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Histologic aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure*

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Abstract. *Objective:* To describe histologically pulmonary barotrauma in mechanically ventilated patients with severe acute respiratory failure.
Design: Assessment of histologic pulmonary barotrauma.
Setting: A 14-bed surgical intensive care unit (SICU)
Patients: The lungs of 30 young critically ill patients (mean age 34±10 years) were histologically examined in the immediate post-mortem period. None of them were suspected of pre-existing emphysema.
Measurements and results: Clinical events and ventilatory settings used during mechanical ventilation were compared with lung histology. Airspace enlargement, defined as the presence of either alveolar overdistension in aerated lung areas or intraparenchymal pseudocysts in non-aerated lung areas, was found in 26 of the 30 lungs examined (86%). Patients with severe airspace enlargement (2.6–40 mm internal diameter) had a significantly greater incidence of pneumothorax (8 versus 2, $p<0.05$), were ventilated using higher peak airway pressures (56±18 cmH_2O versus 44±10 cmH_2O, $p<0.05$) and tidal volumes (12±3 ml/kg versus 9±2 ml/kg, $p<0.05$), were exposed significantly longer to toxic levels of oxygen (8.6±9.4 days versus 1.9±2 days at $FIO_2>0.6$, $p<0.05$) and lost more weight (6.3±9.2 kg versus 0.75±5.8 kg, $p<0.05$) than patients with mild airspace enlargement (1–2.5 mm internal diameter).
Conclusion: Underlying histologic lesions responsible for clinical lung barotrauma consist of pleural cysts, bronchiolar dilatation, alveolar overdistension and intraparenchymal pseudocysts. Mechanical ventilation appears to be an aggravating factor, particularly when high peak airway pressures and large tidal volumes are delivered by the ventilator.

Key words: Mechanical ventilation – Barotrauma – Respiratory failure – Alveolar overdistension – Pneumothorax

Pneumothorax, pulmonary interstitial emphysema, pneumomediastinum, pneumoperitoneum and subcutaneous emphysema are characteristic features of lung barotrauma complicating acute respiratory failure. Because the issue of gas into the pleura or into the subcutaneous space appears related to bronchoalveolar rupture, positive pressure ventilation is generally considered as a contributing factor. Alveolar rupture and perivascular interstitial emphysema can be produced experimentally in rabbits whose lungs are being mechanically ventilated, by applying intrabronchial pressures equal or greater than 50 cmH_2O [1]. Following alveolar rupture, air travels back along the perivascular sheaths, passing into the mediastinum, the subcutaneous tissue and the retroperitoneum, producing pneumothorax, pneumomediastinum, subcutaneous emphysema and pneumoperitoneum. In the early 40s, prior to the use of mechanical ventilation, these lesions were described in patients deceased from various acute respiratory diseases [2]. In the late 70s, during the multihospital collaborative extracorporeal membrane oxygenation project, rounded cyst-like airspaces (1–2 mm internal diameter) were reported in several individuals among 59 patients with severe adult respiratory failure whose lungs were being histologically examined [3]. These lesions were interpreted as "bubbles of interstitial emphysema", probably resulting from the high inflation pressure used to ventilate the patients. Other lesions, described very early in neonates with hyaline membrane disease [4–6] and entitled bronchopulmonary dysplasia, have been reported only episodically in adults [7, 8]. The aims of our study were twofold: 1) to assess histologically the incidence of airspace enlargement in patients with severe respiratory failure requiring prolonged mechanical ventilation; 2) to examine whether the size of airspace enlargement could

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be correlated with some specific clinical events prospectively recorded during patients' stay in the surgical intensive care unit (SICU).

Methods

Patients

Between April 1987 and August 1990, 236 critically ill patients died in the Surgical Intensive Care Unit (SICU) of La Pitié Hospital in Paris after a period of mechanical ventilation. During their stay in the SICU, 93 patients were mechanically ventilated for an acute parenchymal lung disease. In the immediate post-mortem period, 84 of these patients had one lung removed for histologic evaluation according to French legislation (see below). There were 54 patients excluded from the present study because they met one or several of the following criteria: 1) age above 50 years; 2) presence of severe malnutrition at the time of admission defined as a weight loss >20% of theoretical body weight; 3) presence of past history of chronic obstructive pulmonary disease or asthma; 4) presence of smoking >5 pack years. These exclusion criteria were chosen to study the lungs of mechanically-ventilated patients with an acute lung disease, which could not be suspected of pre-existing emphysema or airspace enlargement at the time of admission to the SICU.

The 30 patients finally included in the study (mean age 34±10 years, 16 males and 14 females) were initially admitted to the SICU for complications following major surgical procedures ($n = 7$), for an acute medical disease ($n = 7$) or for multiple trauma ($n = 16$). All were mechanically ventilated for a mean time of 13±11 days (range 2–47 days). During their stay in the SICU, all developed acute respiratory failure characterized by bilateral radiologic pulmonary infiltrates and impaired arterial oxygenation. All were monitored using a Swan-Ganz catheter. At the initial phase of their acute respiratory failure, they had a mean PaO_2 of 187±53 mmHg (intermittent positive pressure ventilation, FIO_2 1), a mean $PaCO_2$ of 35±6 mmHg (tidal volume of 10 ml/kg, respiratory frequency of 15 bpm), a mean pulmonary arterial pressure of 26±3 mmHg and a pulmonary wedge pressure of 9±2 mmHg. According to clinical and autopsy findings, 20 met the criteria of ARDS, whereas 6 had severe confluent bronchopneumonia and 4 extensive pulmonary contusion. Septic shock was present in 21 patients (for a mean time of 6 days, range 1–29 days) and was the cause of death in 13 patients. Other causes of death were: refractory hypoxemia ($n = 10$); brain death ($n = 5$) and cardiac arrest ($n = 2$). Patients had a mean body weight of 70±11 kg at admission (range 53 to 97 kg), and lost 4±8 kg during their stay in the SICU (range +7 to −28 kg).

Mechanical ventilation

During their stay in the SICU, each patient was mechanically ventilated using continuous positive pressure ventilation (CPPV) delivered by a CPU 1 ventilator. Positive end-expiratory pressure, FIO_2 and respiratory frequency were daily adjusted in order to obtain a $PaO_2 > 70$ mmHg and a $PaCO_2$ between 35 and 40 mmHg. In 6 patients, high-frequency jet ventilation (HFJV) was secondarily used, since conventional mechanical ventilation failed to ensure adequate gas exchange. The delay between HFJV and CPPV ranged from 1 to 30 days. HFJV was delivered by an Acutronic ventilator using a technique previously described in detail [9]. Mean airway pressure, FIO_2 and respiratory frequency were daily adjusted in order to obtain a $PaO_2 > 70$ mmHg and a $PaCO_2$ between 35 and 40 mmHg [10, 11]. HFJV was administered for a mean time of 8±7 days (range 3–26 days). In both ventilatory modes, peak airway pressure (Peak Paw) and FIO_2 were monitored every 3 h. Peak Paw (cmH_2O) and tidal volume (ml/kg) were expressed by averaging the 8 per day measurements and the highest value for 24 h was considered characteristic for a given patient. Number of days during which FIO_2 had to be maintained above 0.6 was also noted.

Pathologic study

In all patients, post-mortem pneumonectomies were performed according to French legislation which allows the taking of organs for the purpose of scientific research or transplantation, unless the patient prohibits it before death (law 781181, December 22, 1976 followed by the statutory order 78501 of March 1978 and the implementation order of April 3, 1978). Within the 20 min following death, a thoracotomy was performed at the bedside under surgical conditions. The patient was positioned in the lateral decubitus position and a large posterior incision was performed in the fifth intercostal space, while maintaining mechanical ventilation [12]. A right thoracotomy was performed when radiologic infiltrates were bilateral or predominant on the right. A left thoracotomy was performed when radiologic infiltrates were predominant on the left. After opening the pleura, the entire lung was largely exposed using a thoracic retractor, each pulmonary lobe was individualized and mechanical ventilation was stopped. After section of main bronchus and pulmonary vessels, the entire lung was removed, weighed and fixed by intrabronchial infusion of 10% formalin. Each lung was expanded to the size of the thorax in order to reach a pulmonary volume close to the functional residual capacity. Formalin instillation was stopped when the lung replaced in the thorax exactly fit the rib cage volume. This technique of fixation was used to avoid artefactual overexpansion of normally aerated lung areas the volume of which are usually markedly reduced in ARDS. After a 24 h fixation, the external aspect of the lung was carefully examined, searching for pleural cysts and areas of consolidation. Each lung was sectioned into 5–10 mm thick sections to localize airspace enlargement and inflammatory areas. Tissue blocks were selected according to the following protocol. At least 2 random tissue blocks were chosen from each segment separately and taken from the margin as well as from the centers of grossly normal and abnormal lung areas. Between 20 and 30 tissue blocks were available per lung examined. All obtained tissue blocks were embedded in paraffin and cut into sections at 4 μm. Between 3 and 5 sections were obtained per tissue block, and each deparaffined section was stained with hematoxylin-eosin-safran. The mean linear intercept was measured on each section following the technique of Thurlbeck [13].

Histologic aspects were classified in 5 categories: alveolar overdistension; intraparenchymal pseudocysts; bronchiolar dilatation; lesions of bronchopneumonia and non-specific acute alveolar damage. Alveolar overdistension was defined as abnormal enlargement of airspaces distal to the terminal bronchioles, frequently accompanied by a destruction of the alveolar septa, and located within non-inflammatory and non-fibrotic lung areas. Intraparenchymal pseudocysts were defined as enlarged airspaces located within inflammatory and fibrotic areas of the lung. Bronchiolar dilatation was defined as abnormal dilatation of terminal bronchioles associated with bronchial epithelial necrosis and metaplasia. Airspace enlargement was defined as the presence of intraparenchymal pseudocysts or alveolar overdistension having an internal diameter greater than 0.8 mm. Mild airspace enlargement was defined as the presence of intraparenchymal pseudocysts or alveolar overdistension whose internal diameter ranged between 0.8 and 2.5 mm and never exceeded 10fold the mean linear intercept measured between alveolar walls within normal lung [13]. Severe airspace enlargement was defined as the presence of intraparenchymal pseudocysts or alveolar overdistension whose internal diameter ranged between 2.6 and 40 mm and always exceeded 10 fold the normal mean linear intercept. Bronchopneumonia was defined as an accumulation of numerous polymorphonuclear leucocytes within the lumen of bronchioles and surrounding alveoli, involving one or several pulmonary lobules [12]. Non-specific acute alveolar damage was defined as the presence of three or more of the following lesions: diffuse interstitial fibrosis; alveolar edema; hemorrhagic alveolitis; capillary thrombosis; presence of hyaline membranes and pulmonary artery abnormalities.

Statistical analysis

All data are expressed as mean±SD. The χ^2 test (and for small numbers the Fischer's exact test) and Student's t-test for unpaired data were used to compare patients with mild and severe airspace enlargement. Results were considered significant at $p < 0.05$.

Results

Incidence and clinical characteristics of pulmonary barotrauma in the study population

One or several episodes of pneumothorax were observed in 10 patients during the period of mechanical ventilation (30%). Tension pneumothorax occurred in 6 patients and subsequent bronchopleural fistula was observed in 2 patients. Pneumothorax was associated with generalized subcutaneous emphysema in 3 patients and with pneumomediastinum in 2 patients. Peak Paw was 57 ± 11 cmH_2O in the 10 patients with pneumothorax versus 53 ± 21 cmH_2O in the 20 patients without pneumothorax (NS). The period of time during which FIO_2 had to be maintained above 0.6 was longer in the 10 patients with pneumothorax than in the 20 patients without clinical evidence of barotrauma (11 ± 11 days vs 7 ± 8 days, $p < 0.05$).

Histologic results

Seventeen right lungs and 13 left lungs served for the evaluation. Twenty lungs were characterized by diffuse nonspecific alveolar damage with alveolar edema, hyaline membranes, interstitial fibrosis, type 2 pneumocyte proliferation and pulmonary artery abnormalities (wall thickening and thrombosis). Of these 20 lungs, 85% were superinfected with widespread bronchopneumonic foci. Six lungs were characterized by lesions of confluent bronchopneumonia predominating in posterior lung segments. Four lungs were characterized in posterior lung segments. Four lungs were characterized by massive pulmonary contusion with extensive lung hematoma.

Airspace enlargement was identified in 26 of the 30 lungs examined (87%); alveolar overdistension was observed in 16 lungs and intraparenchymal pseudocysts in 23 lungs. Alveolar overdistension was found isolated in 2 patients and associated with intraparenchymal pseudocysts in 14 patients. In 7 patients with alveolar overdistension, one or several pleural aircysts were identified at gross examination (Fig. 1). Pleural aircysts were predominantly found in upper lobes and non-dependent lung segments, were characterized by internal diameters ranging from 0.5–4 cm, and were constantly associated with the presence of subpleural alveolar overdistension. Intraparenchymal pseudocysts were found in inflammatory and fibrotic areas of the lung along pulmonary vascular axis and around foci of bronchopneumonia. Some of them were clearly derived from alveolar ducts when considering their branching pattern and their walls were made of epithelial alveolar cells. In 20 patients, intraparenchymal pseudocysts were surrounded by condensed and inflammatory lung parenchyma (Fig. 2) whereas in 3 patients intraparenchymal pseudocysts were surrounded by fibrotic lung parenchyma (Fig. 3). Mild airspace enlargement (0.8–2.5 mm internal diameter) was observed in 12 lungs, and severe airspace enlargement (2.6–40 mm internal diameter) was observed in 14 lungs (Fig. 4). In 6 lungs, severe damage to terminal bronchioles were observed characterized by bronchiolar dilation, epithelial hyperplasia and metaplasia. Terminal airways entering intraparenchymal pseudocysts were frequently dilated with thickened walls and partial obliteration of the bronchial lumen. Mucosal alterations were also found in larger bronchi.

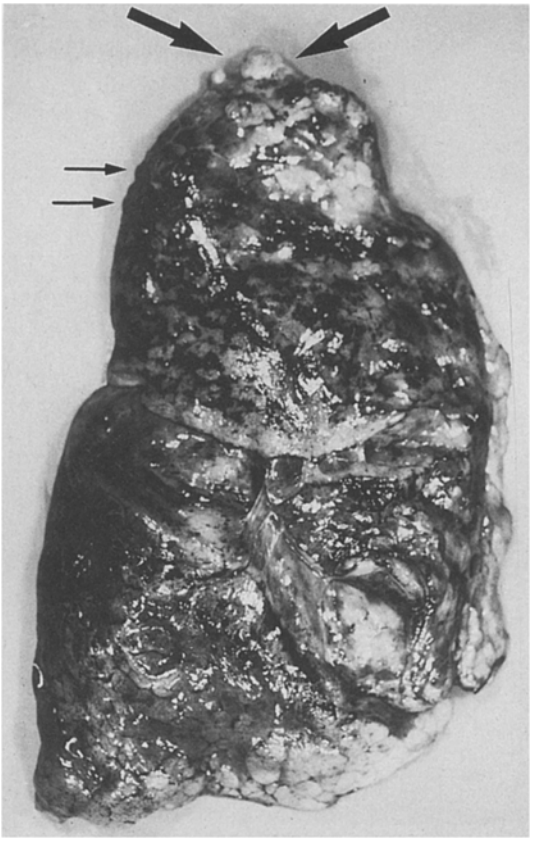

Fig. 1. The photo shows the right lung of a 21-year-old patient who died in the SICU from severe ARDS after 12 days of continuous positive pressure ventilation. He was initially admitted for a combination of head trauma, bone fractures and pulmonary contusion following a motorbike accident. The entire lung is markedly altered with areas of consolidation predominating on upper lobe and posterior segments of the inferior lobe (lung weight: 880 g). A large subpleural aircyst, 4 cm internal diameter is present on the apical segment of the upper lobe (*large arrows*). The pleural surface of anterior and posterior segments of the upper lobe are distorted by numerous underlying cysts (*small arrows*)

As shown in Table 1, patients with severe airspace enlargement had a significantly greater rate of pneumothorax, were ventilated using greater peak airway pressures and higher tidal volumes, were exposed significantly longer to toxic levels of oxygen ($FIO_2 > 0.6$) and lost more weight than patients with mild airspace enlargement. Alveolar rupture was commonly observed in patients with mild and severe airspace enlargement (Fig. 6). The 10 pneumothoraces were observed in the 26 patients with airspace enlargement and the 2 bronchopleural fistulae were observed in 2 patients with severe airspace enlargement.

Discussion

This study shows that bronchiolar distension, alveolar overdistension and intraparenchymal pseudocysts are

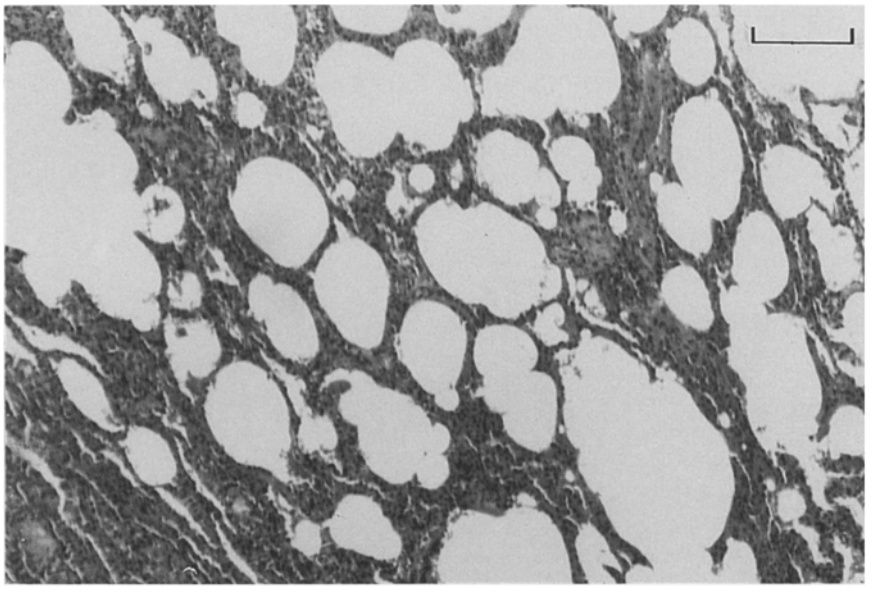

Fig. 2. Photomicrograph of a lung section obtained from an inflammatory lung area of the left lower lobe of a 28-year-old man who died from severe ARDS after 7 days of continuous positive pressure ventilation (tidal volume = 650 ml, peak inspiratory pressure = 45 cmH_2O, PEEP = 10 cmH_2O). He was initially admitted for a peritonitis complicating an appendicectomy. Typical intraparenchymal pseudocysts are present, made of distended alveolar spaces and surrounded by atelectatic and inflammatory lung parenchyma (hematoxylin-eosin-safran stain; magnification×10; *horizontal bar* represents 1000 μm)

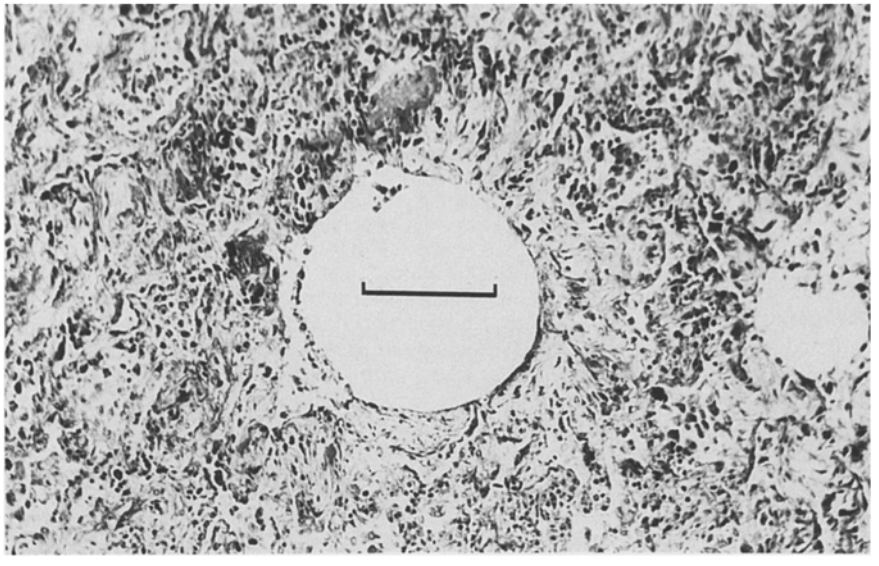

Fig. 3. Photomicrograph of a lung section obtained from the right inferior lobe of a 41-year-old woman who died in the SICU with a severe ARDS after 29 days of continuous positive pressure ventilation (tidal volume = 720 ml, peak inspiratory pressure = 31 cmH_2O, PEEP = 8 cmH_2O). She was initially admitted for a toxic shock syndrome. The lung parenchyma is dense and markedly fibrotic. A typical intraparenchymal pseudocyst is present with an internal diameter of 1.8 mm (trichrome stain; magnification×10; *horizontal bar* represents 1000 μm)

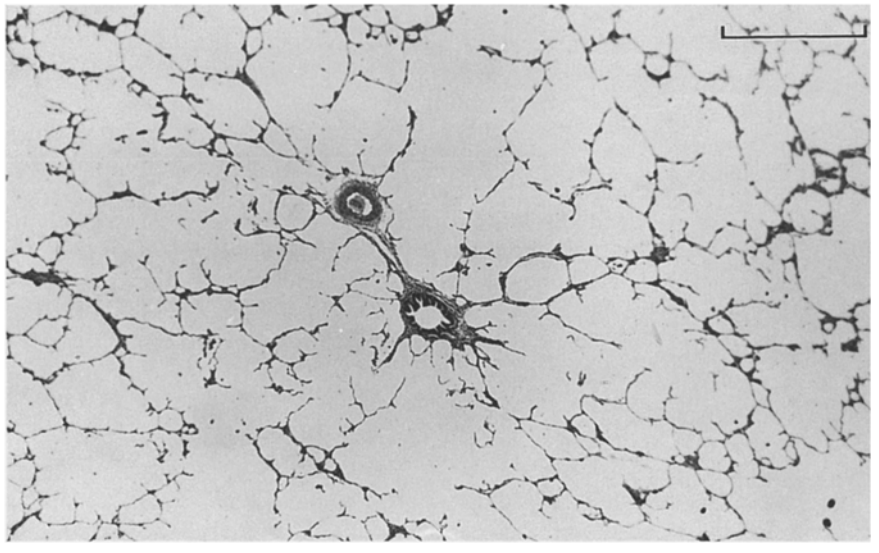

Fig. 4. Photomicrograph of a lung section obtained from a non-inflammatory lung area of the right upper lobe of a 31-year-old man who died in the SICU with an extensive bronchopneumonia of both inferior lobes after 14 days of continuous positive pressure ventilation (tidal volume = 690 ml, peak inspiratory pressure = 39 cmH_2O, PEEP = 12 cmH_2O). He was initially admitted for multiple trauma following a car accident. Mild airspace enlargement, made of alveolar overdistension is present around a bronchovascular axis (hematoxylin-eosin stain; magnification×10; *horizontal bar* represents 1000 μm)

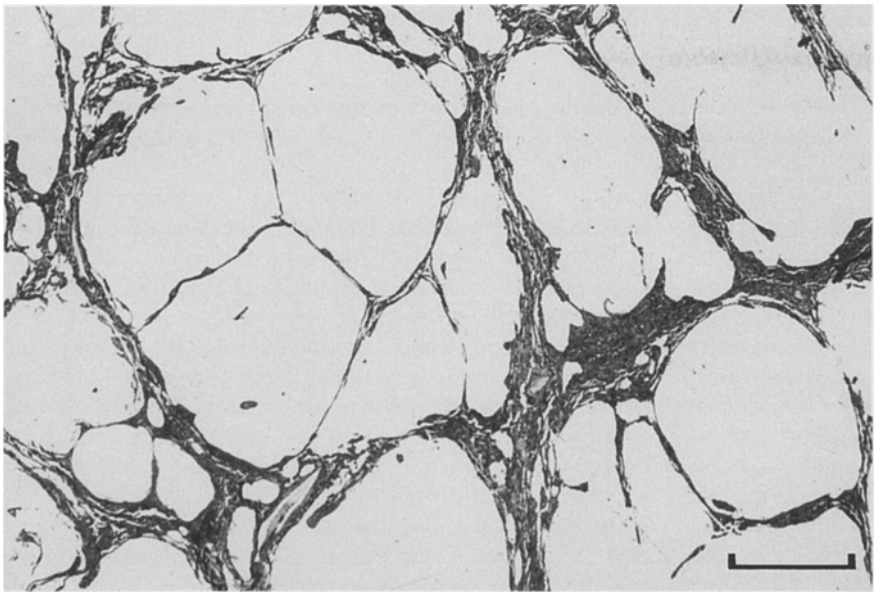

Fig. 5. Photomicrograph of a lung section obtained from a non-inflammatory lung area of the left upper lobe of the same patient as in Fig. 2. Severe airspace enlargement made of alveolar overdistension with destruction of alveolar septa is present (hematoxylin-eosin-safran stain; magnification×10; *horizontal bar* represents 1000 μm)

commonplace in ventilated adult patients with severe acute lung disease. We found that 87% of the lungs of young adult patients who died after a period of mechanical ventilation required for severe acute respiratory failure, had airspace enlargement varying in size, ranging from 0.8 mm–4 cm. These lesions appear different from bronchopulmonary dysplasia observed in neonates with hyaline membrane disease [4] and reported only episodically in adults [7, 8]. In lung areas free of inflammatory lesions, airspace enlargement was made of alveolar overdistension characterized by an increase in alveolar airspace size frequently associated with rupture and destruction of alveolar septa and without fibrotic thickening of alveolar walls. In lung areas characterized by inflammatory and fibrotic lesions, airspace enlargement was made of intraparenchymal pseudocysts clearly derived from alveolar ducts and terminal bronchioles. The high incidence of distended terminal airways and overexpanded airspaces suggests that pseudocyst formation was generated by mechanical ventilation-induced hyperpressure within poorly aerated lung areas. Pleural aircysts were identified in 7 patients at gross examination. As previously described [14], these pleural cysts were not connected to the bronchial tree since lung fixation was not associated with an increase in their size. In fact, as pneumothorax, subcutaneous emphysema and pneumomediastinum, they represent one aspect of pulmonary interstitial emphysema. The typical aspect of bronchopulmonary dysplasia, characterized by overexpanded airspaces with fibrotic wall thickening was never observed in this series of patients. As well, no cavitating lung infarction due to pulmonary thromboembolism [15] was observed in any of the lungs examined. Airspace enlargement found at autopsy was associated with a high incidence of clinical barotrauma; 38% of the patients with airspace enlargement had clinical evidence of pulmonary barotrauma while on mechanical ventilation. Conversely, all patients with clinical evidence of lung barotrauma were found to have airspace enlargement at autopsy. The more severe airspace enlargement, the more frequent the occurrence of pneumothorax. These results suggest that lung barotrauma complicating mechanical ventilation is

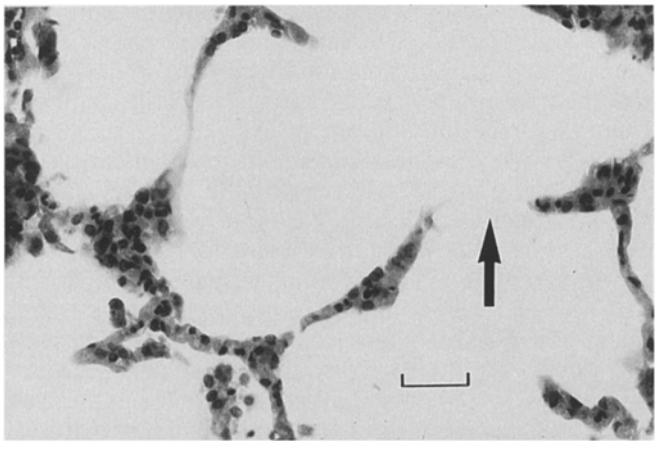

Fig. 6. Photomicrograph of a lung section of one of the patients, showing alveolar rupture (*large arrow*) and thinning of an alveolar septa preceding alveolar rupture (hematoxylin-eosin stain; magnification×250; *horizontal bar* represents 40 μm)

Table 1. Clinical characteristics of patients with mild ($n = 12$) and severe ($n = 14$) airspace enlargement (alveolar overdistension and/or intraparenchymal pseudocysts)

Airspace enlargement	Mild ($n = 12$)	Severe ($n = 14$)
Pneumothorax	2	8 NS
Peak Paw (cmH_2O)	44±10	56±18*
Tidal volume (ml/kg)	9±2	12±3*
Lung weight (kg)	0.714±0.329	0.703±0.262 NS
Days in septic shock	3.4±4.2	3.4±3.2 NS
Days at $FIO_2 > 0.6$	1.9±2	8.6±9.4*
Weight loss (kg)	0.75±5.8	6.3±9.2*

*$p < 0.05$

related to the existence of alveolar overdistension and intraparenchymal pseudocysts. When alveolar overdistension was associated with destruction of alveolar septa without any associated fibrotic proliferation, the lesions were virtually undistinguishable from pulmonary emphysema.

Causes of lung emphysema can be multifactorial, involving destruction of lung tissue related to the acute lung disease itself, prolonged exposition to toxic levels of oxygen [16], denutrition [17], chronic endotoxinemia [18] and, possibly, positive pressure mechanical ventilation. Experimentally, it is possible to produce emphysematous lesions in rats exposed to 98% O_2 for 60 h [16]. A relatively short exposure to toxic amounts of O_2 induces lung collagen degradation, disruption of alveolar connective tissue and progressive airspace enlargement. In this study, we found that the longer the patient was exposed to $FIO_2 > 0.6$, the higher was the risk of pneumothorax and the more severe was alveolar overdistension at autopsy. Food restriction and starvation also invariably produce emphysema-like lesions in experimental rats [17, 19]. We found that the severity of airspace enlargement at autopsy was statistically related to the amount of weight lost during the patient's stay in the SICU. Experimentally, endotoxin-induced chronic leucocyte sequestration in the lungs results in mild emphysema [18]. Dogs receiving 50 injections of small doses of *Escherichia coli* endotoxin during 17 weeks, develop histologic evidence of airspace enlargement and emphysema characterized by a significant increase in mean linear intercept. Because proteolytic pulmonary injury due to the repetitive release of leukocyte elastase is the most attractive hypothesis, it has been suggested that alterations typical of chronic lung diseases share some pathogenic mechanisms with acute lung diseases [20]. Neutrophil elastase, which can be found in the bronchoalveolar lavage fluid of patients with bronchopneumonia and ARDS [21], might induce lung elastin degradation and could contribute to alveolar rupture and airspace enlargement. More than 80% of our patients with airspace enlargement were in septic shock (8 of them for a period longer than 7 days) and, in two-thirds, intraparenchymal pseudocysts were predominantly found in areas of bronchopneumonia. Prolonged septic shock and lung superinfection, through accumulation of polymorphonuclear leucocytes into the pulmonary circulation [22] and the alveolar spaces [14], might have been important pathogenic factors in the development of airspace enlargement.

Can mechanical ventilation alone be the cause of airspace enlargement in adult patients with acute respiratory failure? The answer is unknown. However, some indirect arguments suggest a negative answer. First, airspace enlargement was initially described prior to the use of mechanical ventilation in spontaneously breathing patients with various forms of acute respiratory failure [2]. Second, experimental mechanical ventilation-induced lung damage consists of a pulmonary permeability-type edema and airspace enlargement is not observed at autopsy [23–26]. Third, perivascular intersittial emphysema and alveolar rupture can be produced experimentally by applying high peak airway pressures and lung hyperinflation to anesthetized rabbits with normal pulmonary function [1]. However, intertitial emphysema appears as a perivascular cuff of air around pulmonary arterioles and intraparenchymal aircysts are not observed. Fourth, as previously discussed, emphysema-like lesions can be reproduced experimentally by several methods including exposure to hypoxia [16], starvation [17] and repetitive endotoxemia [18], all factors often present in critically ill patients independent of mechanical ventilation. If it is very likely that mechanical ventilation per se cannot directly produce emphysema-like lesions, its aggravating role is quasi-certain. In neonates with hyaline membrane disease, it has been clearly suggested that the use of high peak airway pressures during mechanical ventilation induces terminal airway injury characterized by narrowing and obstruction of the lumens by epithelial hyperplasia and fibroblastic proliferation [6]. It has been hypothetized that bronchial obliteration contributes to cyst formation by compensatory dilatation of neighboring bronchioles and by valvular mechanisms in which bronchioles enter cysts in a tangential or angulated fashion [5]. The fact that we found a high incidence of bronchial injury in our patients with airspace enlargement, supports the idea that mechanical ventilation with high peak airway pressure played a role in its pathogenesis. We found that pneumothorax incidence and peak airway pressure related to mechanical ventilation were greater in patients with severe airspace enlargement than in patients with mild airspace enlargement. This result could be related to the fact that lungs with severe airspace enlargement were more severely injured than lungs with mild airspace enlargement. However, lung weight, which is a good index of the severity of the respiratory disease, was exactly comparable in both groups, rendering this explanation unlikely. More likely, our results suggest that the use of high peak airway pressures and large tidal volumes during mechanical ventilation tends to increase the size of alveolar overdistension and intraparenchymal pseudocysts and to augment the risk of pneumothorax.

In conclusion, underlying histologic lesions likely responsible for clinical lung barotrauma consist of alveolar overdistension and intraparenchymal pseudocysts. These lesions are commonplace in adult patients with severe acute respiratory failure requiring mechanical ventilation, and are likely of multifactorial origin. Rather than being the direct cause of airspace enlargement, mechanical ventilation appears an aggravating factor, particularly when high peak airway pressures and large tidal volumes are generated by the ventilator. As suggested by a recent experimental study performed in premature baboons with hyaline membrane disease [27], reducing peak airway pressures and cyclic volume expansion in patients with severe acute respiratory failure, might be one among many other factors which could contribute to decrease the extent of intraparenchymal pseudocysts, alveolar overdistension, pulmonary interstitial emphysema and air leaks, all factors leading to acute pulmonary barotrauma.

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