDS group and the total population of resected lung cancer patients (control group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
</tr>
<tr>
<td>Stage II</td>
</tr>
<tr>
<td>Stage IIIa</td>
</tr>
<tr>
<td>Stage IIIb</td>
</tr>
<tr>
<td>Stage IV</td>
</tr>
<tr>
<td>RT pre-op</td>
</tr>
<tr>
<td>PaO₂ (mmHg) (mean)</td>
</tr>
<tr>
<td>PaCO₂ (mmHg) (mean)</td>
</tr>
<tr>
<td>FEV₁% of pred (mean)</td>
</tr>
</tbody>
</table>

a Data refer to a sample of 200 randomly selected patients out of the total population of patients submitted to lung resection for primary bronchogenic carcinoma.
after pneumonectomy (57%) (one out of three following left pneumonectomy and three out of four following right pneumonectomy); seven out of 16 patients died after lobectomy (44%) (three out of seven on the left and four out of nine on the right); all patients died after sublobar resections (3/3); three out of four patients died after extended resections. Mortality rates by the extent of the operation calculated by dividing the number of patients who died following a given operation by the number of patients who received the corresponding operation in the total population are indicated in Table 4.

Finally, using logistic regression analysis considering outcome (dead/alive) as dependent binary variable and the post-operative PaO\(_2\) at FiO\(_2\) = 1.0 as an independent variable, we found no correlation between post-operative PaO\(_2\) and outcome in the patients with ALI/ARDS (\(P = 0.08\)).

4. Discussion

The results of the present study indicate that (1) ALI/ARDS is a severe complication following resection for primary bronchogenic carcinoma; (2) no significant difference was found between the ALI/ARDS group and the control group for several peri-operative variables including age, pre-operative lung function, staging and pre-operative radiotherapy; (3) despite aggressive therapy, ALI/ARDS is associated with a high mortality, the highest mortality rates having been observed following right pneumonectomy and extended operation; and (4) ALI/ARDS may also occur after sublobar resection with an associated high mortality rate.

In 1994, the American–European Consensus Conference [14] agreed to use the term acute lung injury (ALI) to indicate a syndrome of inflammation and increased permeability with pulmonary oedema associated with a constellation of clinical, radiologic and physiologic abnormalities that cannot be explained, although coexisting with, left atrial or pulmonary capillary hypertension. The term acute respiratory distress syndrome (ARDS) should indicate the most severe form of ALI. The recommended criteria for ALI and ARDS were: (1) acute onset; (2) bilateral infiltrates at chest X-rays; (3) pulmonary arterial wedge pressure ≤18 mmHg or no clinical evidence of left atrial hypertension; and (4) PaO\(_2\)/FiO\(_2\) ≤ 300 mmHg for ALI and ≤200 mmHg for ARDS. The risk factors for the development of ALI/ARDS were identified as: (1) direct lung injury, including gastric aspiration, diffuse pulmonary infections and near drowning; and (2) indirect lung injury, including sepsis syndrome, thoracic trauma and multiple transfusions. It might be hypothesised that ARDS may also be induced in patients with ALI by clinical situations, which further deteriorate gas exchange, notably pulmonary infections.

The occurrence of lung injury following lung resection, in particular after pneumonectomy had long been recognised and in 1984, the term post-pneumonectomy pulmonary oedema (PPE) was coined [12] to indicate the acute onset of hypoxemia and respiratory insufficiency with radiologic appearance of non-cardiogenic pulmonary oedema. It was soon realised that PPE was identical to ALI/ARDS and its occurrence was gradually reported as a major complication of pulmonary resection.

Unfortunately, the exact prevalence of ALI/ARDS following lung resection is unknown, since in most reports the specific inclusion criteria were not clearly indicated. Most authors report a prevalence of the syndrome ranging from 2.6 to 7% after pneumonectomy [13,15] and from less than 1% to as high as 3% following lobectomy [15,16]. Our prevalence of 3.8 and 2% following pneumonectomy and lobectomy, respectively, are in the range reported in the literature.

Contrary to other studies indicating minimal if any prevalence following sublobar resections [17,18], we have a 3.2% prevalence (three patients). All patients had ALI and all died: two patients were older than 70 years, all had limited pulmonary reserve and one had pre-operative rhythm disorder, which represented our indications to perform a sublobar resection. All patients had a relatively short operative time (about 2 h) and received limited intra-operative fluid intake (less than 1500 ml). We have no explanation for the development of the syndrome in these patients, apart from advanced age, limited pulmonary reserve and cardiac arrhythmia.

A number of factors have been investigated to explain and predict the occurrence of ALI/ARDS following lung resection. Among others, there were sex, age, impaired lymphatic drainage, peri-operative fluid overload (>2000 ml intra-operatively or >3000 ml post-operatively), surgical manipulation of the lung, prolonged one-lung ventilation, pre-operative lung function, pre-operative rhythm disorder, which represented our indications to perform a sublobar resection. All patients had a relatively short operative time (about 2 h) and received limited intra-operative fluid intake (less than 1500 ml). We have no explanation for the development of the syndrome in these patients, apart from advanced age, limited pulmonary reserve and cardiac arrhythmia.

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Goldstraw and co-workers [16] found a higher prevalence of ALI/ARDS in male patients and in patients older than 60 years. In our patient population, neither of these variables was associated with a prevalence difference. The different composition of the patient population in the two studies, which include only lung cancer patients in ours versus all patients submitted to lung resection in Goldstraw’s, may account for the different results.

Table 4
Mortality of ALI/ARDS by the extent of operation\(^b\)

<table>
<thead>
<tr>
<th></th>
<th>ALI/ARDS</th>
<th>Control group</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended operation(^b)</td>
<td>3</td>
<td>101</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>4</td>
<td>188</td>
<td>2.1</td>
</tr>
<tr>
<td>Bilobectomy</td>
<td>0</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>7</td>
<td>820</td>
<td>0.8</td>
</tr>
<tr>
<td>Sublobar resection</td>
<td>3</td>
<td>93</td>
<td>3.2</td>
</tr>
<tr>
<td>Exploratory thoracotomy</td>
<td>0</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>1221</td>
<td></td>
</tr>
</tbody>
</table>

\(^b\) Extended operations include patients from other groups and are therefore excluded from the total count.
It has been suggested [17] that impaired lymphatic drainage may play a role in the development of ALI/ARDS and this hypothesis has been proposed to explain the reported increased frequency of the syndrome in patients submitted to lung resection for lung cancer, in whom systematic lymph node dissection is routinely carried out. Our study on a population of patients with resected lung cancer is in contrast to this observation and we did not have an increased frequency as compared to a recent series [16] on a total population of patients undergoing lung resection for various causes. Impaired lymphatic drainage has also been proposed to explain the reported discrepancy in ALI/ARDS frequency between the sides on which lung resection is performed. Experimental and clinical evidences exist that for the left lung, the lymphatic drainage is to a considerable extent via the contralateral lymphatic channels. This asymmetry may imply a higher prevalence of ALI/ARDS following right as compared to left lung resections. This finding has been reported by some authors [12,13] although not by others [15,18,20]. In the present study, we found no significant difference between right and left resections following either pneumonectomy or lobectomy; the occurrence of all ALI/ARDS after sublobar resections on the left may reflect a casual finding due to the small number of cases.

Among other pre-operative or peri-operative variables examined in the present study, including pre-operative radiotherapy, pre-operative lung function, peri-operative fluid intake and time of one-lung anesthesia, none was found to be significantly associated with the occurrence of ALI/ARDS, although a trend was observed for pre-operative radiotherapy. This issue has been addressed and discussed in the literature [21]: Parquin et al. [20] found that pre-operative radiotherapy and intra-operative fluid overload are independent risk factors for the development of post-pneumonectomy pulmonary edema; Fowler et al. [6] had a 23% mortality rate after lung resection performed in patients submitted to combined neoadjuvant treatment, of which two-thirds were attributable to ALI/ARDS. The lack of significant association between ALI/ARDS and the other variables is confirmed by most studies [16,18,20] and it may, therefore, be hypothesised that the syndrome can be regarded as a complex, multi-factorial condition in which no single precipitating factor can be identified.

Recent clinical and experimental studies have indicated that altered endothelial permeability has a central role in the pathogenesis of ALI/ARDS following lung resection [17,21]. Although the exact mechanism remains unclear, a growing body of evidence suggests that ischemia–reperfusion injury resulting from collapse and re-expansion of the operative lung during one-lung anaesthesia combined with the oxygen toxicity due to the high inspired oxygen concentrations required to counterbalance the effects of shunt in the deflated lung further associated with lung manipulation during surgery, all induce the build-up of reactive oxygen species (ROS) and reactive nitrogen species (RNS) as well as reduction of endogenous antioxidant systems; this, in turn, produces alteration of redox balance and endothelial damage. In a recent report, Williams et al. [22], measuring plasma indices of oxidative damage such as protein thiols and protein carbonyls, demonstrated that oxidative damage occurs after lung resection and lasts for 24 h post-operatively. The damage is most severe in pneumonectomy and lobectomy and was not observed after minor resections. The conclusion of the authors is that all patients submitted to major lung resection suffer from an oxidative damage post-operatively, which results in acute lung injury. If confirmed by further studies, this observation may be of help to elucidate, at least in part, the complex pathogenesis of the syndrome.

Mortality of ALI/ARDS following lung resection remains high despite aggressive intensive therapy. Turnage and Lunn [13] reported no survivors in their series of 21 patients with PPE. Most studies indicate a mortality of ARDS ranging from 53 to 74% [23,24], depending upon inclusion criteria for the definition of the syndrome. In a recent report, Goldstraw and co-workers [16] had a mortality of 64%. In the present study, mortality was 52%, broadly comparable with other series. As expected, mortality of ALI is lower than mortality of ARDS (40 versus 59% in our series). Interestingly, however, in our study, mortality was not correlated with the post-operative PaO₂.

The major causes of post-operative mortality following lung resection are cardiac, pulmonary embolic and respiratory. Our total post-operative mortality in the past 7 years was 2.8% (34 cases) and the causes were mostly classified in the aforementioned three groups. Of the 34 post-operative deaths, 14 (41%) were attributable to ALI/ARDS, which therefore represents our leading cause of death following lung resection for bronchogenic carcinoma. The same conclusion was reached by Goldstraw and co-workers [16] in their total patient population submitted to lung resection, in which the condition represented 72% of post-operative mortality.

In our study, as confirmed by other authors [16], mortality was highest following right pneumonectomy and extended resection, in which an anticipated 75–80% mortality rate can be expected. The development of ALI/ARDS following lobectomy and left pneumonectomy seems to be associated with a somewhat better prognosis (30–40% mortality rate in our series). Unexpectedly, all our patients in whom ALI developed following sublobar resections died and this finding represents a somewhat new observation, which demands confirmation by further studies. A possible explanation for this finding is that very often patients receiving sublobar resection for bronchogenic carcinoma have associated risk factors, which contraindicate major lung resection, including age older than 70, reduced pulmonary reserve and associated cardiac diseases: all three patients in our series who developed ALI following sublobar resection had either age older than 70 years (two patients), or limited pulmonary reserve (three patients) or cardiac rhythm disorders (one patient). After the development of the ALI/ARDS in these
patients, these comorbidity factors may therefore contribute to increase the mortality rate.

In conclusion, ALI/ARDS represents a well-defined clinical entity, which complicates lung surgery for bronchogenic carcinoma. With the reduction of mortality from other causes along with the progressive diagnostic refinement and awareness of the syndrome, it represents the current leading cause of post-operative mortality following pulmonary resection for bronchogenic carcinoma. Any clinical and experimental effort should, therefore, be made to clarify the pathogenesis and improve therapy of this condition, in order to lower its unacceptably high mortality rate.

References


Appendix A. Conference discussion

Dr D. van Raemdonck (Leaven, Belgium): I would like to ask you what type of endotracheal intubation you are using, single-lumen tube versus double-lumen tube, and whether or not from your study there is any evidence that continuous ventilation during pulmonary resection may decrease the incidence of acute lung injury and ARDS.

Dr Parola: We always use a double-lumen tube for resection for lung cancer. The period of time of on-line anaesthesia was not a significant factor associated with occurrence of the syndrome, at least in our study.

Dr M. Perelman (Moscow, Russia): I have a question about post-mortem examination of these patients.

Dr Parola: Unfortunately I have no data for the autopsy specimens and I have to trust my intensivists for the diagnostic criteria of this. So I have no data for autopsy specimens.

Dr P. Thomas (Marseille, France): I was very interested by your paper, and we have, in Marseille, strictly similar rates. My question will deal with the treatment of ARDS. I noted that you have a 50% mortality, which is a very common rate over time, whatever the etiology of this syndrome. Do you think that in this particular subset of patients the new therapies to palliate hypoxemia are associated with a better prognosis? I mean nitric oxide ventilation, partial liquid ventilation, prone position ventilation, and so on.

Dr Parola: We have some experience only recently with some new intra-operative techniques: nitric oxide, for example. We have no experience with ECMO. I know that our Italian centre, for example,Gattanoni in Milan has some experience, but as far as I know, there is no major improvement in the therapy of acute respiratory distress syndrome. I recently read a paper about it, which was very pessimistic. We have only supportive measures for this, and this is reflected by our very, very high mortality rates. And in a recent paper, Goldstraw from the Brompton Hospital, which conducted a very important study on this, still has a 70% mortality for this syndrome, even with the new modern techniques.

Dr Thomas: Do you have any experience with high-dose steroids?

Dr Parola: Our intensivist doesn’t like the use of steroids, so we have no experience with this.
Dr F. Venuta (Rome, Italy): Could you give us more information about your management of the post-pneumonectomy space? There is evidence in the literature that a balanced drainage may reduce the incidence of complications and their outcome.

Dr Parola: Usually our post-operative protocol for fluid balance is about 1500 mm of crystalloid, and we use a drain just for the first 24 h after pneumonectomy and then we remove the drainage. So we, of course, tend to maintain these patients as dry as possible in the post-operative period, usually with a net fluid balance almost zero negative. So this is our policy.

Dr K. Jeyasingham (Winterbourne Down, UK): It’s surprising to note that your sublobar resections have also produced a high incidence of lung injury. Could you tell us if there was any underlying pathology in the lungs apart from the lesion that you were removing that predisposed to development of the injury? Secondly, as a routine for lobectomies and pneumonectomies, do you perform a radical lymph node dissection or a sampling?

Dr Parola: With regard to the first question, the 3 patients who developed the syndrome and who had sublobar resection, 2 out of 3 were older than 70. All 3 had reduced pulmonary reserve and one had an associated arrhythmia. These were the only comorbidity factors that we could identify in these patients, and I suspect that these comorbidity factors may have played a role either in the development of the syndrome and in causing the very high mortality rate. Otherwise, we have no explanation for the occurrence of acute lung injury following sublobar resection. And, interestingly, all 3 patients had acute lung injury, not acute respiratory distress syndrome. This was the first. And the second, in all lung cancer patients we do a sampling of the mediastinal nodes.