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BRIEF REPORT

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# Recovery from lung injury in survivors of acute respiratory distress syndrome: difference between pulmonary and extrapulmonary subtypes

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**Abstract** *Objective:* To determine whether long-term outcome differs between acute respiratory distress syndrome (ARDS) resulting from pulmonary (ARDSp) and extrapulmonary (ARDSexp) causes. *Design:* Observational study. *Setting:* Medical intensive care unit of a university hospital. *Patients:* Twenty-nine ARDS patients (16 ARDSp and 13 ARDSexp) who survived over 6 months after diagnosis. *Measurements and results:* The two groups did not differ according to demographic data and severity indices on admission. The duration of ICU stay (median 21 days [interquartile range, 12–43 days] vs 12 [6.5–20] days, $p$=0.097) tended to be longer and total ventilation time (360 [96–700] h vs 144 [42.5–216] h, $p$=0.045) were longer in the patients with ARDSp. The ARDSp patients showed more severe abnormalities on thin-section computed tomography (CT), including ground-glass opacity (GGO; 6 [3–16] vs 0 [0–2.5], $p$=0.002), reticular density (12 [8–14] vs 5 [2–9], $p$=0.033) and the sum of all four patterns of lesion (20 [11–27] vs 5 [2–12], $p$=0.006). There were no between-group differences in Spitzer's Quality of Life index and the Chronic Respiratory Questionnaire. *Conclusions:* These results suggest that ARDSp would leave more severe lung sequelae than ARDSexp, but the clinical relevance of their difference is questionable.

**Keywords** Acute respiratory distress syndrome · Pulmonary · Extrapulmonary · Long-term outcome

## Introduction

The acute respiratory distress syndrome (ARDS) can be classified as pulmonary (ARDSp) or extrapulmonary (ARDSexp) according to lung insult mechanisms. That is, ARDSexp lungs seem to respond more favorably to alveolar-recruiting maneuvers than do ARDSp lungs [1, 2, 3]. Alveolar cyclic collapse, however, occurs more often in ARDSexp at low end-expiratory volumes, and overdistension is observed more with ARDSp at high lung volumes. These differences appear to lead to different damages to the lung during mechanical ventilatory support. The aim of this study was to determine the differences in pulmonary function, radiological appearance of the lungs and quality of life between ARDSexp and ARDSp survivors.

## Methods

### Patient selection

Of the 172 ARDS patients admitted to the medical intensive care unit of a university hospital between January 1997 and September 2000, 84 patients who survived over 6 months after the onset of ARDS were studied. ARDS was defined according to the criteria established by the American European Consensus Guidelines [4]. Patients were classified as having ARDSp or ARDSexp by two specialists. Patients with overlapping mechanisms of ARDS (7 patients), patients who had factors that could influence the pulmonary function tests (PFT) (12 patients) and patients older than 75 years of age (17 patients) or who expired before the study (11 patients) were excluded. Of the remaining 26 ARDSp and 18 ARDSexp patients, 10 (7 and 3, respectively) could not be found and 5 (3 and 2, respectively) refused to participate, leaving 16 ARDSp and 13 ARDSexp patients who participated in this study. We adopted a low tidal ventilatory strategy (6–8 ml/kg of body weight), permissive hypercapnia, NO gas inhalation, prone positioning and PEEP titration, during the study period. The study was approved by the institutional review board for clinical studies. Written informed consent was obtained from each patient enrolled.

### Measurements

We collected subjects' demographic data retrospectively, including duration of ICU stay, total ventilation time (TVT), maximum level of applied positive end-expiratory pressure (PEEPmax), duration of ventilatory support with $FIO_2$ greater than 0.6, duration of prone positioning and presence of pneumothorax.

Each subject completed a Chronic Respiratory Questionnaire (CRQ) and we used Spitzer's Quality of Life index (QOL) [5]. Each patient had an arterial blood gas analysis (ABGA) at peak exercise using a bicycle ergometer. For each patient, spirometry, diffusing capacity, lung volume by plethysmography and thin-section computed tomography (CT) was obtained. An experienced thoracic radiologist scored all CT scans while blinded to each patient's clinical and lung function information. Radiological terms were used according to the Fleischner Society Nomenclature. CT scores for each pattern were presented as the sum of the scores at apex, mid and lower levels.

### Statistical analysis

All data are reported as medians (interquartile range), unless otherwise specified. The ARDSp and ARDSexp groups were compared using the Mann-Whitney U test for continuous variables, Wilcoxon's signed-rank test for matched pairs for continuous variables and a chi-square test or Fisher's exact test for dichotomous variables. Statistical significance was defined as a *p* value less than 0.05.

## Results

### Patient demographics

There were no statistical differences in demographic characteristics between the ARDSp and ARDSexp groups, including smoking (30 [2–40] vs 5 [0–40] packs/year), lung injury scores (3 [2.6–3.3] vs 2.6 [2.6–3.0]), APACHE III scores (74 [53–88] vs 74 [60.5–100]) and multi-organ dysfunction scores (6 [4–10] vs 9 [4.5–12]) on admission, as well as length of ICU stay (21 [12–43] days vs 12 [6.5–20] days). We did, however, observe a statistical difference in TVT (360 [96–700] h vs 144 [42.5–216] h, $p$=0.045).

### Questionnaire results

The questionnaires were filled in by 29 patients. Spitzer's QOL score for the overall population was 8.4±1.4, which was similar to the score reported in healthy persons (8.8±1.6) [5]. The scores of CRQ and each domain did not differ between the two groups.

### Pulmonary function tests (PFT)

Pulmonary function tests were performed in 27 patients (Table 1). Eight patients showed decreased forced vital capacity (FVC) (5 in the ARDSp group vs 3 in the ARDSexp group) and decreased forced expiratory volume at 1 s ($FEV_1$) (4 in each group) according to American Thoracic Society criteria. Eleven patients (7 vs 4) showed reduced diffusing capacity and six patients (5 vs 1) showed decreased total lung capacity (TLC). Impaired diffusion was the most prevalent abnormality in our subjects, with 16 of 27 patients (59.2%) showing im-

**Table 1** Pulmonary function test (PFT)

| | ARDSp (*n*)* | ARDSexp (*n*)* | *p* |
|---|---|---|---|
| Spirometry | | | |
| FVC | 82±15 (5) | 94±17 (3) | 0.102 |
| $FEV_1$ | 89±20 (4) | 94±17 (4) | 0.494 |
| $FEV_1$/FVC | 83±11 (1) | 74±11 (3) | 0.020 |
| DL/VA | 83±15 (7) | 88±21 (4) | 0.392 |
| TLC | 89±11 (4) | 99±18 (1) | 0.108 |
| Exercise PFT | | | |
| $VO_2$max | 72.0±12.5 | 80.0±15.1 | 0.211 |
| AT | 45.4±13.5 | 45.1±9.4 | 0.853 |

Values are mean ± standard deviation of percent predicted, except for $FEV_1$/FVC (%) and AT (% of own $VO_2$max).
* Numbers in parentheses are the numbers of patients with abnormal values.
*FVC* forced vital capacity, *$FEV_1$* forced expiratory volume in 1 s, *DL/VA* carbon monoxide transfer coefficient compensated alveolar volume, *TLC* total lung capacity, *$VO_2max$* maximum oxygen uptake, *AT* anaerobic threshold

**Table 2** Correlation matrix for the clinical characteristics and pulmonary function test and quality of life*

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| 1. ICU stay | 1.0 | | | | | | | | |
| 2. TVT | 0.896 | 1.0 | | | | | | | |
| 3. FVC | –0.655 | –0.579 | 1.0 | | | | | | |
| 4. $FEV_1$ | –0.636 | –0.585 | 0.819 | 1.0 | | | | | |
| 5. $DL_{CO}$ | –0.638 | –0.642 | 0.667 | 0.663 | 1.0 | | | | |
| 6. TLC | –0.597 | –0.489 | 0.826 | 0.582 | 0.619 | 1.0 | | | |
| 7. $VO_2$max | –0.603 | –0.547 | 0.614 | 0.597 | 0.453 | 0.542 | 1.0 | | |
| 8. AT | –0.380 | –0.233 | 0.268 | 0.163 | 0.194 | 0.467 | 0.669 | 1.0 | |
| 9. QOL | –0.028 | 0.013 | –0.004 | 0.156 | –0.021 | 0.083 | 0.442 | 0.441 | 1.0 |

* Pearson correlation coefficient. Strength of the correlation can be divided into weak ($0.1\leq |r| <0.3$), moderate ($0.3\leq |r| <0.5$) or strong ($|r| \geq 0.5$). The square estimates the percentage of shared variance between the two variables.
*TVT* total ventilation time, *FVC* forced vital capacity, *$FEV_1$* forced expiratory volume in 1 s, *$DL_{CO}$* diffusing capacity for carbon monoxide, *TLC* total lung capacity, *$VO_2max$* maximum oxygen uptake, *AT* anaerobic threshold, *QOL* Spitzer's Quality of Life index

**Table 3** High resolution computed tomography scores

| | GGO | CON | Reti | Low-att | Sum |
|---|---|---|---|---|---|
| | (120[a]) | (120[a]) | (120[a]) | (120[a]) | (120[a]) |
| ARDSp | 9.7±8.0[b] | 0.7±1.5 | 10.0±4.4[b] | 4.6±2.4 | 25.2±3.6[b] |
| ARDSexp | 1.6±4.3 | 0.5±1.7 | 5.4±5.1 | 3.5±2.0 | 11.0±3.0 |

Values are mean ± standard deviation.
[a] Full marks of each pattern of density
[b] $p<0.05$. The extent of CT patterns was scored by 10% scales.
*GGO* ground-glass opacity, *CON* consolidation, *Reti* reticular density, *Low-att* low attenuation, *Sum* sum of all four patterns of lesions

pairment on the PFT, with only 4 of these (25%) having moderate impairment. The $FEV_1$/FVC ratio of the ARDSexp group was lower than that of the ARDSp group ($p$=0.020), but the mean $FEV_1$/FVC ratio of the ARDSexp group was almost normal (83 vs 74).

## Arterial blood gas analysis and exercise pulmonary function test

Exercise PFT with ABGA was performed in 25 patients. Only one ARDSp patient showed mild resting hypoxemia at baseline. Hypercapnia ranging from 41 to 45 mmHg was observed in four ARDSp and one ARDSexp patient. The mean ABGA index at rest did not differ between the two groups. Six patients (3 in each group) showed decreased $PaO_2$ and increased (A-a)$DO_2$ at peak exercise. The maximum oxygen uptake ($VO_2$max) was abnormal in 13 patients and correlated with FVC, $FEV_1$, TLC and QOL scores ($p<0.050$ for each) (Table 2). $VO_2$max and anaerobic threshold (AT) values did not differ between the two groups.

## Thin-section computed tomography scans

The mean interval between ARDS onset and CT scanning was 20.2(±11.9) months with no difference between the two groups. The mean extent of lesions in all patients was 15.3(±11.1)% of the total lung volume, but the lesions were more extensive in the ARDSp than in the ARDSexp group ($p<0.050$) (Table 3). The CT lesion scores of patients with ARDSp were not significantly different between the right and left lung zones. There were significant inverse correlations between $PaO_2$ at peak exercise and ground-glass opacities (GGO), reticular densities and the sum of all four types of lesions ($p<0.050$ for each). GGO correlated inversely with $VO_2$max ($r$= –0.39, $p$=0.057) and AT ($r$= –0.53, $p$=0.010). The $VO_2$max and $PaO_2$ at peak exercise correlated inversely with the sum of all four types of lesions ($r$= –0.41, $p$=0.055) and there was also an inverse correlation between diffusing capacity and low attenuation ($r$= –0.61, $p$=0.001).

## Correlations between initial characteristics, severity index and outcomes

The duration of ICU stay and TVT correlated directly with FVC, $FEV_1$, diffusing capacity for carbon monoxide ($DL_{CO}$), TLC, $VO_2$max and (A-a)$DO_2$ at peak exercise (Table 2) and inversely with $PaO_2$ at peak exercise ($p<0.010$ for each). The PEEPmax correlated inversely with FVC and $VO_2$max ($p<0.010$ for each). Smoking amounts and duration of $fiO_2$ more than 0.6 correlated inversely with diffusing capacity ($p<0.050$ for each). The type of ARDS, duration of ICU stay and TVT correlated directly with GGO and reticular densities on CT ($p<0.050$

for each). Smoking amounts were associated with low attenuation ($p<0.010$).

## Discussion

There have been few studies to determine whether the long-term outcomes of patients with ARDS were dependent on etiologic subtype [6]. Similar to recent findings [7], we found that the most prevalent abnormality on PFT was decreased diffusing capacity. Using ATS criteria, these abnormalities were mild in our patients. The ARDS subtype was associated with the extent of CT lesions in ARDS survivors in univariate analysis. Due to differences in lung mechanics in the early stages of ARDS and the refractoriness of ARDSp to alveolar recruitment [1, 2], our findings suggest that ARDSp may be more vulnerable to ventilator-induced lung injury, leading to more severe sequelae, compared with ARDSexp, after long-term recovery.

Previous studies have reported that ARDS survivors have a reduced health-related quality of life [7, 8, 9]. Our results, however, showed little difference between ARDS survivors and normal individuals. This difference may be related to our rigorous exclusion of patients who had factors that would influence PFT data. We found no significant correlations between the extent of lesions on CT and the indices of spirometry, diffusing capacity and lung volumes. The findings were similar to recently reported results [10]. The extent of lesions on CT, however, correlated significantly with the parameters of exercise PFT. Moreover, decreased $VO_2$max was prevalent (51.8%) and demonstrated a correlation with QOL score. The exercise test, then, may be the single reliable test for assessing sequelae after recovery from ARDS.

The limitations of this study included the small number of patients enrolled and the weak, although statistically significant, correlations between the variables.

In summary, our results suggest that pulmonary causes of ARDS may result in more serious sequelae than extrapulmonary causes. These differences, however, may not be clinically significant.

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