Open Lung Biopsy Does Not Correlate with Pulmonary Function after the Adult Respiratory Distress Syndrome

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Abnormalities of pulmonary function occur following the adult respiratory distress syndrome (ARDS). To determine if open lung biopsy (OLB) during ARDS predicts late pulmonary function abnormalities, we examined nine survivors of ARDS who had OLB during ARDS. Open lung biopsy was performed within two weeks of the diagnosis of ARDS, and the following were scored by a pulmonary pathologist as to extent and severity: hyaline membranes (HM), interstitial fibrosis (IF), air space organization (AO), interstitial cellularity (IC), and type 2 cell proliferation (T2C). Pulmonary function tests performed at least one year after ARDS were also used for analysis. Percent predicted Dco, TLC, DL/VA, and FVC were regressed against extent, severity, and combined scores. No significant correlation was found despite impressive histologic abnormalities. These data suggest that the severity and extent of HM, IF, AO, T2C, or IC do not correlate with lung function following ARDS.

METHODS

Seventy-eight survivors of ARDS were identified by review of intensive care unit logbooks as well as by prospective screening at the LDS Hospital, Salt Lake City, UT, from February 1976 through October 1987. Medical records were reviewed to ascertain survivors of ARDS who had undergone open lung biopsy to assess their acute lung injury. ARDS was defined by the following: (1) PaO2/FIO2 < 200; (2) pulmonary capillary wedge pressure ≤ 15 mm Hg before diuretic therapy or no evidence of congestive heart failure; (3) bilateral diffuse infiltrates on chest roentgenogram (CXR); (4) static thoracic compliance ≤ 50 ml/cm H2O; and (5) an appropriate clinical setting for ARDS. Ten of the 78 survivors had undergone open lung biopsy during the ARDS episode. One of these ten patients was unwilling to return for follow-up pulmonary function studies. No patient had had pulmonary function studies prior to their ARDS illness.

All ten patients were intubated and mechanically ventilated with positive end-expiratory pressure (PEEP) at the time of biopsy. The specimens were routinely fixed and processed for light microscopy. Special stains (Gomori methenamine silver, acid fast, Brown and Brenn, and Legionella) were performed on seven biopsy specimens. Sample size varied from 1.2 × 0.5 × 0.2 cm to 9.3 × 1.5 × 0.3 cm. Biopsy specimens were obtained from areas believed to be most...

AO = air space organization; COM = combined score; CH = total thoracic compliance; E = extent; HM = hyaline membrane; IC = interstitial cellularity; IF = interstitial fibroblast proliferation; PAP = pulmonary artery pressure; Qt/Qt = right-to-left intrapulmonary shunt; S = severity; T2C = type 2 cellularity; TLC = total lung capacity.
involved on CXR. Two patients had samples taken from two lobes, and the two lobes were found to be histologically similar in both patients.

Quantitative and semi-quantitative histologic evaluation of lung tissue has been reported in a number of studies with as many as 140 different histologic entries being evaluated. A scoring system assessing both severity and extent was used in this study and the parameters scored were those that were abnormal and therefore thought to be of significance. Histologic examination and tissue scoring were performed by a pulmonary pathologist who was unaware of the results of the pulmonary function tests. Scoring was based on representative pathologic features of all specimens available for evaluation. For the purpose of this study, five pathologic patterns were identified and scored (Fig 1): (1) hyaline membranes (HMs); (2) interstitial fibroblast proliferation (IF); (3) air space organization (AO); (4) interstitial cellularity (IC); and (5) type 2 cellularity (T2C). Each pattern was scored for severity and extent. Severity (S) was scored on a scale of 0 to 4 and was defined as the severity of the category scored; 0 being normal, 1 being slight, and 4 being most severe. Extent (E) was scored on a scale of 0 to 4, 0 being normal and 1 to 4 representing increasing percentage of involvement in quartiles (1 = 1 to 25 percent; 2 = 26 to 50 percent; 3 = 51 to 75 percent; 4 = 76 to 100 percent) A combined score (COM) was then obtained by multiplying extent and severity to give an estimate of overall damage for each pattern. Based on one author's (T.C.) pathologic review of specimens in the Denver Intersitial Lung Disease Project, assessment of both the extent and severity of pathologic changes was deemed necessary. The scoring system used in the Denver project has been reported in the literature but has not yet been published in its entirety.

Pulmonary function studies were performed on the nine patients whose cases were reported herein according to Intermountain Thoracic Society standards as previously described. The following studies were performed: spirometry, single breath helium dilution total lung capacity (TLC), single breath diffusing capacity for carbon monoxide (Dco) with corrections for hemoglobin concentration and carbon monoxide back pressure. Predicted normal values were calculated with regression equations derived from studies of healthy nonsmoking adults using identical techniques performed in the same laboratory. Measurements of pulmonary function were expressed as percent predicted values. All pulmonary function studies were performed at least one year after the onset of ARDS to allow for maximal recovery of lung function. Survivors studied after July 1, 1983, completed a modified form of the respiratory disease questionnaire developed by the American Thoracic Society (ATS) for epidemiologic research to rule out new lung disease during the year following the ARDS event. The percent predicted FVC, TLC, Dco, and DLVA were regressed against severity, extent, and combined scores. Measurements of pulmonary function were classified as abnormal if they were more than one 95 percent confidence interval below the predicted value.

RESULTS

Patient Characteristics

Age at onset of ARDS ranged from 7 to 67 years (Table 1). The illnesses associated with ARDS included proven or probable viral pneumonia (n = 4), intra-abdominal infection associated with sepsis (n = 2), mycoplasma pneumonia (n = 1), and Goodpasture's syndrome (n = 2). Six of the nine patients were non-smokers. The remaining three patients had a history of smoking that ranged from 10 to 25 pack years. At the time of biopsy, all patients were intubated and mechanically ventilated with positive pressure and PEEP ranging from 5 to 25 cm H2O. Biopsies were performed within 2 weeks of the onset of ARDS (range, 1 to 14 days).

Physiologic data obtained for these patients included measurements of initial right to left intrapulmonary shunt (Qs/Qt), initial and maximum mean pulmonary

![Figure 1. The five pathologic patterns that were identified and scored are illustrated: (1) hyaline membranes (HM); (2) interstitial fibroblast proliferation (IF); (3) air space organization (AO); (4) interstitial cellularity (IC); and (5) type 2 cellularity (TC).](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21628/ on 06/26/2017)
artery pressure (PAP), lowest total thoracic compliance (Cth), maximum PEEP level, total ventilatory support time, and total hours spent at an FIO₂ of greater than 0.6. Three of the patients did not have recorded measurements of pulmonary hemodynamics and, therefore, have no Qs/Qt or PAP measurements. The mean ± SEM of these parameters included the following: an initial Qs/Qt of 33 ± 7 percent; an initial PAP of 25 ± 3 mm Hg and maximum PAP of 42 ± 5 mm Hg; a lowest Cth of 19 ± 3 mL/cm H₂O; a maximum PEEP of 20 ± 4 cm H₂O; total ventilatory support time of 31 ± 11 days; and time spent at a FIO₂ > 0.6 of 79 ± 54 hours.

Two of the patients (1 and 8) had computerized axial tomographic examinations of the chest (CT) during the course of their hospitalization. Both CT examinations were performed more than two weeks after open lung biopsy, and concurrent CXRs at the time had nonhomogenous distribution of infiltrates. The CT scan of patient 1 revealed a right pneumothorax, bilateral parenchymal infiltrates with consolidation of the left upper lobe, loculated fluid in the right side of the chest, and left basilar pneumatoceles. The CT scan on patient 8 revealed extensive bullae, right pneumothorax, parenchymal infiltrates more prominent in the right middle lobe and left lower lobe, atelectasis of the right lower lobe, and blood in the right lung base.

Clinical Status

Four of nine patients reported symptoms on their respiratory disease questionnaire. Two patients reported wheezing, and one reported cough with sputum production. Two of the three patients who complained of wheezing were noted to wheeze on physical examination. Two of the patients who were asymptomatic were noted to have fine inspiratory crackles on physical examination. Results of the remaining cardiopulmonary examinations were normal. All four patients who reported symptoms had impairment on pulmonary function studies.

One patient refused to return for follow-up. He was contacted more than one year after his ARDS event and denies symptoms of exertional dyspnea, cough,

### Table 1—Clinical Characteristics of Nine ARDS Survivors

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age,* yr</th>
<th>Predisposing Illness</th>
<th>PEEP cm H₂O</th>
<th>Site Lobe</th>
<th>Days to Biopsy</th>
<th>Tobacco History, Pack Years</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>53</td>
<td>Adenovirus pneumonia</td>
<td>15</td>
<td>RUL, RLL</td>
<td>14</td>
<td>0</td>
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<td>2</td>
<td>F</td>
<td>36</td>
<td>Influenza pneumonia</td>
<td>10</td>
<td>RUL</td>
<td>14</td>
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<td>Peritonitis-sepsis</td>
<td>10</td>
<td>RLL</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>30</td>
<td>Mycoplasma pneumonia</td>
<td>25</td>
<td>LUL</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>21</td>
<td>Goodpasture's syndrome</td>
<td>10</td>
<td>RLL</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>7</td>
<td>Viral pneumonia</td>
<td>5</td>
<td>LLL</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>23</td>
<td>Endometritus-sepsis</td>
<td>5</td>
<td>RML</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>24</td>
<td>Goodpasture's syndrome</td>
<td>25</td>
<td>RUL</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>67</td>
<td>Viral pneumonia</td>
<td>5</td>
<td>LLL, LUL</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

x ± SEM: 30 ± 6

12 ± 3
8 ± 2

*Age at ARDS onset.

### Table 2—Pulmonary Function Studies

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Height, cm</th>
<th>Age,* yr</th>
<th>FVC, L</th>
<th>TLC, L</th>
<th>Dco, ml CO/min/mm Hg</th>
<th>DLVA, ml CO/min/mm Hg/L</th>
<th>FEV₁, L</th>
<th>FEV₁/FVC, %</th>
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<tr>
<td>1</td>
<td>153</td>
<td>56</td>
<td>1.14 (43)†</td>
<td>1.91 (43)†</td>
<td>16.1 (69)†</td>
<td>8.43 (157)</td>
<td>0.72 (33)†</td>
<td>63.8†</td>
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<tr>
<td>2</td>
<td>167</td>
<td>38</td>
<td>4.01 (89)</td>
<td>5.25 (88)</td>
<td>28.4 (83)</td>
<td>8.07 (91)</td>
<td>3.28 (93)</td>
<td>81.0</td>
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<tr>
<td>3</td>
<td>161</td>
<td>18</td>
<td>2.22 (76)†</td>
<td>2.94 (76)†</td>
<td>35.9 (114)</td>
<td>9.49 (147)</td>
<td>2.72 (75)†</td>
<td>80.2</td>
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<tr>
<td>4</td>
<td>171</td>
<td>35</td>
<td>5.27 (106)</td>
<td>6.82 (107)</td>
<td>28.1 (77)†</td>
<td>4.13 (71)†</td>
<td>3.64 (90)</td>
<td>69.1†</td>
</tr>
<tr>
<td>5</td>
<td>166</td>
<td>22</td>
<td>6.70 (7)</td>
<td>5.28 (89)</td>
<td>31.7 (85)</td>
<td>6.01 (97)</td>
<td>3.85 (93)</td>
<td>82.0</td>
</tr>
<tr>
<td>6</td>
<td>140</td>
<td>8</td>
<td>2.26 (95) BP:6.6</td>
<td>2.64 (87)</td>
<td>14.8 (85)</td>
<td>5.61 (91)</td>
<td>2.24 (106)</td>
<td>98.9</td>
</tr>
<tr>
<td>7</td>
<td>159</td>
<td>29</td>
<td>3.21 (91)</td>
<td>4.38 (92)</td>
<td>20.8 (71)†</td>
<td>4.76 (78)†</td>
<td>2.66 (85)</td>
<td>82.9</td>
</tr>
<tr>
<td>8</td>
<td>173</td>
<td>25</td>
<td>6.00 (116)</td>
<td>7.20 (111)</td>
<td>34.1 (87)</td>
<td>4.73 (78)</td>
<td>4.44 (102)</td>
<td>73.6†</td>
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<tr>
<td>9</td>
<td>153</td>
<td>68</td>
<td>2.40 (98)</td>
<td>3.07 (68)†</td>
<td>9.0 (42)†</td>
<td>2.92 (58)†</td>
<td>1.91 (100)</td>
<td>79.8</td>
</tr>
</tbody>
</table>

x ± SEM: 161 ± 3

33 ± 6
3.60 ± .52
4.49 ± .61
24.3 ± 3.2
6.02 ± .73
2.83 ± .36
79.0 ± 3.3

†Abnormal (exceeds 95 percent confidence interval for normals—see “Methods”). Numbers in parentheses represent percent of predicted (reference 14). BP = body plethysmography.

Pulmonary Function after ARDS (Suchyta et al)
sputum production, or wheezing. He had returned to his previous employment and considered himself fully functional.

**Pulmonary Function**

All pulmonary function studies were performed at least one year after the onset of ARDS (mean, 2.8 years; range, one to six years). Three survivors had normal results of studies. Six of nine ARDS survivors had at least one abnormal result of pulmonary function study (Table 2). The most common abnormality was a decreased Dco that was identified in four survivors. The DL/VA of three of these four was less than predicted. Measurements of Dco ranged from 42 percent to 114 percent of predicted. One ARDS survivor had a restrictive pulmonary function deficit characterized by decreased FEV1, FVC, and TLCHe with a normal FEV1/FVC. Three survivors had mild airway obstruction defined by a low FEV1/FVC. Three patients had TLC measured by body plethysmography; one of these three had air trapping.

**Biopsy Results**

All nine patients had abnormalities identified in at least three of the five scored categories (Table 3). Combined scores ranged from 0 to 16. HMs were present in six of nine patients, IF often with marked architectural disruption in eight of nine, AO in eight of nine, IC in nine of nine, and T2C in nine of nine. Extent scores varied from 0 (HM, IF, OF) to 4 (T2C, IC). Severity scores varied from 0 (HM, IF, OF) to 4 (T2C, IC). Four patients had their biopsies performed within the first week of ARDS, while five had biopsies 12 to 14 days after ARDS was diagnosed. There were no obvious differences (p>0.05) noted between scores in the early and late biopsy groups. Bronchioles were present in all biopsy specimens. Abnormalities other than bronchiolitis obliterans (scored with AO) were not seen. Bronchiolectasis was not seen. Likewise, abnormalities in vessels were not found other than an occasional organizing thrombus, considered an incidental finding related to the severe diffuse lung disease. Pulmonary capillaries were not easily examined because they were obscured by pathologic changes.

One patient (case 7) underwent two biopsies 7 and 19 days following the onset of sepsis and ARDS. These biopsy specimens demonstrated repair of interstitial fibrosis during the 12-day interval.

**Relationships between Open Lung Biopsy and Residual Lung Function**

Percent predicted Dco, TLC, DL/VA, and FVC were linearly regressed against extent, severity, and combined scores for each of the five categories (n = 60). Using Bonferroni’s criteria to adjust the p value for 60 regression analyses, no significant correlation was found. The severity score for organizing fibrosis regressed against the percent predicted Dco provided the single best correlation (p value = 0.01).

**DISCUSSION**

The present study demonstrates that quantitative scores of acute and subacute histologic abnormalities in open lung biopsy specimens associated with ARDS do not correlate significantly with predicted lung function more than one year after ARDS. We found no relationship between the extent and severity of HM formation, IF, or IC and pulmonary function. Similarly, the extent of T2C, an important component of the repair process,27 did not correlate with indices of recovery from ARDS. These observations add to previous reports that suggested that IF observed early in ARDS is potentially reversible.3,28 In the present series, one patient (case 6) with severe and extensive interstitial fibrosis observed on a biopsy specimen early in the course of ARDS recovered normal pulmonary function one year later.

There are at least four possible explanations for the lack of correlation between histologic scores and indices of pulmonary function after recovery from ARDS. First, inhomogeneities of histopathologic features associated with ARDS may confound the relation between biopsy specimen interpretation and residual

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*See "Methods" for pathologic definitions. Com = combined score; E/S = extent/severity (see "Methods" for description).
lung function. Investigators have reported heterogeneity of lung injury based on pathologic,\textsuperscript{10} biochemical,\textsuperscript{10,29} and CT studies.\textsuperscript{29,30} Pratt et al\textsuperscript{29} observed that HMs and alveolar duct fibrosis were present where the lung was well ventilated and suggested that high oxygen fractions and positive pressure injured these airways. In the present study, a biopsy specimen was taken from lung parenchyma from an area of roentgenographic infiltrate. The HMs were not a prominent finding perhaps because well-ventilated lung parenchyma was not sampled or because HMs had already resolved. Maunder et al\textsuperscript{30} reported that chest CT showed areas of well-aerated, normal-appearing lung interspersed with patches of abnormal lung density. Two patients in our study had chest CTS that demonstrated nonuniform parenchymal infiltrates more than two weeks after the lung biopsies. The inhomogeneity of lung injury associated with ARDS may explain why physiologic measurements are better correlated than pathologic measurements with lung function after recovery from ARDS.\textsuperscript{8,24,31} Physiologic measurements, such as total thoracic compliance, may more accurately reflect the fraction of lung tissue with infiltrates whereas biopsy specimens of parenchymal infiltrates may not reflect the proportions of involved and less severely involved lung tissue. Furthermore, it is possible that areas of focal fibrosis result in overall reductions of TLC.

A second possible reason for the lack of correlation between histologic scores and residual lung function is the timing of the lung biopsies. In the present study, lung tissue was examined within 14 days of the onset of ARDS. Histologic scores of biopsy specimens obtained within the first week of ARDS onset and histologic scores of biopsy specimens 12 to 14 days after ARDS onset did not differ. However, histologic scores of lung tissue obtained more than two weeks after ARDS onset may correlate with residual pulmonary dysfunction. Zapol et al\textsuperscript{10} found increased total collagen content in postmortem lungs of 10 patients who survived 12 to 28 days whereas total collagen content was normal in the lungs of 2 patients who survived 4 and 10 days. Pathologic studies have identified fibrous proliferation during later stages of ARDS.\textsuperscript{8,30} Lakshminarayan et al\textsuperscript{8} reported interstitial fibrosis in each of three survivors who underwent biopsies four weeks to nine months after the onset of ARDS. These survivors had abnormalities of pulmonary function. However, we found no correlation between IF identified early in the course of ARDS and pulmonary function more than one year after ARDS. These results suggest that interstitial fibrosis may contribute to pulmonary function abnormalities after ARDS but that early biopsy specimens that demonstrate interstitial fibrosis do not necessarily predict late abnormalities of lung function.

A third explanation for the lack of correlation between histologic scores and indices of pulmonary function after ARDS is the possibility that physiologically important pathologic changes were not scored. Slavin and associates\textsuperscript{32} described bronchiolectasis, dilatation of terminal and respiratory bronchioles associated with the administration of PEEP in 11 patients who died of respiratory failure. The histologic severity of bronchiolectasis correlated with indirect estimates of pulmonary dead space, suggesting a relationship between acute histologic and physiologic changes. Bronchiolectasis was not graded in our study since we did not find histologic evidence of bronchiolectasis. We also did not observe the changes of bronchopulmonary dysplasia in these early biopsy specimens, although pneumatoceles subsequently were observed in one of two patients who had CT examinations. Evidence of air trapping (trapped air is the difference between plethysmographic TLC and TLC measured by helium dilution) in patient 5 suggests that bronchopulmonary dysplasia may represent a late pathologic change that contributes to abnormal lung function following ARDS. Bronchopulmonary dysplasia in adults has been associated with healed ARDS in autopsy studies.\textsuperscript{33}

In addition to pathologic alterations of airways, pulmonary vascular abnormalities may represent another unmeasured contributor to residual abnormalities of pulmonary function. Snow et al\textsuperscript{34} provided evidence that disruption and disappearance of the pulmonary vascular bed characterized ARDS. These authors hypothesized that these structural changes were irreversible as evidenced by reductions of Dco among ARDS survivors. In the present study, mild pulmonary hypertension (PAP = 25 ± 3 mm Hg, ± SEM) was present early in the course of ARDS, and mean PAPs increased as the disease progressed. Structural alterations of the pulmonary vascular bed were not scored in the present study, but no consistent alterations were noted in the larger vessels. Loss of capillaries and microthrombosis certainly may contribute to reductions of Dco,\textsuperscript{35} but potential abnormalities in these vessels could not be assessed adequately by light microscopy. Quantitative scoring of pulmonary microvascular abnormalities may predict residual pulmonary dysfunction better than the indices measured in the present study. Snow et al\textsuperscript{34} observed that vascular changes were more fully developed in patients with ARDS of long duration (death after 12 or more days of symptoms). Thus, biopsy specimens later in the course of ARDS may better correlate residual pulmonary function with pulmonary vascular abnormalities.

A fourth explanation is that the fibroblastic proliferation and AO that we identified does not correlate with later interstitial fibrosis that is more mature,
irreversible, and of the type seen in idiopathic pulmonary fibrosis. This possibility is consistent with the observations of Lamy et al.1 that 3 of 13 ARDS patients with biopsy evidence of extensive fibrosis survived with moderate to good pulmonary function. The mechanisms that regulate fibrosis following ARDS remain poorly understood. The presence of collagenases and collagenases make degradation of poorly cross-linked collagen fibers one possible explanation for the disparity between acute histologic observations and subsequent pulmonary function observed in the present study.

In summary, these observations indicate that lung biopsy results in the early (first 7 days) and subacute (days 12 to 14) stages of ARDS do not correlate with pulmonary function after recovery from ARDS.

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