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Open-lung Biopsy in Patients with Acute Respiratory Distress Syndrome

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Background: **It has been suggested that fibrosis present during the fibroproliferative phase of acute respiratory distress syndrome (ARDS) can be treated by corticosteroids. However, neither clinical nor microbiologic criteria permit differentiation of this fibroproliferative phase from a nosocomial pneumonia. The aim of this observational case series was to evaluate the safety and utility of open-lung biopsy (OLB) performed in patients receiving ventilatory support who had persistent ARDS despite negative bacterial cultures.**

Methods: **During a 4-yr period, 37 OLBs were performed in 36 of 197 patients receiving ventilatory support who had ARDS. The severity of ARDS was assessed by a lung injury score of 3.1 ± 0.4 (mean ± SD) and a median ratio of the partial pressure of oxygen (Pa_{O_2}) to the fraction of inspired oxygen (FiO_2) of 118 mmHg. Histologic examination; bacterial, fungal, and acid-fast staining; and cultures of the tissue sample were performed.**

Results: **Fibrosis was present in only 41% of the lung specimens obtained by OLB. Only six patients received corticosteroids (17%). In 9 of the 15 patients with fibrosis, cytomegalovirus pneumonia precluded the use of corticosteroids. Histologic cytomegalovirus pneumonia was diagnosed in 18 cases. Histologic bacterial or mycobacterial pneumonia was diagnosed in five cases. No significant change in arterial blood gases was noted as linked to the biopsy procedure except an increase of the Pa_{O_2}/FiO_2 ratio. One pneumothorax was diagnosed on a chest roentgenogram 12 h after OLB. Only one patient required blood transfusion during the 48-h period after OLB (for an hemothorax). Five patients had moderate air leaks from operative chest tubes for 2–10 days.**

Conclusions: **Open lung biopsy appeared to be a useful and acceptably safe diagnostic technique in patients with ARDS. It permitted the diagnosis of unexpected cytomegalovirus pneumonia. (Key words: Biopsy; corticosteroids; cytomegalovirus; pneumonia.)**

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ACUTE respiratory distress syndrome (ARDS) was first described in 1967[1] and since that time has been the subject of many studies. It has been suggested that the acute phase is related to an increase in the permeability of the alveolar capillary membrane, leading to edema, proteinaceous exudates, hyaline membranes, congestion, and hemorrhage.[2] Acute interstitial fibrosis will develop in some of these patients, some of whom will die. A recent published study[3] showed that fibrosis is strongly correlated with outcome. Others studies have suggested that this fibrosis is potentially reversible.[4,5] Meduri *et al.*[6,7] proposed using corticosteroids at the fibroproliferative phase of ARDS and found, in nonrandomized studies, a decrease in the mortality rate among patients treated with corticosteroids.

The sensitivity of the available microbiologic sampling techniques is not sufficient to determine a cause of ARDS in all cases.[8–10] Further, viral agents can be the cause of certain nosocomial pneumonias.[11] Consequently, in these patients with ARDS, negative microbiological cultures, and a clinical picture mimicking nosocomial pneumonia, it is difficult to separate true infection from inflammatory response.

The rapid clinical deterioration of patients with ARDS, who often progress to multiple organ failure, creates a diagnostic and therapeutic dilemma. Open-lung biopsy

(OLB) is highly sensitive in diagnosing chronic diffuse parenchymal disease.[12,13] However, because it is an invasive procedure, some clinicians may be reluctant to perform OLB in critically ill patients with ARDS. In a previous study,[3] we used transbronchial biopsy (TBB) to rule out the presence or the absence of fibrosis. In 3 of the 25 patients studied, no lung specimen was obtained. Further, because of the limited size of the samples, no lung specimen could have been sent to the microbiology laboratory for processing. Therefore, despite the good tolerance of this procedure, we decided to use OLB to obtain larger samples for histologic and microbiological processing.

The aim of this observational case series was to evaluate the safety and the utility of OLB performed in patients with ARDS who were thought to be free of bacterial pneumonia. This area is potentially important because the fibroproliferative phase of ARDS may be steroid responsive (a hypothesis to be tested in the National Heart, Lung, and Blood Institute multicenter study), and differentiating that entity from infection may require, in certain circumstances, histologic lung assessment.

Materials and Methods

Study Design

This study was conducted during a 4-yr period (January 1, 1993 to December 31, 1996) in our 14-bed medicosurgical intensive care unit (ICU). After approval by the institutional ethics committee, informed consent was obtained from each patient's family. The decision to perform an OLB required the agreement of the four senior physicians in charge of the ICU. Open lung biopsy was indicated, after at least 5 days of evolution of ARDS, for a lack of improvement in respiratory status (defined as the absence of decrease of the Lung Injury Score[14]) despite negative bacterial cultures and a potential indication for corticosteroid treatment.

Patients

All patients met the criteria of ARDS defined by the American-European consensus conference.[15] The following data were prospectively recorded and computed: age, sex, diagnosis on admission, Acute Physiology and Chronic Health Evaluation III score on admission,[16] the number of organ failures on admission evaluated by the Organ System Failures score,[17] and the date of onset of ARDS. The following data were recorded the day of OLB: temperature, leukocyte count, radiologic classification using Weinberg's score,[18] and Lung Injury Score.[14] At least four arterial blood gas (at least every 6 h) determinations per day were done before and after the biopsy procedure. Finally, the duration of mechanical ventilation, duration of hospitalization, and final outcome were recorded.

Microbiological Examinations Performed before Open-lung Biopsy

Blind and directed sampling procedures were performed in the three days before OLB. The presence of bacteria was assessed by blinded bronchial sampling, bronchoalveolar lavage (BAL), and protected specimen brush.[9] The results of these examinations were considered to be positive when at least one microorganism grew to a concentration exceeding 10^3 cfu/ml for protected specimen brush[19] and 10^4 cfu/ml for BAL[19] and blinded bronchial sampling.[9] Viral cultures for cytomegalovirus (BAL and blood cultures) were performed in all patients using the shell-vial culture technique. Lung tissue culture for cytomegalovirus was not performed in all patients. Specimens for these cultures were inoculated onto MRC-5 cells in tissue culture.[20] Monoclonal antibodies directed against immediate early antigen (E 13; Biosoft, Clonatec, Paris, France) were applied 48 h after inoculation to detect viral antigen expression.[21] When bacterial and cytomegalovirus cultures were negative, we systematically performed a BAL to diagnose pneumonia due to the Herpes virus, *Legionella*, *Mycoplasma pneumoniae*, *Mycobacteria* (direct examination and culture), *Pneumocystis carinii,* and *aspergillosis*. When the results of these examinations were negative (except for mycobacterial culture, which requires several weeks), we decided to perform OLB. This procedure was done within the following 24 h.

Open-lung Biopsy

Open lung biopsy was done in the ICU (at the bedside) or in the operating room by the same experienced thoracic surgeon (P.T.). When the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pa_{O_2}:FI_{O_2}) was <120 mmHg, OLB was performed in the ICU. No blood gas value contraindicated the procedure. In patients with a risk of bleeding, pleural symphyses (evaluated by the patient's history and/or CT scan), or both, the procedure was performed in the operating room. A sterile operating room technique was used in the ICU, where each patient stayed in a separate room with continuous air recycling. All patients were mechanically ventilated *via* a cuffed trache-

ostomy tube and anesthetized with sufentanil and midazolam and paralyzed with vecuronium to manage ARDS. Anticoagulant therapy was stopped for at least 12 h before the procedure. The FiO_2 was increased to 1.0 during the biopsy procedure. Electric activity of the heart, pulse oximetry, and arterial blood pressure were monitored continuously. The chest was elevated slightly with a pad under the homolateral shoulder with the arm at the side but more posterior and out of the way. Local anesthesia was not used. A 10-cm lateral thoracotomy incision was made in the fifth intercostal space. A rib spreader and atraumatic graspers were used. The biopsy was obtained using automatic linear stapling devices (reloadable linear cutter TLC 75; Ethicon Endosurgery, Sommerville, NJ). All pleural adherences were freed. After inspection of the lung, biopsy specimens were taken from the most involved area, usually in dependent areas of the middle lobe (or lingula) or the lower lobe. Average operative time was 30 min. The biopsy procedure was facilitated by disconnecting the patient from the ventilator when the stapler was applied. Once the biopsy specimen was removed, the ventilator was reconnected immediately. Two chest tubes were inserted before closing the chest. Chest roentgenograms were obtained in each patient after the procedure. Chest tubes were removed once patients had been weaned from the ventilators. A thoracoscopic lung biopsy was not attempted in any of these ventilator-dependent patients due to their inability to tolerate single-lung ventilation. Possible pleural space infection, air leak, and pneumothorax were recorded during the patients' stay in the ICU. The therapeutic impact of OLB was also assessed. Change in therapy was defined as the addition or substraction of one or more drugs.

Open-lung Biopsy Processing

Biopsy samples were fixed in 10% buffered formalin for 24 h at room temperature. Then samples were dehydrated in a modified alcohol series: 95% for 15 min, 100% for 15 min, and xylene for 15 min. After dehydration, samples were embedded in a single paraffin block and serially cut at 4-μm thickness using standard microtomes with disposable blades. Slides were stained with hematoxylin-eosin-saffran. Focal fibrosis was not a criteria for the administration of corticosteroids. Corticosteroids were indicated when patients had the following degree of diffuse fibrosis: myxoid interstitial fibrosis, interstitial and intra-alveolar fibrosis, or a distortion of the usual pulmonary architecture by dense fibrous tissue (fig. 1). Cytomegalovirus pneumonia was diagnosed on pulmonary samples by the identification of large cells with large nuclei containing a basophilic or eosinophilic inclusion surrounded by a light halo.[22,23] These typical findings were always associated with a diffuse interstitial pneumonia characterized by the presence of inflammatory cells (predominantly lymphocytes), thickened alveolar septi, and an interstitial inflammation. Bacterial pneumonia was defined by the presence of scattered neutrophilic infiltrates localized to terminal bronchioles and surrounding alveoli with evident confluence of infiltrates between adjacent lobules.[8] Bacteriologic investigation performed on open lung biopsy samples included Gram and Ziehl-Neelsen staining and culture for bacteria, mycobacteria, and fungi.

Statistics

Median values and ranges are reported for non-normally distributed data. For normally distributed data, values are reported as means ± SD.

Results

Characteristics of the Patients at Admission

During the study period, 2,074 patients were admitted to our medicosurgical ICU. Of these 2,074 patients, ARDS developed in 197. In all, 37 OLBs were performed in 36 of these patients with ARDS (mean age, 59 ± 15 yr; Acute Physiology and Chronic Health Evaluation III score on admission, 65 ± 25). None of the families refused OLB. Of these 37 OLBs, 5 cases had also been included in a previously published study of cytomegalovirus pneumonia.[11] Six patients were admitted to the ICU for ARDS, whereas ARDS developed in the other 30 patients during their ICU stay. Among the 36 patients enrolled in the study, 3 were admitted to the ICU after multiple trauma, 15 were admitted with postoperative complications after major surgery, and 18 were admitted for an acute medical illness (community-acquired pneumonia, 7; aspiration pneumonia, 5; coma, 2; polyneuritis, 1; mediastinitis, 1; myocardial infarction, 1; status asthmaticus, 1).

Characteristics of the Patients at the Time of Biopsy

Twelve of the 36 patients had computerized axial tomographic examination of the chest during the 72-h period preceding OLB. They showed bilateral diffuse infiltrates predominantly in the dependent regions.

Table 1 shows the clinical and respiratory parameters

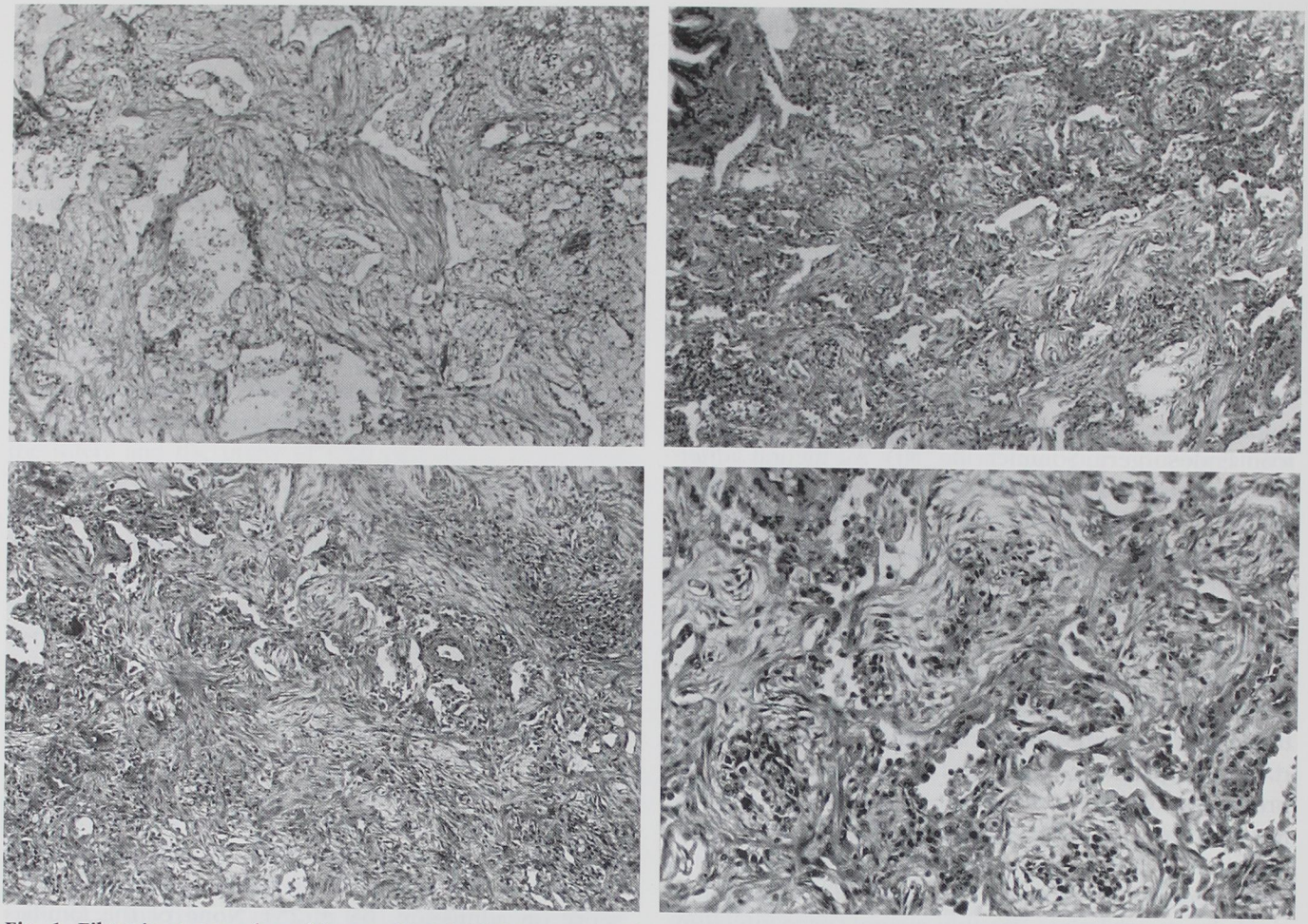

Fig. 1. Fibrosis at open-lung biopsy. (*Top left*) Low-power photomicrograph of an open-lung biopsy (magnification, ×100; hematoxylin-eosin-safran stain) showing diffuse interstitial myxoid fibrosis and fibroblastic and chronic inflammatory cell infiltration of the interstitium. (*Top right*) Low-power photomicrograph of an open lung biopsy (magnification, ×40; hematoxylin-eosin-safran stain) showing interstitial septal and diffuse endoalveolar fibrosis with thickening of the alveolar septa. (*Bottom left*) Low-power photomicrograph of an open lung biopsy (magnification, ×40; hematoxylin-eosin-safran stain). The upper part shows interstitial septal and diffuse endoalveolar fibrosis with thickening of the alveolar septa. The lower part shows a distortion of the usual pulmonary architecture by a dense fibrous tissue. (*Bottom right*) Low-power photomicrograph of an open lung biopsy (magnification, ×250; hematoxylin-eosin-safran stain) showing cellular and nodular septal fibrosis. Also evident is alveolar lining cell hypertrophy and marked septal thickening with moderate distortion of the usual pulmonary architecture, including obliteration of the alveoli.

recorded on the day of OLB. The median time for mechanical ventilatory support was 14 days (range, 5–89 days). OLB was performed 10 days (range, 5–55 days) after the onset of ARDS. On the day of OLB, all patients had a Lung Injury Score >2.5 (mean, 3.1 ± 0.4). Fifteen patients presented at least two visceral dysfunctions as defined by the Organ Systems Failure scoring scheme.

Clinical presentation was not specific to an infectious process. The mean temperature was 37.9 ± 1°C (range, 36–40.5°C). The mean white blood cell count was 13.6 ± 6.7 G/l, with a predominance of neutrophils (82 ± 9%). Weinberg's radiologic score was 11 ± 1.6.

The platelet count was >100 G/l in all but six patients. All patients were hemodynamically stable, but 19 patients (53%) were receiving cardiovasoactive drugs. Twenty-six of the 36 patients were receiving volume-controlled ventilatory support at the time of OLB. The other 10 patients received ventilatory support according to a pressure-controlled mode. Ventilation was with a positive end-expiratory pressure of at least 5 cm H_2O in all patients. In addition, 21 of these 36 patients received nitric oxide and 15 of these 21 patients received a concomitant continuous infusion of almitrine.

Arterial blood gas samples for gas analysis taken dur-

Table 1. Clinical and Respiratory Parameters at Time of Biopsy and Pa_{O_2}/FI_{O_2} Ratio after Open Lung Biopsy

Patient No.	Duration of ARDS (days)	Duration of MV (days)	OSF	LIS	Vt (ml)	PEEP (cmH_2O)	P_{CO_2} (mmHg)	V_E (L/min)	Pa_{O_2}/FI_{O_2} (mmHg) before OLB	Pa_{O_2}/FI_{O_2} (mmHg) after OLB
1	13	13	1	3.3	460	10	68	8.3	98	105
2	18	21	1	3.3	460	12	44	13.8	118	110
3	30	32	1	2.7	410	5	42	11	151	211
4	10	25	1	2.7	710	9	38	10.7	189	304
5	20	20	1	2.7	450	5	47	19.6	60	117
6	13	17	3	3.0	800	14	38	20	149	118
7	5	40	1	3.3	740	10	33	14.8	105	107
8	26	33	3	3.0	340	9	45	18.2	190	210
9	5	5	2	2.7	570	7	47	17.1	109	127
10	11	11	1	2.7	660	6	57	22.4	86	274
11	5	6	2	4.0	240	15	74	12	75	122
12	6	6	3	4.0	500	16	36	26.3	98	110
13	7	8	2	3.3	600	13	35	15.6	91	145
14	6	6	1	2.8	600	10	30	11.4	126	135
15	5	5	2	3.0	500	13	58	8	109	97
16	44	44	2	2.7	550	6	26	18.7	99	121
17	5	9	2	3.0	500	12	50	8	67	164
18	16	26	1	3.0	500	10	35	11	190	161
19	9	28	1	3.0	600	11	48	18	115	97
20	21	21	1	2.7	500	8	36	11.5	135	165
21	10	11	1	3.3	350	14	38	9.8	160	172
22	20	25	1	2.7	400	8	52	12.4	180	248
23	55	56	1	3.3	370	12	50	10	75	159
24	31	45	2	3.3	450	11	38	14.4	112	161
25	16	21	1	3.0	350	10	49	9.8	161	180
26	5	5	1	3.3	500	11	40	11.0	90	104
27	7	7	1	3.0	515	9	32	10.8	140	220
28	8	14	3	3.7	650	14	48	13.0	87	79
29	6	6	2	3.0	530	10	36	10.6	140	119
30	7	7	2	3.3	550	10	39	13.8	127	136
31	13	13	1	3.3	500	9	52	15.0	134	133
	35	35	1	3.0	380	10	74	15.2	115	127
32	6	6	1	3.3	500	10	78	15.0	129	225
33	15	20	2	2.7	460	10	40	13.8	190	247
34	5	89	1	3.0	450	10	51	8.0	129	115
35	6	6	2	3.7	570	11	42	10.8	85	100
36	8	8	1	3.0	600	10	46	10.2	131	114

MV = mechanical ventilation; OSF = organ system failures score;[18] LIS = lung injury score[20]; Vt = tidal volume; PEEP = positive end-expiratory pressure; V_E = minute ventilation.

ing the 24-h period before OLB showed that the most abnormal Pa_{O_2}:FIO_2 ratio was <150 mmHg in 30 cases and <100 mmHg in 12 of these 30 cases.

At the time of biopsy, 23 patients were receiving antibiotic treatment. Antibiotics had been stopped for at least 48 h in seven other patients. The remaining six patients had never received antibiotics while they were in the hospital. All patients had negative bacterial cultures from the samples obtained from protected and blinded techniques during the 72-h period before OLB.

Tolerance of the Biopsy Procedure

Open-lung biopsy was performed at the bedside in 25 cases and in the operating room in the remaining 12 cases. It was performed on the right side in 20 cases and on the left side in the remaining 17 cases. There were no intraoperative complications or deaths. One pneumothorax was diagnosed by chest roentgenogram and required chest tube drainage 12 h after OLB. Only one patient required blood transfusion during the 48-h period after OLB for a hemothorax of 350 ml. In all

Table 2. Arterial Blood Gas and Ventilator Settings before and after Open Lung Biopsy (OLB)

	Before OLB	After OLB
Pa_{O_2}/FI_{O_2} (mmHg)	118 (60–190)	133 (79–304)*
P_{CO_2} (mmHg)	44 (26–78)	41 (31–105)
Vt (ml)	500 (240–800)	500 (280–880)
Minute ventilation (L/min)	12 (8–26)	12 (8–23)
PEEP (cmH_2O)	10.3 ± 2.6 (5–16)†	10.3 ± 2.5 (5–16)†
Peak pressure (cmH_2O)	36 ± 6 (27–49)†	34 ± 5 (25–46)†

Values are median (range).

* $P < 0.01$ (Wilcoxon signed-rank test).

† Mean ± SD.

instances, the FiO_2 returned to preoperative levels within a mean of 15 min (range, 5–22 min). No arrhythmia or hemodynamic instability was precipitated by OLB. No significant change in arterial blood gases or ventilator parameters was noted as linked to the biopsy procedure except the Pa_{O_2}:FIO_2 ratio (tables 2 and 3). As shown in table 2, median values were calculated from the most abnormal results of blood gas analysis performed during the 24-h period before and after OLB. Intraoperative blood gas values were never performed. Intraoperative monitoring included pulse oximetry, which always remained greater or equal to the preoperative value. The slight increase of the Pa_{O_2}:FIO_2 ratio was probably related to the evacuation of pleural effusions consisting of 80 ml (range, 0–800 ml) of serofibrinous exudate. We noted a decrease of the Pa_{O_2}:FIO_2 ratio in only 10 cases and an increase in the remaining 27 procedures (table 1). Nitric oxide administration and almitrine infusion remained constant throughout the pre- and postbiopsy period. Five patients (14%) had a moderate air leak from operative chest tubes for at least 24 h that did not require surgery (three in patients with OLB in the ICU and two with OLB in the operating room). The air leak lasted from 2–10 days (2 days in one patient, 3 days in two patients, 4 days in one patient, and 10 days in one patient).

Diagnostic Results and Changes in Therapy

Table 3 shows the diagnostic results of OLB. Only one lung biopsy was performed per patient. Dimensions were 3–5 cm in length, 1.5–3 cm in width, and 0.5–1.2 cm in thickness. All biopsy specimens had abnormal findings. Fibrosis was noted in 15 cases (41%). Cytomegalovirus pneumonia was diagnosed by histologic analysis in 18 cases. Lung tissue culture for cytomegalovirus was performed in 9 of these 18 cases and was positive for this virus in 4 cases. Immunocytochemical analysis for cytomegalovirus was performed in only four patients and was positive in two cases. Cytomegalovirus pneumonia was always observed in non-immunocompromised patients who were not receiving corticosteroids at the time of OLB. In 10 patients, cytomegalovirus was present on BAL, blood, or both (five times before OLB, five times after OLB). Although OLB could miss some cytomegalovirus infections because of the small size of the sample, an OLB demonstrating characteristic viral inclusions surrounded by a light halo can be considered the gold standard. This fact allowed us to determine the operative characteristics of BAL fluid and blood cultures. The sensitivity rate was 44% for both techniques. The specificity rate for the diagnosis of cytomegalovirus pneumonia was 95% for BAL fluid cultures and 100% for viremia. Cytomegalovirus pneumonia contraindicated the use of corticosteroids in 9 of the 15 patients with fibrosis. Corticosteroid therapy was initiated in only six patients. For one patient (patient 23), corticosteroids were contraindicated by the surgical team, because of impaired healing of an esophageal perforation. The results of OLB directly altered the therapeutic management in 34 cases (table 3).

Outcome

The mean duration of mechanical ventilation of these 36 patients was 40 ± 23 days, and the mean duration of hospitalization in the ICU was 46 ± 26 days. Despite changes in therapy, the survival rate was low (table 3). Only 18 patients (50%) survived to be discharged from the ICU and from the hospital. Survival was not modified when we considered only those patients in whom therapeutic changes resulted from OLB (53%). When only the six patients with fibrosis evident on OLB and who subsequently received corticosteroids were considered, four of them survived and were discharged from the hospital. For those patients who died in the ICU, survival time after OLB was 7 days (range, 4–37 days). The most common cause of death was multiple organ failure in 13 patients (72%), followed by cardiac failure in 2 (11%) and pulmonary failure in 3 (17%). Autopsy was performed in six patients (33%). The postmortem histologic examination of the lung parenchyma corresponded with the pathologic findings of OLB in five patients (patients 5, 8, 10, 11, and 26). The remaining autopsy (patient 19) revealed a bacterial superinfection (6 days after OLB). The ICU mortality rate for

Table 3. Open Lung Biopsy Diagnoses and Survival to Hospital Discharge

Patient No.	Histological Result	Therapeutic Alterations	Outcome
1	Foreign body reaction/fibrosis	Corticosteroid therapy	Survived
2	Cytomegalovirus pneumonia/fibrosis	Ganciclovir	Survived
3	Cytomegalovirus pneumonia	Ganciclovir/stop antibiotics	Survived
4	Cytomegalovirus pneumonia/fibrosis	Ganciclovir	Survived
5	Diffuse alveolar damage	No modification	Dead
6	Bacterial pneumonia (abscess)	New antibiotics	Dead
7	Cytomegalovirus pneumonia	Ganciclovir/stop antibiotics	Dead
8	Cytomegalovirus pneumonia	Ganciclovir	Dead
9	Cytomegalovirus pneumonia/fibrosis	Ganciclovir	Dead
10	Cytomegalovirus pneumonia/fibrosis	Ganciclovir	Dead
11	Cytomegalovirus pneumonia	Ganciclovir	Dead
12	Cytomegalovirus pneumonia	Ganciclovir/stop antibiotics	Dead
13	Cytomegalovirus pneumonia/fibrosis	Ganciclovir/stop antibiotics	Dead
14	Diffuse alveolar damage	Stop Ganciclovir	Survived
15	Diffuse alveolar damage	No modification	Dead
16	Systemic lupus erythematosus	Corticosteroid therapy	Survived
17	Bacterial pneumonia	New antibiotics/stop Ganciclovir	Survived
18	Herpetic pneumonia	Acyclovir	Survived
19	Fibrosis	Corticosteroid therapy/stop antibiotics	Dead
20	Diffuse alveolar damage	Stop antibiotics	Survived
21	Diffuse alveolar damage	Stop corticosteroid therapy/stop antibiotics	Survived
22	Cytomegalovirus pneumonia	Ganciclovir/stop antibiotics	Survived
23	Fibrosis	Stop antibiotics	Dead
24	Cytomegalovirus pneumonia/fibrosis	Ganciclovir	Survived
25	Fibrosis	Corticosteroid therapy	Survived
26	Intravascular bronchioloalveolar tumor	No modification	Dead
27	Cytomegalovirus pneumonia	Ganciclovir/stop antibiotics	Survived
28	Bacterial pneumonia–fibrosis	New antibiotics	Dead
29	Mycobacterial infection	New antibiotics	Dead
30	Cytomegalovirus pneumonia/fibrosis	Ganciclovir	Dead
31	Cytomegalovirus pneumonia/fibrosis	Ganciclovir	Survived
	Fibrosis	Corticosteroid therapy	Dead
32	Cytomegalovirus pneumonia	Ganciclovir	Dead
33	Cytomegalovirus pneumonia/fibrosis	Ganciclovir	Survived
34	Tuberculosis	New antibiotics	Dead
35	Wegener's granulomatosis	Corticosteroid therapy	Survived
36	Cytomegalovirus pneumonia	Ganciclovir	Survived

the 161 ARDS patients who did not require OLB was 48%. The reasons for not performing OLB in the 77 patients with ARDS who died in the ICU were related to the presence of a bacteria on at least one of the various sampling procedures, the evolution of the ARDS toward multiple organ failure (without an increase in Lung Injury Score), an extrapulmonary cause of death, a rapidly fatal underlying disease, and do not resuscitate orders (in five patients).

Discussion

The present study shows that OLB is an acceptably safe and useful technique in patients with ARDS who are receiving ventilatory support before corticosteroids are prescribed. Further, we found a particularly high percentage of cytomegalovirus pneumonia in these patients with ARDS. The mechanisms that regulate fibrosis after ARDS are not entirely understood. As described by some authors,[6,7,24] corticosteroids could improve the oxygenation status and the outcome of ARDS at the fibroproliferative phase. Although a recent study[25] has shown that determination of type III procollagen peptide in BAL fluid is highly correlated with an increased risk of fatal outcome, to our knowledge no study has demonstrated a correlation between the presence of fibrosis assessed by lung histologic analysis and the level of type III procollagen peptide in BAL fluid in patients

with ARDS. Biopsy not only establishes the diagnosis of fibrosis but also provides valuable information to rule out pulmonary infection as the continuing cause of respiratory distress. It is well recognized that nosocomial pneumonia is a major complication of ARDS; and the use of corticosteroids, if sepsis is the cause of continuing ARDS, would be contraindicated. On the other hand, the false-negative rate of all sampling procedures in the diagnosis of bacterial nosocomial pneumonia in ventilated patients could require the use of the gold standard—the histologic assessment of lung parenchyma.[8-10] Even the more sensitive technique (blinded bronchial sampling) is associated with a high false-negative rate: 28% for a threshold at 10^4 cfu/ml.[9] Further, in a previous study, we found that, in patients receiving ventilatory support, nosocomial pneumonia could be due to virus, especially cytomegalovirus.[11] During a 5-yr period, cytomegalovirus pneumonia was diagnosed by histologic analysis in 25 non-immunocompromised patients. We also reported a low sensitivity of BAL using shell-vial culture technique with fluorescein-labeled antibody E13 (53%). Although in patients with acute lung injury, reactive type II pneumocytes can assume unusual sizes and shapes (they may have huge reactive nucleoli that can be mistaken for viral inclusions), the fact that, in the present work, histologic signs of cytomegalovirus pneumonia coincided with positive blood, BAL, or lung tissue culture or with positive immunocytochemical results tends to indicate that the histologic modifications were related to cytomegalovirus. The incidence of cytomegalovirus could appear surprising in the late stages of ARDS. Recognition of typical inclusions may be difficult in lungs that are inflamed. Cytomegalovirus may be the initiating factor in some cases of ARDS. However, without longitudinal studies, it is impossible to determine whether ARDS or cytomegalovirus infection occurs first. Tuxen *et al.*[26] described the association of the herpes simplex virus and ARDS in 1982. They reported an incidence of 30% in patients with ARDS, whereas no case was diagnosed in patients receiving ventilatory support who did not have ARDS. However, identification of the herpes simplex virus was performed by cytologic analysis of lower respiratory secretions and not by histologic lung assessment. Speculation regarding the effect of cytomegalovirus on outcome in the present study is not valid, but the strong predilection for patients with ARDS, which was previously unrecognized, indicates the need for further study. OLB is associated with an underestimation of bacterial lung infection, but viral infections and fibrosis are probably less heterogenous and could be diagnosed in a lung tissue sample. However, to assess the accuracy of OLB for the diagnosis of lung infection caused by cytomegalovirus, the technique should be compared with extensive lung histologic results in patients who die in the ICU. In all, we found that in patients with an established ARDS and a potential indication for corticosteroids, fibrosis was present in only 41% of the lung specimens obtained by OLB. Further, in 9 of the 15 patients with fibrosis, the presence of histologic hallmarks of cytomegalovirus pneumonia contraindicated the use of corticosteroids. Finally, only six patients received corticosteroids (17%). However, to our knowledge, no data exist (although this does seem reasonable) indicating that the response to steroid therapy is specific to patients with fibrosis on biopsy. We think that blinded and directed sampling procedures cannot give complete and precise information on underlying infectious processes, specific lung diseases, and the presence of fibrosis.

Some studies have been devoted to the use of OLB in immunocompromised patients.[27,28] All these studies, however, showed that the procedure can be done with a low mortality rate, even in seriously ill patients. The question of the performance and the tolerance of OLB in patients with ARDS has received little attention.[29] Concerning the tolerance and the morbidity related to OLB, our study favors the use of this technique in patients with ARDS. Furthermore, this surgical technique can be performed at the bedside in the ICU when oxygenation status contraindicates any transport of the patient. We had no deaths from this procedure, and our only complication was a minor hemothorax and the development of low-grade air leak in five patients. One of these five patients had a pneumothorax that required pleural space drainage. To minimize these complications, we disconnected the patient from the ventilator during the stapling procedure. In addition, we used two pleural chest tubes rather than one. Every effort was made to ensure complete pneumostasis before closure.

There were no deaths related to OLB and only minimal complications in the series by Ashbaugh and Maier.[24] Meduri *et al.*[7] noted the same result and reported only one persistent air leak after OLB in 13 patients. Potter *et al.*[30] noted a high incidence of complications (71%) that they attributed directly to the need for general anesthesia, mechanical ventilation, and the surgical procedure in patients undergoing OLB. It appeared that our study differed from that by Potter *et al.*[30] in two important ways: Our patients were not immunocom-

promised (except for one lung transplant recipient), whereas those of Potter *et al.* had non-neutropenic cancer; and our patients were all mechanically ventilated before OLB, whereas those of Potter *et al.* were spontaneously breathing.

An alternative approach for invasive diagnosis, TBB, has commonly been limited to autonomously ventilating patients. Only a few reports[3,31,32] have evaluated the feasibility of TBB during mechanical ventilation. However, there are factors that may limit the utility of TBB. These factors are generally believed to be related to its small size or nonrepresentativeness of the tissue specimen or both. Fraire *et al.*[33] identified a statistically significant association between the specific pathologic diagnosis of infection and biopsy specimens containing a greater number of alveoli. Further, Burt *et al.*[34] performed synchronous TBB and OLB in 20 patients. The open procedure yielded a diagnosis in 94% compared with 59% for TBB. In our study, the number of samples necessary for pathologic examination and microbiological cultures underscores the need for large samples. Further, hemorrhage and pneumothorax are the potentially life-threatening complications of TBB. Two pneumothoraces (15%) were encountered in the study of Pincus *et al.*[32] and one by Papin *et al.*[31] in their series of 15 patients. In a previous study,[3] we did not observe pneumothorax in a series of 25 patients undergoing TBB. However, the respiratory status of the patients included in the present study was much more altered than that of the patients included in our previous work. For example, at the time of biopsy, the Pa_{O_2}:FiO_2 ratio was 187 ± 64 mmHg in the TBB study compared with 123 ± 36 mmHg in the present investigation.

In the present series of patients with ARDS, the findings of OLB enabled the initiation or the discontinuation of therapy in 34 cases. However, the principal findings of this study remains that OLB is an acceptably safe and useful technique in a disease process as serious as ARDS. Nevertheless, although OLB is undoubtedly valuable in making or confirming diagnoses, the design of the present study did not allow us to show that this information improves overall patient survival rates.

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