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Changes in lung parenchyma after acute respiratory distress syndrome (ARDS): assessment with high-resolution computed tomography

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Abstract The aim of this study was to evaluate the appearance, extent, and distribution of parenchymal changes in the lung after acute respiratory distress syndrome (ARDS) as a function of disease severity and therapeutic procedures. High-resolution computed tomography (HRCT), clinical examination, and lung function tests were performed in 15 patients, 6–10 months after ARDS. The appearance and extent of parenchymal changes were compared with the severity of ARDS, as well as with clinical and therapeutic data. Lung parenchymal changes resembling those found in the presence of pulmonary fibrosis were observed in 13 of 15 patients (87 %). The changes were significantly more frequent and more pronounced in the ventral than in the dorsal portions of the lung ($p < 0.01$). A significant correlation was observed between the extent of lung alterations and the severity of ARDS ($p < 0.01$), and the duration in which patients had received mechanical ventilation either with a peak inspiratory pressure greater than 30 mmHg ($p < 0.05$), or with more than 70 % oxygen ($p < 0.01$). Acute respiratory distress syndrome frequently is followed by fibrotic changes in lung parenchyma. The predominantly ventral distribution of these changes indicates that they may be caused by the ventilation regimen and the oxygen therapy rather than by the ARDS.

Keywords Acute respiratory distress syndrome · CT · Lung fibrosis

Introduction

The acute respiratory distress syndrome (ARDS) is a life-threatening complication of various types of lung injury [1]. The disease affects approximately 150,000 individuals each year in the United States [2]. Some of the etiologic factors underlying ARDS are shock, contusion, infection, sepsis, aspiration, drug abuse, and inhalation of noxious substances. The diagnosis is based on three hallmarks of the disease: impaired diffusion capacity; reduced compliance of the lung; and radiologically detectable lung opacities [3]. Despite aggressive treatment strategies, the mortality rate for ARDS has not changed significantly over the past few decades and remains approximately 50 % [4, 5].

The follow-up and treatment of patients who survive ARDS episodes is of major importance for economic, social, and forensic reasons; however, there are few definite statements in the literature regarding the frequency and nature of the persistent changes in lung parenchyma after ARDS episodes [6]. In some studies histopathologic analysis has revealed fibrotic changes and vicarious emphysema in patients who had experienced ARDS [7, 8, 9]; however, these findings are based

on a few isolated case reports of patients who survived ARDS but died a few months later of some other disease, and were subsequently autopsied. Previous reports have stated [2, 10] that ARDS itself is responsible for these fibrotic alterations in the lung; however, it is also known that treatment with high concentrations of oxygen and prolonged positive pressure breathing cause fibrotic changes in the lung [11, 12]. It is unclear to which extent therapeutic measures prevent or influence the development of chronic changes in lung parenchyma.

The aims of this study were to evaluate the incidence and nature of morphologic lung parenchymal changes after ARDS, using high-resolution computed tomography (HRCT), and to determine the impact of therapeutic measures and the disease course on the appearance and the extent of parenchymal damage (morphologic changes), clinical parameters, and lung function impairment.

Materials and methods

Research plan and patients

We prospectively examined 15 patients who had developed ARDS after polytrauma: examinations were performed 6–10 months (mean 8.3 months) after ICU discharge. No patient was older than 45 years of age and all had been treated for ARDS after polytrauma at the general intensive care unit of a university hospital within a recruitment period of 12 months. The ARDS was diagnosed if the following three criteria were fulfilled:

1. A PaO_2/FIO_2 ratio of less than 150 mmHg
2. Diffuse infiltrates involving all lung fields on chest radiographs
3. Pulmonary artery wedge pressure less than 18 mmHg [4, 13].

Patients with a history of pre-existent lung disease were excluded from the study. Five of the 15 study patients presented with primary thoracic injuries after polytrauma, in 1 patient no sufficient information was available, and in 9 patients no initial pulmonary injury was present. Of the patients with primary thoracic injury, 1 patient suffered from rib fractures, 1 patient had a lung laceration and rib fractures, and 3 patients suffered from pulmonary contusions. In one of the 5 patients the opacifications were located predominantly ventrally. In 3 patients they were situated dorsally, being considered contusional in 2 patients and due to atelectasis in 1 patient. The fifth patient showed diffuse infiltrations in the basal segments of the right lung (ventrally and dorsally). Five of the 15 patients were smokers (5–20 cigarettes per day; mean 12.5 cigarettes). The ages of the 11 men and 4 women ranged from 10 to 45 years (mean age 22 years). The severity of the ARDS was assessed according to the criteria proposed by Murray et al. [3] on a scale of 0–4.

During the acute phase of ARDS, all patients had been admitted to the intensive care unit for 26–65 days (mean 34 days). The patients were maintained on a respirator for 17–63 days (mean 34 days), with a positive end-expiratory pressure of 9–13 mmHg (mean 11 mmHg) applied for 12–38 days (mean 22 days). The maximum inspiratory pressure varied from 32 to 50 mmHg (mean 41 mmHg), whereas maximum levels of oxygenation (FiO_2) varied from 70 to 100% (mean 86%). More than 70% oxygen concentration was administered for 2–11 days (mean 3 days). Three patients were treated with high-frequency respiration (jet-ventilation) for 4–12 days (mean 9 days). Hemofiltration was performed in 11 patients for 3–24 days (mean 11 days) and inverse ratio ventilation (IRV with a longer time period for inspiration than for expiration) in 13 patients for 9–27 days (mean 16 days). The number of nonpulmonary organ systems affected by ARDS (multi-organ failure) varied between 1 and 3 (mean 2.1), and a sepsis syndrome was observed in 10 patients [14].

Methods

The post-ARDS evaluation consisted of a clinical examination, lung function tests, and high-resolution computed tomography (HRCT) of the chest, all performed within 1 day. Each patient gave informed consent.

Clinical examination

Intra-arterial blood gas analysis was performed and O_2 and CO_2 partial pressures were determined. A $PaO_2 > 80$ mmHg and a $PaCO_2 < 46$ mmHg were considered normal and were assigned a blood gas score of 0 (zero). All other values were assigned a blood gas score of 1. Diffusion capacity was not assessed because not all post-traumatic patients were able to perform the necessary procedure. Dyspnea was registered if reported by the patient and was graded on a rating scale from 0 to 3 (0 = no dyspnea; 1 = dyspnea on heavy exertion; 2 = dyspnea on slight exertion; 3 = dyspnea at rest). The extent of cardiac failure was assessed in each patient according to the guidelines recommended by the New York Heart Association (NYHA) and was rated on the NYHA rating scale from 0 to 4 (0 = normal; 1 = NYHA I; 2 = NYHA II; 3 = NYHA III; 4 = NYHA IV). The patients' rehabilitation status was graded from 0 to 3 as follows: 0 if the patient was back at work; 1 if the patient was not at work but could take care of himself or herself; 2 if the patient needed support; and 3 if the patient was in need of regular care.

An overall clinical score was calculated by averaging these scores. We classified mean values of 1.3 or below as normal, values above 1.3 and below 1.7 as minor clinical abnormalities, values above 1.7 and below 2.0 as moderate, and values above 2.0 as severe abnormalities.

Pulmonary function tests

The forced vital capacity (FVC) and the forced expiratory volume in one second (FEV1) were determined using a Pneumoscreen (Jaeger, Wuerzburg, Germany). Residual volume was determined by the helium dilution method. The total lung capacity (TLC) was calculated by adding the residual volume to the inspiratory vital capacity. The predicted values for each subject, based on gender, age, and height were obtained from standard tables [15]. Data were expressed as percentages of predicted values. Lung function was regarded as abnormal if lung volumes were less than 80% of predicted values. Obstruction was defined as FEV1/VC less than 80% of the predicted value, whereas restriction was defined as VC less than 80% of the predicted value.

Computed tomography

The CT scanning was performed using either a Tomoscan 2000 (Toshiba, Tokyo, Japan) or a Somatom Plus (Siemens, Erlangen,

Table 1 Radiological findings: high-resolution CT patterns in acute respiratory distress syndrome follow-up

	Patients *(n)*	Distribution
Septal lines	13	3 widespread, 10 localized
Non-septal lines	6	Localized
Parenchymal bands	5	Localized
Subpleural or intrapulmonary cysts	2	Localized
Areas of decreased attenuation	3	Widespread
Areas of ground-glass attenuation	1	Localized
Architectural distortion	2	Localized
Consolidation, traction bronchiectasis	1	Localized
Honeycombing	3	Localized

Germany) scanner, with 2-mm collimation at 20-mm intervals from the apex of the lungs to below the costophrenic angle. The scans were obtained using a 512 × 512 matrix of reconstruction, and either 130 kV and 420 mA (Toshiba), or 137 kV and 255 mA (Siemens). The lung was evaluated at suspended end-inspiratory volume. The images were reconstructed with a high spatial frequency algorithm for lung analysis and were viewed at lung window settings (window width 1600 HU; window level –600 HU). All patients underwent scanning in the supine position and no intravenous contrast material was used.

Radiologic analysis

The CT images were reviewed in random order by three radiologists who were blinded to the patients' clinical condition and lung function. Final conclusions were reached by consensus.

To quantify the lung parenchymal changes the following scoring system was defined: The lung parenchyma was divided into 12 compartments on each side, namely the apical, middle, and basal zones, each consisting of a central, ventral, lateral, and dorsal compartment. Parenchymal changes were considered "localized" when they were present in less than one-third of each compartment. For each patient the presence and extent of the following morphologic changes were separately assessed and grouped into three severity classes of parenchymal destruction.

Linear opacities (septal lines, nonseptal lines, and parenchymal bands) and subpleural or intrapulmonary cysts were graded as minor lung parenchymal changes. Each compartment was assigned a score of 0 if none of these signs were found, 1 if at least one of these findings was seen in a localized distribution, and 2 if at least one of the findings was widespread.

Areas with decreased lung attenuation, ground-glass opacities, and architectural distortion, as indicated by bronchiectasis, vascular rarification and distraction, and hyperinflation were classified as lung parenchymal changes of moderate severity. These areas were given a score of 0 if none of these signs were found, 2 if at least one of these findings was seen in a localized distribution, and 4 if at least one of the findings was widespread.

Honeycombing (cystic spaces with thickened walls) or consolidation with traction bronchiectasis were graded as severe lung parenchymal changes and were given a score of 0 if none of these signs were found, 3 if at least one of these findings was seen in a localized distribution, and 6 if at least one of the findings was widespread.

The radiologists determined radiologic changes for each of the 24 compartments per patient. In addition, an overall HRCT score for each patient was calculated by averaging all compartment scores. The distribution of findings was assessed by calculating the mean score of the compartments according to anatomic location.

Statistical analysis

For statistical evaluation, the mean HRCT score was correlated to clinical and functional data and to the patient's history of illness using the Spearman rank correlation; a p-value of $p \leq 0.05$ was considered significant. Significance of difference between the radiologic scores for the various compartments was tested by Student's t-test.

Results

Clinical examination

In the clinical examination, 13 of 15 patients (86.7 %) showed a normal or slightly impaired status, with 7 reporting only shortness of breath on heavy exercise. The remaining 2 patients had moderate to severe problems which were attributable to the trauma itself rather than to the ARDS. One patient was paralyzed on the left side due to polytrauma, and the other patient suffered from a lesion of the right brachial plexus after an accident but was not in need of regular care.

Pulmonary function test

The pulmonary function tests showed a mild restrictive pattern in 5 of 15 cases (33 %) with vital capacities between 60 and 79 % of predicted value. Vital capacity was < 60 % of predicted values in 2 of 15 cases (13 %). A mild obstructive disorder (FEV1/VC ratio < 80 % but > 60 % of predicted values) was observed in 5 of 15 patients (33 %).

Evaluation of HRCT

Table 1 shows the frequency of parenchymal changes. The most commonly seen abnormalities were thickened interlobular septa, which were found in 13 of 15 patients (87 %). Thickened septa were present in a widespread distribution in 3 cases in at least one compartment. The remaining changes were observed in less than 50 % of patients. Less frequent changes were non-septal lines (6 patients), parenchymal bands (5 patients), and subpleural or intrapulmonary cysts (2 patients). All these findings were seen only in a localized distribution.

Areas of decreased attenuation were seen in 3 patients and were widespread in all of them in at least one compartment. Localized ground-glass opacification was

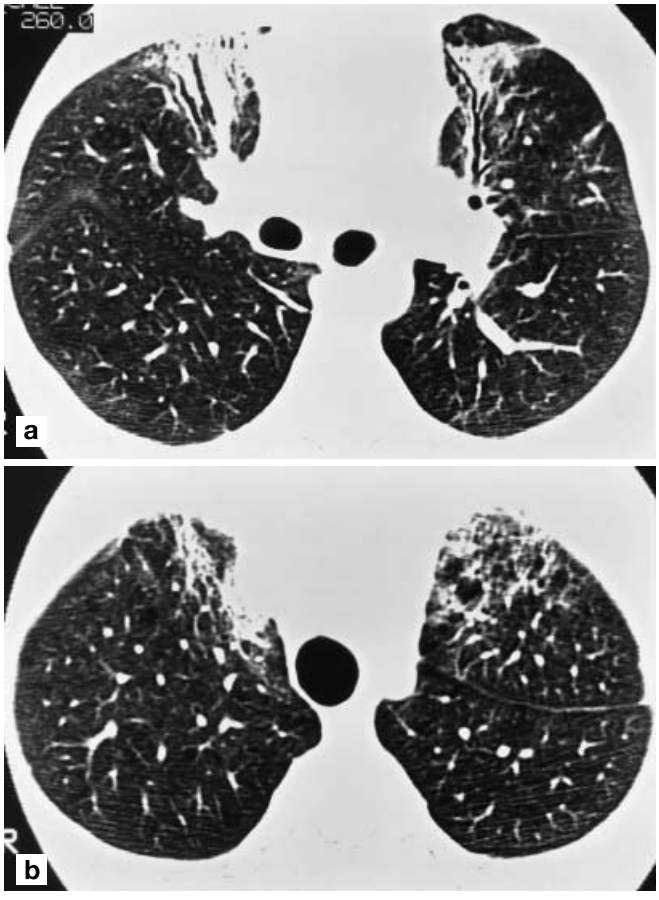

Fig. 1 **a** A 21-year-old man, 9 months after acute respiratory distress syndrome (ARDS). High-resolution computed tomography (HRCT) scan of the level of the hila shows localized parenchymal opacification with traction bronchiectasis in the ventral lung zone, probably representing localized fibrosis. **b** In the same patient, HRCT scan through the upper lobes shows architectural distortion and honeycombing exclusively located in the ventral lung zone

seen in 1 patient. Architectural distortion and honeycombing were always localized and seen only in 2 and 3 patients, respectively. One patient presented with intense opacification/consolidation with traction bronchiectasis also in a localized distribution.

Parenchymal changes were significantly more frequent and more pronounced in the ventral compartments compared with the dorsal sections of the lungs (Figs. 1a, b, 2); Table 2). Subpleural cysts, observed in 2 patients, and honeycombing, the most severe type of parenchymal changes and observed in 3 patients, were found exclusively in the ventral zones of the lung. No statistically significant difference was found between the apical and basal zones of the lung with regard to the frequency of the parenchymal changes.

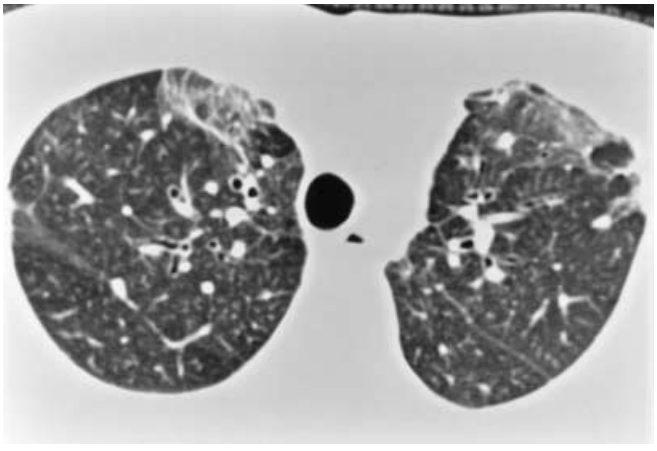

Fig. 2 A 23-year-old woman, 8 months after ARDS. The HRCT scan through the upper lobes presents ground-glass opacities in the ventral zone, thickened interlobular septa, and few parenchymal strands in the ventral and lateral parenchymal lung zone

Statistical correlation of HRCT with other findings

Statistical analysis showed a significant correlation between the severity of CT findings and the severity of ARDS (Murray score; $p < 0.05$; (Table 3). With respect to the breathing regimen, the duration of mechanical ventilation with an O_2 peak > 70 % ($p < 0.05$) and a peak pressure over 30 mmHg ($p < 0.05$) significantly correlated with the CT score. Duration of mechanical ventilation, PEEP level, Jet, maximal pressure, and peak oxygen pressure did not show a significant correlation. Both clinical score and total lung function also did not correlate with CT findings.

Discussion

The ARDS is a severe disorder with only approximately 50 % of patients surviving the full-blown disease [4, 5]. Those patients may suffer from long-term changes in lung parenchyma that impair quality of life to varying degrees and result in economic consequences for both community and patients.

Despite the similarities in the clinical features of the acute stage, and despite very sophisticated and aggressive treatment, the prognosis of ARDS survivors varies from complete recovery to severe clinical impairment. Most investigations who have tried to predict and influence the course of the disease and the outcome have concentrated on data from the acute phase [5, 11, 12, 16, 17]. To date, most studies of the sequelae of ARDS have focused on either lung function [7, 18, 19], histopathologic findings in autopsies of non-survivors [20, 21], or laboratory studies [22]. As far as we know, only a few follow-up studies have evaluated radiologic examina-

Table 2 Distribution of parenchymal changes: severity (mean high-resolution CT score) in each zone and significance of the differences

Zones	Score	Significance *(p)*[a]
Apical	0.44	
Middle	0.44	
Basal	0.44	n.s.
Central	0.19	
Peripheral	0.21	n.s.
Ventral	1.11	
Lateral	0.21	
Dorsal	0.20	< 0.05

[a] Significance of the zonal differences

tions in survivors [6, 23]. The mechanisms that finally lead to fibrotic changes in ARDS are still a subject of discussion [2, 6, 10, 11, 12]. In our study, we characterized the sequelae of ARDS radiographically and correlated them with clinical and functional data.

The clinical impairment in our patients was mild in almost all patients without a statistically significant correlation with the radiographic changes. In the literature, the incidence of clinical abnormalities following ARDS varies: whereas in one study mild to moderate dyspnea occurred in only 10 % of patients with 83 % of patients being totally asymptomatic [2], other studies reported symptoms in 30 % [24] to 55 % [25]. In most previous studies, radiologic findings were compared with lung function abnormalities and not with clinical symptoms [2, 10, 24, 26, 27]. There is only one study that reported a positive correlation between clinical symptoms and the length of exposure to ventilation with a high concentration of oxygen ($Fi_O2 > 0.6$) and duration of ARDS [7], indicating that both parameters are likely to influence the severity of radiographic findings.

Analysis of lung function tests demonstrated a restrictive ventilation disorder in nearly half (47 %) of our patients, with a severe disorder evident in only 2 patients. Restriction was accompanied by obstruction in a few cases. In previous studies, the incidence of restrictive disorders in ARDS survivors varied between 22 and 100 % [2, 24, 26, 27]. We believe that the restrictive disorder in our patients was caused by the fibrotic changes seen with HRCT, although a significant correlation could not be found. The sensitivity of HRCT for the depiction of parenchymal changes is known to be superior to other imaging methods [28]. In our study, HRCT revealed parenchymal abnormalities in 3 patients with normal lung function tests. In 2 patients severe HRCT abnormalities with only slightly impaired lung function tests were found. In those 2 patients the abnormalities were predominantly located in the upper lung zones while the middle and basal lung areas were well ventilated. So we assume that the discrepancy between severity of HRCT changes and pulmonary function is due to the fact that the upper lobes represent a relatively silent region where extensive destruction might occur before functional abnormalities become known [29]. This underlines the fact that HRCT reveals parenchymal changes prior to the development of consecutive clinical symptoms.

High-resolution CT failed to show a clear morphologic substrate in only 1 patient who did have evidence of functional impairment; however, this patient also suffered from partial paralysis resulting in lower thoracic excursions.

In the majority of patients, the parenchymal changes seen with CT were similar to those described in the presence of interstitial lung disease and fibrosis [30]. Of our group, 87 % of the patients showed parenchymal changes. The majority of observed abnormalities were classified as mild. Thickened interlobular septa were the

Table 3 Radiologic score vs clinical and therapeutic data using Spearman rank correlation

		Correlation coefficient *(r)*	Significance
Clinical score		0.48	0.09
Lung function	Total	0.24	0.68
	TLC	0.01	1.0
	VC	0.23	0.54
	FEV1	0.01	0.99
	FEV1/VC	0.09	0.75
Murray score		0.58	0.03
Sepsis score		0.57	0.06
Breathing regimen	Duration of O_2 peak > 70 %	0.80	0.006
	Duration of high inspiratory pressure	0.62	0.03
	P-max	0.52	0.07
	Duration of mechanical ventilation	0.32	0.28
	PEEP level	0.24	0.34
	Jet	0.26	0.47
	Peak O_2 pressure	0.20	0.49

most frequently found feature, and the only one that was found in a widespread distribution in 3 patients. Less frequent and always localized changes included non-septal lines, parenchymal bands, and subpleural or intrapulmonary cysts.

In 33 % of patients, moderate to severe lesions were detected. Ground-glass attenuation occurred in only 1 patient, which may be partially due to the fact that we examined patients at least 6 months after extubation and ground-glass opacification represents a feature seen more frequently in the acute and earlier post-ARDS phase. Desai [6] and co-authors saw ground-glass opacification more frequently, but they performed follow-up examinations after a mean of 196 days (range 110–267 days) compared with a delay in our examinations of 250 days (range 180–300 days).

Architectural distortion, consolidation with bronchiectasis, and honeycombing were found in only a minority of patients ($n = 2$) and were always localized. It is well known that ARDS may lead to lung fibrosis [22]. Histologic examinations revealed fibrotic changes and vicarious emphysema after ARDS accompanied by interstitial pneumonia, lymphocytic infiltrates, fibrosis of the alveolar walls, arterial thickening, thickening of bronchi, and proliferation of type-II alveolar epithelial cells [7, 8, 9]. It is assumed that the inflammatory irritation caused by injury to the alveolar wall during an episode of ARDS triggers a certain reaction leading to fibrous residues in the lung parenchyma; however, ARDS does not always result in fibrotic lung changes and, moreover, if it does, the alterations differ in extent. To date, it is unclear which factors eventually determine this process.

Remarkably, in our patients the lesions were predominantly located in the ventral zones of the lung (< 0.05). The most severe alterations, honeycombing and massive fibrosis with bronchiectasis, were exclusively found in the ventral compartment. This distribution pattern of fibrotic changes after ARDS is in contrast to the widely accepted notion that the morphologic changes seen in acute ARDS primarily affect the dorsal sections of the lung with the patients in the supine position [11, 12, 31]. Our findings correlate well with a study by Finfer and Rocker [32] and a recent study by Desai and co-authors [6]; the latter describe an anterior distribution of follow-up changes in patients after ARDS, whereas in their initial examinations during the acute phase, hyperattenuated areas were predominantly located in the dependent areas. In addition, the extent of intense parenchymal opacification on initial CT scans correlated inversely with a reticular pattern on follow-up scans in their study.

Thus, our results confirm the arguments of previous discussions that this distribution of parenchymal changes in CT in ARDS survivors may be due to the fact that patients during the acute phase of ARDS develop atelectasis in the dorsal sections of the lung that potentially protects the lung from the consequences of aggressive mechanical ventilation and O_2 effects. The dorsal zones therefore can survive the acute phase of the disease without major damage, whereas mechanical ventilation has a more severe traumatizing effect on the ventral sections of the lung, causing persistent lung injury. Further evidence of the role of barotrauma is offered by the presence of subpleural parenchymal cysts [27, 33]. We found them in two of our patients, in both cases localized in the ventral compartments.

There was a positive correlation between the severity of ARDS and the severity of the radiologic findings in our study. On one side, this result could lead to the conclusion that ARDS itself results in fibrotic changes. On the other hand, severe forms of ARDS necessitate highly aggressive and prolonged mechanical ventilation. Moreover, the duration of positive pressure respiration and the duration in which patients received > 70 % oxygen were shown to have a statistically significant influence on the extent of parenchymal changes. This relationship is elucidated by various reports about pulmonary toxicity of high oxygen [18, 34] and barotrauma [33, 35].

There are also histologic studies indicating that parenchymal damage may be attributable to the treatment rather than to the ARDS itself. Collins et al. [20] compared patients who died of ARDS of comparable severity (with respect to primary diagnosis and ventilation time). They found that patients with elevated collagen levels at autopsy had received a higher level of positive end-expiratory pressure and had been on high oxygen ventilation for a longer period than patients without elevated collagen. In another study [21], observed interstitial fibrosis and duration of respiratory failure treatment correlated more strongly than total duration of the original disease.

There are several limitations in our study. The study group was small, yet we could confirm a significant predominance of affected ventral lung portions. Potentially present preexisting diseases of the lung, such as smoking-related emphysema or post-infectious scarring, were only excluded by clinical history but not by an imaging modality. Another problem was the differentiation between direct trauma-related alterations in lung parenchyma and parenchymal changes caused by ARDS. Five of the 15 study patients presented with primary lung injuries after polytrauma; however, in only 1 of the 5 patients those opacifications were located predominantly ventrally which could interfere with the long-term effects due to ARDS in the ventral part of the lung as described in our paper. We did not observe any differences in late changes in the smokers, but the reported number of cigarettes per day and onset of smoking varied, and moreover, the group of patients was very small. The interpretations of the clinical examination and the pul-

monary function tests were based on clinical history. Lung diffusion capacity was not included because its determination was technically impossible in several of our patients.

Conclusion

In conclusion, we were able to show that HRCT permits detection of a wide spectrum of lung parenchymal changes in survivors of ARDS, all of which can also be seen in patients with pulmonary fibrosis. Parenchymal abnormalities do not occur in all cases, they are generally localized, and they show a significant ventral predominance. The exact etiology of these changes remains unclear; however, morphology and distribution of the parenchymal lesions are highly suggestive of the fact that they represent predominantly effects of the ventilation treatment (mechanical ventilation with high pressure and high oxygen) rather than effects of the ARDS itself. Further evaluation with larger study groups, however, is needed to support this finding.

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