ROLE OF OPEN LUNG BIOPSY IN PATIENTS WITH DIFFUSE LUNG INFILTRATES AND ACUTE RESPIRATORY FAILURE

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Background and Purpose: Open lung biopsy (OLB) is the standard procedure for the diagnosis of specific parenchymal lung diseases. The purpose of this study was to investigate the influence of OLB on subsequent treatment strategy and outcome in patients with diffuse lung infiltrates and acute respiratory failure.

Methods: This retrospective review included 32 patients (aged 50.6 ± 21.7 years) with acute respiratory failure and diffuse pulmonary infiltrates who underwent OLB from 1990-2002. Data analyzed included diagnoses, treatment alterations, 30-day survival, oxygenation status, and histologic results.

Results: Specific diagnoses were made in 53.1% of patients (17/32), 23 (71.9%) of whom had acute respiratory distress syndrome (ARDS). Diagnostic yields did not differ with immunity status or ARDS. OLB led to specific decisions of treatment in 46.9% of patients (15/32), and only 7 of these 32 patients (21.8%) survived. Overall mortality was 56.2% (18/32) and was not influenced by pre-OLB oxygenation or histologic results. Although perioperative complications affected 40.6% of patients (13/32), none of the deaths were surgery-related. Complication rates were significantly higher in patients with ARDS (p = 0.04).

Conclusions: OLB is associated with a low perioperative mortality rate and acceptable morbidity rate in patients with diffuse lung infiltrates and acute respiratory failure, including those patients with ARDS. In this study, a specific diagnosis was obtained by OLB in more than half of patients with diffuse pulmonary infiltrates and ARDS. In addition, OLB resulted in either use of a new therapeutic strategy or elimination of unnecessary treatment in nearly one-half of patients (46.9%).

Key words: APACHE; Biopsy; Lung diseases, interstitial; Respiratory insufficiency

This study evaluated OLB in terms of its diagnostic yield, morbidity and mortality rates, influence on treatment and outcome in patients with acute respiratory failure associated with diffuse pulmonary infiltrates.

Methods

We retrospectively reviewed the medical records of 32 patients with diffuse pulmonary infiltrates on chest roentgenogram and an acute onset of respiratory failure who underwent OLB at our hospital between 1990 and 2002. Respiratory failure was defined as \( \text{PaO}_2 \) of less than 50 mm Hg while breathing room air, or a ratio of partial pressure of arterial oxygen-to-fraction of inspired oxygen (\( \text{PaO}_2/\text{FiO}_2 \)) less than 200 while breathing supplemental oxygen. OLB was performed at the request of attending physicians due to...
progressive deterioration of clinical condition despite therapy or undetermined etiology.

Patients were defined as ventilator-dependent if they had received ventilator assistance for more than 30 consecutive days. Patients who had deteriorating chronic disease were excluded. Patients who fulfilled the criteria for ARDS, including: 1) bilateral pulmonary infiltrates, 2) no clinical evidence of left atrial hypertension, and 3) a PaO$_2$:FiO$_2$ ratio $\leq$ 200 mm Hg based on the American-European Consensus Conference definition were further grouped.1

Data collected for each patient included demographic characteristics, laboratory results, clinical data before and after OLB, histologic diagnosis, postoperative therapeutic changes (addition or subtraction of drugs), survival at 30 days after OLB, postoperative complications, and cause of death. Severity of illness was evaluated based on Acute Physiology and Chronic Health Evaluation (APACHE) II scores at admission. Statistical analysis was performed using Mann-Whitney U test and Fisher’s exact test. A $p$ value of $< 0.05$ was considered to indicate a statistically significant difference.

**Results**

**Patient characteristics**

Of a total of 756 patients with acute respiratory failure associated with diffuse pulmonary infiltrates between 1990 and 2002, 32 (4%) were identified who fulfilled the study criteria. These 32 patients included 24 men and 8 women with a mean age of 50.6 $\pm$ 21.7 years (range, 18-80 years). The criteria for ARDS were met before OLB in 23/32 (71.9%) of these patients. Infectious diseases were the dominant pre-OLB diagnosis, followed by malignancies (n = 3), radiation pneumonitis (n = 2), and interstitial lung disease (n = 2). Fourteen patients had a history of malignant disease or had recently received or were undergoing chemotherapy; these patients were considered to be immunocompromised.

Twenty-five patients required mechanical ventilation preoperatively, and the other 7 were intubated and receiving ventilator support on the day of surgery. The mean duration between the onset of diffuse pulmonary infiltrates and OLB was 11.3 days (range, 1-38 days). The duration of ventilator support before OLB was 6.7 days (range, 0-31 days). The mean PaO$_2$:FiO$_2$ value before OLB was 163.0 $\pm$ 90.4 (range, 40.8-379.6). The clinical characteristics of survivors and non-survivors are compared in Table 1.

The mean APACHE II score of patients on the day of admission to the ICU was 19.2 $\pm$ 5.5 (range, 9-28). APACHE II scores at admission failed to predict subsequent mortality and complication rates.

Bacteriologic cultures were positive in 17 patients prior to OLB. All patients had received empirical antibiotics, steroid treatment was given in 13 of 32 patients (40.6%), and 1 patient received chemotherapy concurrently before undergoing OLB.

**Procedures and diagnostic results**

The OLB procedures were performed in the operating room under general anesthesia. Video-assisted thoracotomy surgery was done in 5 patients, and the remaining patients underwent limited anterior thoracotomy. Specimens were sent for bacteriologic, virologic, and histologic analysis. Table 2 compares the survival and immune status of patients with specific and nonspecific histological diagnoses from OLB. A nonspecific diagnosis (n = 15) was defined as a histologic result indicating interstitial pneumonitis, fibrosis, diffuse alveolar injury, or alveolar edema. Seventeen of 32 (53.1%) patients had a specific OLB diagnosis, including 6 malignancies (6/32, 18.8%), 6 infections including 4 viral pneumonitis (6/32, 18.8%), 2 cases of bronchiolitis obliterans organizing pneumonia, 1 case of Wegener’s granulomatosis, 1 case of alveolar proteinosis, and 1 case of Goodpasture’s syndrome. No pathogens (bacterial, fungus, or viral) were cultured in any biopsy sample. There were no significant differences in the histological diagnostic yield between survivors and non-survivors ($p = 0.48$) or between immunocompromised and immunocompetent patients ($p = 0.54$).

**Table 1.** Comparison of clinical characteristics of survivors and non-survivors with diffuse lung infiltrates and acute respiratory failure.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Survivors (n = 14)</th>
<th>Non-survivors (n = 18)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47.2 $\pm$ 24.7</td>
<td>53.2 $\pm$ 19.4</td>
<td>0.45</td>
</tr>
<tr>
<td>Immunosuppression (%)</td>
<td>5/14 (35.7)</td>
<td>7/18 (38.9)</td>
<td>0.57</td>
</tr>
<tr>
<td>PaO$_2$:FiO$_2$</td>
<td>Before OLB</td>
<td>188.1 $\pm$ 107.4</td>
<td>0.20</td>
</tr>
<tr>
<td>After OLB</td>
<td>206.5 $\pm$ 139.7</td>
<td>134.6 $\pm$ 97.8</td>
<td>0.10</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>Before OLB</td>
<td>18.2 $\pm$ 5.7</td>
<td>0.37</td>
</tr>
<tr>
<td>Ventilator use before OLB (days)</td>
<td>4.8</td>
<td>8.1</td>
<td>0.32</td>
</tr>
</tbody>
</table>

SD = standard deviation; PaO$_2$:FiO$_2$ = partial pressure of arterial oxygen-to-fraction of inspired oxygen; OLB = open lung biopsy; APACHE = Acute Physiology and Chronic Health Evaluation.
Alteration of treatment

OLB findings led to a change of therapy in 15 of 32 patients (46.9%) [Table 3], with alterations in 50% (7/14) and 44.4% (8/18) of survivors and non-survivors, respectively ($p = 0.52$). After OLB, 6 patients were treated with additional corticosteroids or an increased dose of corticosteroids. Chemotherapy was added in 5 patients, and 3 patients were treated with antiviral agents because the histologic results after OLB suggested viral infection. One patient underwent whole-lung lavage for alveolar proteinosis. Treatment was not changed in 17 of 32 patients (53.1%). Two of these patients had malignancy but did not receive chemotherapy. Survival rates were not correlated with an OLB histological diagnosis or a change in therapy.

Complications

The complication rate of OLB was 40.6% (13/32). Persistent air-leak ($n = 9$), bronchopleural fistula ($n = 2$), empyema ($n = 1$) and wound infection ($n = 1$) were the reasons for prolonged chest-tube retention. No complication directly resulted in death.

Patients with ARDS

Table 4 compares the APACHE II scores, OLB histologic diagnoses, complications of OLB, and changes of therapy resulting from OLB between the ARDS and non-ARDS groups. No significant differences were observed between patients with and without ARDS in terms of severity of illness, pre-OLB and post-OLB oxygenation ratios, and histologic findings. OLB histologic results and subsequent treatments were not correlated with survival. However, the OLB complication rate was significantly higher in patients with ARDS (12 of 23) than in patients without ARDS (1 of 9; $p = 0.04$).

Discussion

OLB is an invasive diagnostic procedure with diagnostic yield of 80-94%. Complete history and physical examination, radiologic studies, sputum cytologic analysis, and cultures provide a reliable diagnosis in only approximately 30% of patients. Rates of specific diagnoses resulting from OLB vary among studies of patients with different disease entities. The rate of specific diagnosis was 55-95%
in the review by Cheson et al.\textsuperscript{8} The specific and nonspecific diagnostic rates in our study were 53.1% (17/32) and 46.9% (15/32), respectively. This is comparable to the rates of 68% and 32% reported by Lachapelle and Morin\textsuperscript{10} and 46% and 46 reported by Flavouris and Myburgh.\textsuperscript{11} Our 50% (6/12) rate of specific diagnosis is also compatible with those from series of OLB in immunocompromised patients, which ranged from 55% to 83%.\textsuperscript{6,8,12,13} However, the likelihood of achieving a specific histologic diagnosis in immunosuppressed patients could not be determined from our data because the rate of specific diagnoses in both immunocompromised and immunocompetent patients is 50% (6/12) and 55% (11/18) respectively ($p = 0.04$). In 15/32 patients (46.9%), histologic results from OLB led to an alteration in therapy. In this study, OLB-guided therapy benefited only 7 patients (7/32, 21.9%), as determined by their survival at 30 days after OLB-guided alteration of treatment. Survival did not differ between patients whose therapy was changed and those whose therapy was unchanged after OLB ($p > 0.5$). Neither immunocompetent patients nor immunocompromised patients gained additional survival benefits from OLB. Alterations in therapy occurred as a result of OLB in 46.9% of patients in this study. This is similar to the range of 59-75% in previous reports.\textsuperscript{11,13,14}

This study found OLB complication rates of 40.6% in patients with diffuse pulmonary infiltrates. This is the upper end of the range of 17-40% reported in previous studies.\textsuperscript{11,14,15} OLB-related mortality occurred, and OLB complication were not correlated with the high mortality rate of patients with acute respiratory failure who require mechanical ventilation (Table 3). Flavouris and Myburgh\textsuperscript{11} also found a low operative mortality rate for OLB.

In this study, the overall mortality rate in patients with diffuse lung infiltrates and ARDS who received OLB was 56.2% (18/32), and multiple organ failure or respiratory failure was the main cause of death in most cases. Therefore, the assessment of parameters to predict outcomes such as APACHE II score may be helpful to predict morbidity and mortality risks associated with OLB. Poe et al\textsuperscript{14} found that early mechanical ventilation ($PaO_2 < 50$ mm Hg on room air) and corticosteroid therapy at the onset of symptoms are significant predictors of mortality in patients with pulmonary infiltrates and ARDS receiving OLB. While Warner et al\textsuperscript{8} found that age was a predictor of mortality in these patients, Flavouris and Myburgh\textsuperscript{11} found that no patient with $\geq 2$ organ failures survived. Rossiter et al\textsuperscript{12} and Lachapelle and Morin\textsuperscript{10} found that an early OLB tended toward a survival advantage; however, we did not find a significant difference between surviving and nonsurviving patients in terms of the timing of OLB, gender, age, number of ventilator days before OLB, and pre-biopsy oxygenation status. OLB histologic findings and subsequent alterations in therapy were not significantly associated with survival rate in our study. This is in contrast to findings by Rossiter et al\textsuperscript{12} and Lachapelle and Morin\textsuperscript{10}, who found that an early OLB tended toward a survival advantage.

In this study, patients with ARDS had similar rates of specific OLB histologic results to those without ARDS ($12/23$ (52.2%) vs $5/9$ (55.6%)$). Meduri et al histologically diagnosed cytomegaloviral pneumonia in 18 patients with ARDS.\textsuperscript{16} Viral pneumonitis is likely to be underdiagnosed because its identification depends on the availability of laboratory facilities and on the experience of the pathologists. The complication rate in this study was significantly higher in patients with ARDS ($12/23$) than without ARDS ($1/9$) [52.2% vs 11.1%; $p = 0.04$], possibly because of poorer lung condition. Corticosteroids are commonly instituted before or after OLB in patients with acute respiratory failure, especially ARDS.\textsuperscript{16,17} For some diseases, such as autoimmune diseases, OLB results and steroid therapy may be the keys to survival if they are given immediately. The beneficial effect of corticosteroids on the ARDS survival rate could not be evaluated in our patients because of the heterogeneity of patient characteristics and the different dosages used.

In conclusion, OLB has a low complication rate and a high diagnostic yield rate in patients with respiratory failure and diffuse lung infiltrations. Despite a lack of strong and consistent statistical data to show a positive impact on survival, OLB may aid in the assessment of new therapies or withdrawal of unnecessary treatment. However, any decision to perform OLB in patients with ongoing, deteriorating illness must be highly individualized because of the low survival rate in these patients.

\section*{References}


