Original Article

A Follow-up Study on Acute Respiratory Distress Syndrome Survivors after Extracorporeal Membrane Oxygenation by Pulmonary High-Resolution CT

Xu-Yan Li MD[1], Bing Sun MD[1], Chun-Ting Wang MD[2], Hang-Yong He MD[1], Chun-Yan Zhang MD[1], Yi Ding MD[3], Peng Peng MD[3], Zhao-Hui Tong MD[1], Qing-Yuan Zhan MD•[1]

Abstract

Objective: This study aims to identify morphological changes in the lung parenchyma of acute respiratory distress syndrome (ARDS) survivors after extracorporeal membrane oxygenation (ECMO) by high-resolution computed tomography (HRCT) follow-up. Factors influencing these changes are also examined.

Methods: Information and lung HRCT scans were collected and studied 1, 3, 6, and 12 months after the withdrawal of severe ARDS survivors rescued by ECMO in the Respiratory Care Unit of Beijing Chaoyang Hospital from November 2009 to August 2012. The observation endpoint was set as the time when the lung lesions were basically absorbed or 12 months after withdrawal.

Results: Among nine survivors, one survivor was lost to follow-up. The lesions of two patients, which were attributed to bacterial pneumonia and pneumocystis pneumonia, were basically absorbed 1 month after surgery. Six patients completed the 12 month follow-up. Although initial morphological changes varied, different degrees of absorption improvement were observed in later stages of treatment. Lung HRCT analysis on the sixth month indicated that the degree of involvement of the ventral region was greater than that of the dorsal area. No significant difference was observed in patients in terms of ECMO support time, pre-ECMO Murray score, and APACHE II score, among others.

Conclusion: Lung HRCT of severe ARDS survivors after ECMO treatment showed various degrees of morphological changes in the lung parenchyma. The severity of these changes may be associated with the disease duration.

Keywords: Acute respiratory distress syndrome, extracorporeal membrane oxygenation, lung high resolution CT

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Introduction

Acute respiratory distress syndrome (ARDS) is a clinical syndrome associated with severe dyspnea and refractory hypoxemia. The mortality rate of ARDS remains at about 50% despite the continuous development of comprehensive methods, including mechanical ventilation, to treat the diseases.[1,2] Pulmonary function tests of 38 ARDS survivors who had been released from the hospital for about six months exhibited mild to moderate restrictive ventilatory dysfunction (58%). Lung high-resolution computer tomography (HRCT) showed reticular pattern as a major morphological change (52.6%). The life quality of ARDS patients is significantly lower than that of age- and sex-matched populations in the same region. The lung function and morphological changes in these patients may be correlated with inflammatory responses to acute lung injury caused by excessive airway pressure for extended durations during mechanical ventilation.[3]

Extracorporeal membrane oxygenation (ECMO) is an extracorporeal life support that not only provides oxygen delivery to the patients but also reduces oxygen concentration. Airway pressure and tidal volume allow the lung to rest and reduce the lung injury caused by positive pressure ventilation to some extent.[4,5] Possible improvements in the morphology of the lung parenchyma of ECMO survivors were investigated in this work. A 12 month follow-up study on the lung HRCT of eight severe ARDS survivors after ECMO treatment was conducted with the aim of determining morphological changes in the lung parenchyma, as well as relevant factors affecting these changes. The results will provide a solid basis for the optimization of ECMO-related treatments to improve the long-term prognosis of ARDS patients.

Patients and Methods

Inclusion criteria

A prospective observational study was performed on ARDS survivors who had been treated for vein–vein ECMO (VV-ECMO) at the Respiratory Care Unit of Beijing Chaoyang Hospital from November 2009 to August 2012. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Affiliated Beijing Chaoyang Hospital, Capital Medical University. Written informed consent was obtained from all participants.

Authors' affiliations: [1]Beijing Key Laboratory of Respiratory and Pulmonary Circulation, Beijing Institute of Respiratory Medicine, Department of Respiratory and Critical Care Medicine, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China, [2]Department of Emergency, Peking Union Medical College Hospital, Beijing 100730, China, [3]Department of Radiology, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China.
•Corresponding author and reprints: Qing-Yuan Zhan MD, Beijing Key Laboratory of Respiratory and Pulmonary Circulation, Beijing Institute of Respiratory Medicine, Department of Respiratory and Critical Care Medicine, Beijing Chaoyang Hospital, Capital Medical University, No. 8 Gongren Tiyuchang Nanlu, Chaoyang District, Beijing 100020, China. Tel: +86-10-85231543, Fax: +86-10-65060167, E-mail: qingyuanzhan@126.com.
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Establishment and management of ECMO

The VV-ECMO method was adopted to set up ECMO via a percutaneous approach. The intra-thigh vein was used as the vein end of ECMO, while the internal jugular vein was used as the arterial end. The venous catheter was 19 – 23 F, and the arterial catheter was 15 – 17 F. A MAQUET or Medtronics centrifugal pump was used. First, the ECMO blood flow was regulated to maintain the saturation of pulse oxygen (SpO_2) at 85% – 95%. The oxygen and blood flow were initially set to 1: 1 and then gradually adjusted according to the $PaCO_2$ level, which was maintained at approximately 40 mm Hg (1 mm Hg = 0.133 kPa).

Next, ordinary heparin was used as an anticoagulant to control the whole blood activated clotting time to 140 s – 180 s.

Third, a heat exchanger (water tank) was applied to maintain the body temperature at approximately 37 °C.

Fourth, a routinely low tidal volume was selected (4 – 6 mL/kg) to maintain the expiratory pressure at the positive end at a certain level [PEEP 10 – 15 cm H_2O (1 cm H_2O = 0.098 kPa)] to limit the plateau pressure (< 30 cm H_2O), low respiratory rates (8 to 12 times/min), and low oxygen concentrations (FiO_2 < 50%). The fifth step involved ECMO withdrawal. Gradual recovery of the patients' lung functions resulted in the decrease of ECMO blood flow to 2 – 3 L/min. When recovery of pulmonary function was confirmed, the daily oxygen flow was reduced to 0. SpO_2, respiratory rate, and breathing patterns, among others, were monitored while blood circulation and anticoagulation were maintained under certain mechanical ventilation parameters (PEEP at about 10 cmH_2O, FiO_2 at about 50%, etc). When SpO_2 could be maintained at approximately 95% for 4 – 6 h without significant changes in the respiratory rate and breathing pattern, ECMO withdrawal was considered.

Observational indicators

A unified form was designed, including epidemiological data of the survivors (gender, age, weight, and medical history), general condition before ECMO (diagnosis and infective etiology), observational indicators during ECMO (vital signs during ECMO and hemodynamic parameters, mechanical ventilation mode, parameter settings, etc.), and ECMO treatment time and related complications.

Analysis of lung HRCT

To clarify lung morphological changes in the patients, lung HRCT examinations were performed 1, 3, 6, and 12 month after cessation of ECMO treatment. Follow-up was performed based on the radiological data, and the endpoint was designated as the absorption of lung lesions or the 12th month after ECMO withdrawal. Lung HRCT images of the patients were randomly assigned to two radiologists who were blinded to the patients' clinical manifestations. Final data statistics and score results were performed by the researchers.

According to the literature,[6,7] radiographic changes in lung parenchyma may be evaluated using the scoring method. The ambilateral lungs were divided into 12 regions. Horizontal lines along the eminence and lower pulmonary vein divided the lungs into three parts: the upper lung, the middle lung, and the lower lung. Each part included four subparts, namely, the central zone, the peripheral zone, the ventral region, and the dorsal region. If the lung parenchymal lesion in each region did not cover over one-third of the total surface area of the region, it was defined as a "focal lesion". In this study, pulmonary parenchymal lesions were divided into three types.

Mild pulmonary parenchymal changes mainly included changes in the line shadow, such as strip shadows of the pleural downline, interlobular septal thickening, and fiber ropes, as well as lower pleural or pulmonary cystic changes. A score of 0 denoted the absence of change in each region, a score of 1 denoted the presence of focal lesions, and a score of 2 denoted the widespread presence of lesions.

Moderate pulmonary parenchymal changes mainly included ground glass-like changes, bronchiectasis, grid-like fibrosis, and pulmonary hyperinflation symptoms. A score of 0 denoted absence of change in each region, a score of 2 denoted the development of focal lesions, and a score of 4 denoted the development of widespread lesions.

Severe pulmonary parenchymal changes mainly included honeycombing lesions or solid-shadow changes accompanied by traction bronchiectasis. A score of 0 denoted the absence of changes in each region, a score of 3 denoted the presence of changes in focal lesions, and a score of 6 denoted the widespread presence of lesions.

The aforementioned changes were determined by radiologists. Full region assessments were used for the evaluation and scoring of HRCT in patients for statistical analysis.

Statistical analysis

The data were expressed as mean ± standard deviation (x ± s). Considering the small sample size, comparison of the intergroup data was performed using the Mann-Whitney U (non-normal) rank sum test, also called Wilcoxon rank-sum test or Wilcoxon–Mann–Whitney test which was a non-parametric test of the null hypothesis that two populations were the same against an alternative hypothesis. All data were analyzed using SPSS16.0 statistical software, and $P < 0.05$ was considered statistically significant.

Results

Patients' general situation before ECMO

From November 2009 to August 2012, a total of 29 patients received ECMO in our hospital. Nine of these patients survived after VV-ECMO supporting treatment, and one patient was lost to follow-up. The eight follow-up cases consisted of seven males aged 51 ± 16 (30 – 77) years. The etiological causes of ARDS were as follows: two cases of new type A H1N1 influenza virus infection, two cases of Legionnaires' pneumonia, one case of bacterial pneumonia, one case of pneumocystis pneumonia, and two cases of mixed infection. Table 1 summarizes the general and epidemiological data of the eight patients.

Pulmonary HRCT scan evaluation

The eight follow-up patients completed lung HRCT examinations on the 1st, 3rd, 6th, and 12th months after ECMO. Among these patients, two (disease causes were bacterial pneumonia and pneumocystis pneumonia) were engaged in normal social activities because they recovered better. Lung HRCT of these patients was taken in the first month after ECMO showed only a small amount of strip shadows of fiber ropes and lung lesions appeared basically absorbed. Thus, no further follow-up examination was conducted in these patients. The six other patients completed lung HRCT examinations at corresponding time points.

Table 1. General conditions and epidemiological data of the patients

Parameter	
Age (years)	51 ± 16 (30–77)
Gender	
Male	7
Female	1
PaO_2/FiO_2 before ECMO	62.5 ± 18.5
Murray score	3.5 ± 0.4
APACHE II score	18.8 ± 1.3
Cause of severe respiratory failure	
New type A H1N1 viral pneumonia	2
Bacterial Pneumonia	1
Bacterial + fungal pneumonia	1
Pneumocystis pneumonia	1
Bacterial+EB viral pneumonia	1
Legionnaires pneumonia	2
Invasive mechanical ventilation time before ECMO	44.4 ± 40.8 h
ECMO time	10.5 ± 4.8 d

Table 2. Lung HRCT scores of the 8 patients during 1 – 12 months

	Time			
	1 month	**3 months**	**6 months**	**12 months**
H1N1	49	28	12	8
H1N1	96	12	4	3
Bacterial	16	- - -	- - -	- - -
Bacterial+fungal	61	36	36	28
Pneumocystis	10	- - -	- - -	- - -
Bacterial+EB virus	45	- - -	12	10
Legionnaires	38	21	20	5
Legionnaires	50	47	38	- - -
Z		-2.023	-1.826	-2.023
P		0.043	0.068	0.043

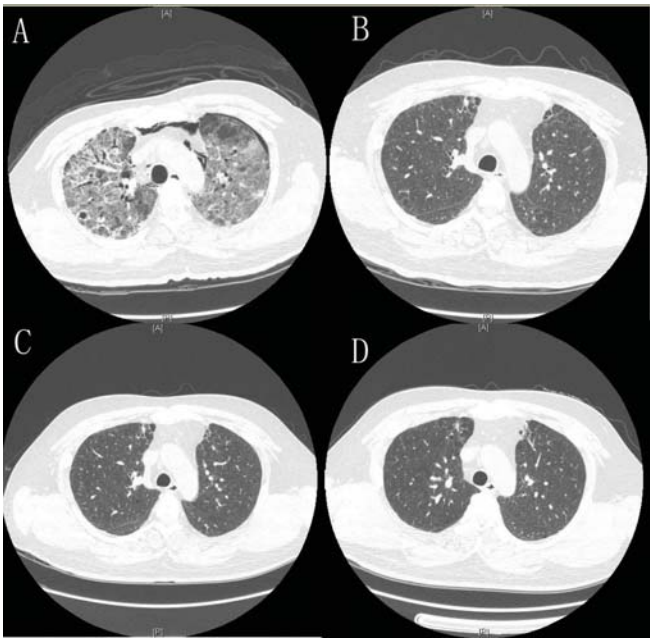

Figure 1. Forty one years old, male, obtained ARDS because of new type A H1N1 influenza virus infection, A, B, C and D were the HRCT appearance after ECMO withdrawal, the 3rd, 6th and 12th month, respectively.

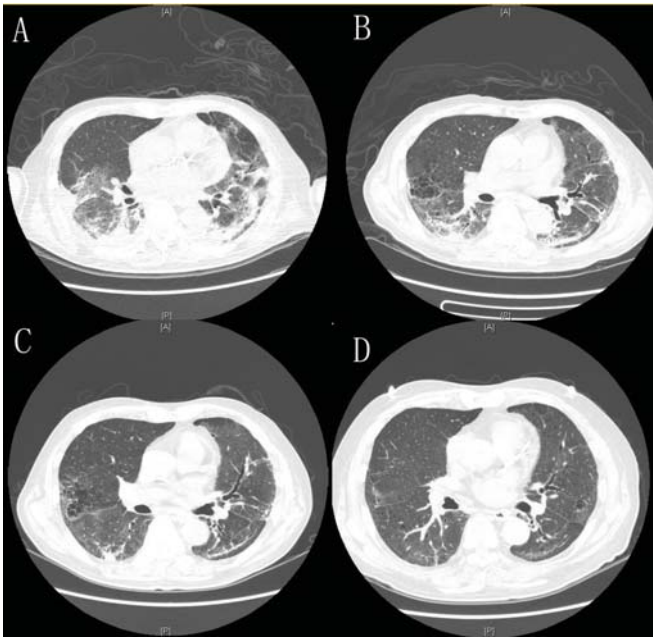

Figure 2. A 77 years old male, obtained ARDS because of legionella pneumophila infection, A, B, C and D were the HRCT appearance after ECMO withdrawal, the 1st, 3rd and 6th month, respectively.

Table 3. Lung HRCT lung scores of different regions of the 6 survivors at the 6th month

	Scores of different lung regions						
	Upper lung	Middle lung	Lower lung	Ventral region	Central region	Lateral region	Dorsal region
H1N1	6	6	0	12	0	0	0
H1N1	2	2	0	4	0	0	0
Mixed	11	11	12	8	6	7	10
mixed	4	4	4	4	0	1	7
Legionnaires	7	5	8	10	4	3	3
Legionnaires	12	10	16	4	8	12	14
Sum	42	38	40	42	18	23	34

Table 4. Related factors of lung radiographic changes

	Score of the 6th month	ECMO time (day)	Parameters before ECMO					
			Murray score	APACHE Ⅱ score	PEEP	72h FiO_2	Peak pressure of airway	MV time (hours)
H1N1	12	13	3.75	17	12	0.6	37	120
H1N1	4	15	3.3	19	10	0.5	26	48
Bacterial	16	8	4.0	20	15	0.4	28	26
Mixed	36	8	4.0	19	0	0.5	20	92
PC	10	8	3.0	21	15	0.4	25	25
mixed	12	4	3.75	18	15	0.35	26	15
Legionnaires	20	7	3.5	19	6	0.4	27	3
Legionnaires	38	16	3.0	21	8	0.5	25	26

Note: PC as Pneumocystis infection; 2 PC patients were terminated the follow-up at the postoperative 1st month, so the 6th month HRCT score used that of the 1st month; APACHE Ⅱ score: acute physiology and chronic health evaluation system, MV time was the invasive mechanical ventilation time before ECMO.

Table 2 shows the HRCT imaging statistical scores of the patients. Various degrees of improvement were observed among the six patients in the 12 month follow-up period. Wilcoxon rank-sum test for comparing lung HRCT scores in different time intervals indicated statistical significance between the scores for the 1st and 3rd months after ECMO ($P = 0.043$), as well as scores for the 6th and 12th months ($P = 0.043$). By contrast, no statistical significance was observed between the scores of the 6th and 3rd months ($P = 0.068$). Two H1N1 patients exhibited good prognosis, showing low scores 12 month later; these patients presented with only a small amount of residual shadows of fiber ropes (Figure 1). The lung images of one case with mixed bacterial + fungal infection and one case with Legionnaires' pneumonia mainly showed grid-like fibrosis and ground glass-like changes; these patients thus exhibited poor recoveries and high scores (Figure 2). Another case of Legionnaires' pneumonia and one case of mixed bacterial + viral infection mainly showed ground glass-like changes during the first 1 – 3 month, as well as various degrees of recovery and improvement.

Regional analysis of pulmonary HRCT changes on the sixth month after ECMO showed no significant difference among the involvements of the upper, middle, and lower lung lesions of six patients. The ventral, dorsal, central, and lateral regions were relatively the most seriously involved regions (Table 3).

Related risk factors of lung imaging changes

Analysis of lung HRCT scores on the sixth month after ECMO indicated no significant differences among the patients in terms of ECMO support time, Murray score before ECMO, APACHE II score, PEEP, oxygen concentration, airway peak pressure, and invasive mechanical ventilation duration, among others (Table 4).

Discussion

Although the patients who were administered conventional ARDS treatment showed similar phenomena in the acute phase, their prognoses differed significantly. Some patients fully recovered, whereas the quality of life of other patients was severely reduced. This finding is mainly related to the morphological changes (degree of pulmonary fibrosis) brought about by pulmonary parenchymal damages during disease progression.[3]

Follow-up investigations on the survivors mainly included tests for lung function, laboratory examination, autopsic histopathological examination, and imaging tracking. Pulmonary function investigations indicate that restrictive ventilatory dysfunction may be observed in 22% to 100% of all ARDS survivors;[8] restrictive ventilatory dysfunction has also been associated with pulmonary fibrosis. A single-center research previously reported the autopsic histopathological analysis of patients who were successfully rescued and died several months later because of other diseases. The analysis indicated the presence of fibrotic lesions and compensatory emphysema in these patients.[9]

Lung HRCT is a non-invasive method that is capable of tracking morphological changes in the lung of patients with high accuracy. Some researchers followed-up lung HRCT changes in successfully rescued ARDS patients for 6 – 10 months, with results showing that 13 of the 15 patients (87%) had lung interstitial fibrosis and that damage to the ventral affected region was much more severe than that to the dorsal region. On the one hand, these changes are associated with ARDS severity. On the other hand, the dam-

age observed was also positively correlated with excessively high oxygen concentrations (FiO_2 > 70%) during long-term mechanical ventilation and high airway peak pressures (> 30 cmH_2O).[10]

Changes observed during late pulmonary fibrosis were mainly attributed to the proliferation of alveolar type II epithelial cells caused by inflammatory changes in lung injury during the disease. The higher severity in the ventral area compared with that in the dorsal region may be attributed to a gravity-dependent mechanism that leads to dorsal alveolar atelectasis in the acute phase of ARDS. This phenomenon could prevent injuries caused by high oxygen concentrations and positive pressure ventilation and play a protective role to a certain extent.[11]

No optimal mechanical ventilation parameter settings are available for ECMO-supported patients, but the "lung rest" strategy may help the lung rest by reducing supporting pressures and respiratory rates while providing an appropriate PEEP to prevent alveolar collapse. The setting of the CESAR research was PA/C mode with the following parameters: Pi20–25H_2O, f10 times/min, PEEP 10 – 15 cmH_2O, and FiO_2 0.30.[12,13] While these settings could prevent high oxygen concentrations and airway peak pressures, whether or not the incidence of pulmonary fibrosis in these patients decreases after ECMO treatment remains unknown.

Linden performed a long-term follow-up investigation on 21 ARDS patients who underwent ECMO. The patients showed improved tests, such as lung function, pulmonary HRCT, and lung scintigraphy. The HRCTs of 16 patients exhibited interstitial lung fibrosis. Five of these 16 patients showed ground glass-like changes and mostly focal lesions. No significant difference between the dorsal and ventral regions was observed, and fibrotic changes positively correlated with the ECMO support time.[14] The locality of lesions and absence of significant difference between the dorsal and ventral regions may be attributed to the "lung rest" strategy applied. This strategy could, to a certain extent, avoid further damage to the lung tissues caused by high peak airway pressures, plateau pressures, and inspired oxygen concentrations.

Combining these results with those obtained in our present study, the morphological prognosis of four cases was better (two cases of new type A H1N1 influenza viral pneumonia, one case of pneumocystis pneumonia, one case of bacterial pneumonia). However, one case of mixed bacterial and fungal infection and one case of Legionnaires' pneumonia showed reticular fibrosis and ground glass-like changes. The morphological changes in the lung of ARDS survivors may be associated with etiology. Legionella and bacterial infection may cause a great degree of lung parenchymal damage. Therefore, the morphological changes are significant. Lung HRCT changes in ARDS immune-suppressed patients induced by pneumocystis pneumonia exhibited ground glass and consolidative shadows in the initial phase. However, after administration of sulfonamides, anti-infective drugs, and adjuvant hormonal therapy, the ground glass shadows were gradually absorbed after approximately 13 days. Application of hormones also reduced the occurrence of late pulmonary fibrosis.[15]

Besides pulmonary fibrosis, other changes have been found in lung radiological investigations of patients with severe novel type A H1N1 influenza virus pneumonia.[16,17] The induced pulmonary fibrosis changes were similar to those caused by severe acute respiratory syndrome and all had self-healing properties.[18,19] Therefore, in this study, the lung morphology of the two H1N1 patients gradually improved with time. Image region analysis showed that the ventral regions of six patients were involved most obviously 6 month after ECMO, which is identical to the prognostic conclusions of ARDS survivors who had not been intervened with ECMO and could also be considered related with the causes. Although ECMO could reduce lung injury caused by invasive mechanical ventilation, it cannot reduce the inflammatory response induced by different etiologies.

Appropriate interventions during the rescue process of pulmonary fibrosis changes in ARDS patients must further be examined. Except in ARDS caused by pneumocystis pneumonia,[20] combined empirical treatment is the most widely performed anti-inflammatory glucocorticoid treatment in ARDS patients. This treatment aims to theoretically reduce the progression of fibrosis by slowing down the inflammatory response. Hormone therapy for ARDS patients remains controversial; however, low- or medium-dose glucocorticoids may improve lung functions and reduce the need for mechanical ventilation within 7 days of onset or between 7 and 14 days. Increases in developing infections and other complications did not significantly decrease the mortality observed.[21] A retrospective survey of the patients with severe H1N1 influenza showed that the mortality of the hormone therapy group is higher than that of the conventional treatment group.[20] No treatment that can definitely improve pulmonary fibrosis has yet been reported. In our study, the eight patients were all given anti fibrotic therapy by the methylprednisolone 40 mg iv Qd for about 10 days, but these methods did not have a significant effect on lung HRCT outcome.

This study is limited in several ways: Firstly, the number of survivors was small. Only nine patients survived, and one patient was lost to follow-up. Secondly, the lung HRCT as the follow-up way was also the limitation of the study. Although the lung HRCT provided clear morphological changes, radiation induced danger of CT scan including carcinogenesis was a true fact and we should use HRCT with clear-cut indications. The risks of iatrogenic radiation exposure along with CT examinations had been a topic of debate among medical professionals, but recent data suggested it may significantly increase the risk of adverse effects.[22] In this particular subject, pulmonary function tests give good clinically applicable information instead of CT scan and are less costly in developing countries like China. But during follow-up, only the lung HRCT data were relatively complete; other important data, such as pulmonary function tests, quality of life rating scale, and other tests, were lacking. Data collection and management of the survivors during the follow-up period must be improved to achieve more conclusive findings.

Lung imaging follow-up showed various degrees of morphological changes in the lung parenchyma of severe ARDS patients who survived ECMO treatment. Levels of pathological changes and durations may be associated with the causes of the disease.

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