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ECMO in ARDS: a long-term follow-up study regarding pulmonary morphology and function and health-related quality of life

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Background: A high survival rate can be achieved in patients with severe acute respiratory distress syndrome (ARDS) using extracorporeal membrane oxygenation (ECMO). The technique and the costs are, however, debated and follow-up studies in survivors are few. The aim of this study was to evaluate long-term pulmonary health after ECMO and severe ARDS.
Methods: Twenty-one long-term survivors of severe ARDS and ECMO were studied in a follow-up program including high-resolution computed tomography (HRCT) of the lungs, extensive pulmonary function tests, pulmonary scintigraphy and the pulmonary disease-specific St George's Respiratory Questionnaire (SGRQ).
Results: The majority of patients had residual lung parenchymal changes on HRCT suggestive of fibrosis, but the extension of morphologic abnormalities was limited and without the typical anterior localization presumed to indicate ventilator-associated lung injury. Pulmonary function tests revealed good restitution with mean values in the lower normal range, while $T\frac{1}{2}$ for outwash of inhaled isotope was abnormal in all patients consistent with subclinical obstructivity. Most patients had reduced health-related quality of life (HRQoL), according to the SGRQ, but were stating less respiratory symptoms than conventionally treated ARDS patients in previous studies. The majority were integrated in normal work.
Conclusion: The majority of ECMO-treated ARDS patients have good physical and social functioning. However, lung parenchymal changes on HRCT suggestive of fibrosis and minor pulmonary function abnormalities remain common and can be detected more than 1 year after ECMO. Furthermore, most patients experience a reduction in HRQoL due to the pulmonary sequelae.

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The acute respiratory distress syndrome (ARDS) is a life-threatening complication of various types of lung injury. It is acute in onset and characterized by arterial hypoxemia resistant to oxygen therapy alone and diffuse radiological infiltrates in the absence of clinical evidence of left atrial hypertension.[1] Treatment of ARDS requires aggressive supportive care, including positive pressure ventilation and increased oxygen concentrations with risks of barotrauma and oxygen toxicity, which can further aggravate the lung injury.[2] There is a number of adjuvant strategies for treatment, for instance protective ventilatory techniques, ventilation in prone position and the use of extracorporeal membrane oxygenation (ECMO) that may reduce the ventilator-induced lung injury and mortality.[3–5]

The number of survivors from ARDS is increasing and there is a growing need to understand the long-term effects of ARDS and its treatment. Several studies have dealt with histopathological[6] and radiological changes[7,8] as well as pulmonary function[9–11] and health-related quality of life (HRQoL)[12,13] late after conventionally treated ARDS. ECMO therapy is today used in severe ARDS unresponsive to conventional intensive care and ventilation.[4] It includes oxygenation of the blood through an extracorporeal artificial lung, thereby enabling reduced aggressive ventilation during recovery of the lungs, which may spare and protect the lungs from ventilator-associated damages.[14]

Several studies indicate that ECMO can increase survival in severe ARDS,[14–16] but follow-up studies

in patients after severe ARDS and ECMO are few in number[10,17,18] and little is known of residual changes and symptoms late after ECMO.

The aim of this study was to evaluate the long-term results from ECMO treatment of severe ARDS with special respect to pulmonary morphology, function and QoL.

Methods

Patients and study design

During a 62-month period, 37 adults were treated with ECMO, due to severe ARDS, at the ECMO department, Karolinska University Hospital, Stockholm, Sweden. Twenty-six patients (70%) survived to discharge while 11 died due to the underlying disease or to complications during ECMO. The survivors were included in a follow-up study of pulmonary function 12 months or more post-ARDS and -ECMO. Of the 26 survivors, one was excluded due to mental retardation, one was residing abroad and three had died after discharge of reasons not related to the ARDS or ECMO. The remaining 21 patients agreed to participate in the study.

The medical records of the 21 study patients were searched for demographic data, diagnosis, time on mechanical ventilation pre-ECMO, PaO_2/FiO_2 ratio and Murray score[19] before ECMO initiation and time on ECMO therapy. The follow-up evaluation consisted of a physical examination, blood gas analysis, high-resolution computed tomography (HRCT) of the lungs, extensive pulmonary function tests, pulmonary scintigraphy and a self-instructed form to assess perceived QoL and impairment in health due to respiratory disease. For each patient, all tests were performed within 2 days at the Karolinska University Hospital.

ECMO technique

A standard ECMO technique was used in all patients.[14] As a standard procedure, the ventilator settings, including fraction of inspired oxygen (FiO_2), were reduced within 3 h from ECMO start in order to prevent further ventilator-associated lung injury.[14,20] This 'gentle ventilation' in combination with the ventilation mode pressure support was maintained during lung recovery until ECMO ending.[20] After ECMO was discontinued, the patients were on conventional ventilation with low settings of pressure support and inspired fraction of oxygen until breathing spontaneously.

CT of the lungs

HRCT of the lungs was performed in all patients using 1 mm sections at 15 mm intervals from the lung apices to the bases. The scans were evaluated independently by two radiologists for a number of CT changes that previously have been described in survivors of conventionally treated ARDS.[7] The extent of (1) reticular pattern, (2) ground-glass opacification, (3) consolidation and (4) decreased attenuation, were evaluated at three levels: the apex, the hilum and the base of the lung by manually tracing regions with the described abnormal CT patterns and total lung area at each level. The distribution was visually estimated as predominantly anterior, posterior or with even distribution.

Pulmonary function and exercise tests

The pulmonary function and exercise tests were carried out as standard examinations at a special pulmonary function laboratory, utilizing continuous calibration routines. Total lung capacity (TLC), functional residual capacity, residual volume, vital capacity, forced expired volume during 1 s (FEV_1) and diffusion capacity for carbon monoxide (DL_{CO}) were assessed. Normal values were calculated following the European Coal and Steel Union guidelines.[21]

The exercise test was performed on a bicycle ergometer, starting at a workload of 30 W, which was increased by 10 W every minute until the patient stopped. Transcutaneous oxygen saturation (SpO_2) was recorded at rest and immediately after exercise using pulse oximetry.

Normal values for working capacity were estimated from gender, age and body weight.[22] Data from the pulmonary function and exercise tests were expressed as percentages of predicted values and a deviation of $>20\%$ of predicted was considered abnormal.

Pulmonary scintigraphy with radiospirometry

Perfusion and ventilation scintigraphy was performed using ^{99m}Tc-labeled macro-aggregates of albumin i.v. for perfusion and ^{133}Xe gas inhalation for ventilation. During ventilation, the patient breathed into a closed-circuit spirometer, where ^{133}Xe gas was introduced. When the xenon had equilibrated in the lungs, the spirometer was opened to the air and xenon was gradually 'washed out' depending on tidal volume and

degree of gas retention in the lungs (radiospirometry). A wash-out time below 30 s was considered normal.[23]

St George's respiratory questionnaire (SGQR)

SGRQ is a self-administered questionnaire that measures QoL and impairment of health in airway disease. SGRQ has 76 items, divided into three sections: (1) *symptoms* caused by respiratory problems, (2) restriction of *activity* caused by dyspnea and (3) *impact* of daily life caused by the disease. The scores range from 0 to 100 units of possible distress and a summary of total scores is calculated according to the SGRQ manual.[24] The questionnaire has been validated and reliability tested in a Swedish population.[25]

Statistical analysis

For statistical evaluation Pearson's correlation coefficient was calculated as a measure of linear association between variables. All tests were two sided and considered significant at $P \leq 0.05$.

Ethics

The study was approved by the institutional board of ethics at the Karolinska Institute. All patients included signed a written form of consent.

Results

The descriptive data for the 21 follow-up patients are summarized in Table 1. All patients were pulmonarily healthy before ARDS and ECMO and had survived extremely severe ARDS unresponsive to conventional treatment, with mean values of Murray score 3.5 and PaO_2/FiO_2 ratio 56 at initiation of the ECMO therapy. By the time of follow-up, all patients were at home, none was in need of extra oxygen and 16 patients (76%) were back in the same occupation as before ECMO. Of the remaining five patients, two had retired, one was in medical rehabilitation and two were receiving disability pension. Blood tests and end-tidal CO_2 at rest were normal in all patients.

Table 1

Patient descriptive data for the 21 follow-up patients at the time of acute respiratory distress syndrome (ARDS) and extracorporeal membrane oxygenation (ECMO).

Variable	
No. (%)	21 (100%)
Female	9 (43%)
Male	12 (57%)
Smoker	6 (28.6%)
Mean value (range)	
Age, year	40 (21–65)
PaO2/FiO2 ratio	56 (33–96)
Murray score	3.5 (3–4)
Origin to ARDS, no. (%)	
Bacterial pneumonia	15 (71%)
Other	6 (29%)
Mean time (range)	
Ventilation pre-ECMO (*h*)	89 (7–380)
Time on ECMO (*h*)	345 (65–1238)
Months to follow up	26 (12–50)

Lung parenchymal findings

The most common residual pathology on HRCT, seen in 16 of the 21 patients (76%), was a reticular pattern in combination with parenchymal distortion that was taken to represent interstitial fibrosis. Ground-glass opacities with architectural distortion as in fine fibrosis were found in five patients (24%). The total extent of pathological parenchyma was, however, limited (mean 10%, range 0–35%) and there was no significant difference in ventrodorsal distribution of HRCT changes. Three patients had normal HRCT findings. The extent of HRCT changes suggestive for fibrosis correlated to the time on ECMO ($P < 0.01$).

Pulmonary function

All 21 patients completed pulmonary function and exercise test. DL_{CO} was assessed in 20 patients and pulmonary scintigraphy in 19 patients (missing values are due to technical reasons). The values are summarized in Fig. 1.

Mean values of all lung spirometry tests were in the lower normal interval. Ten patients had normal spirometry. Signs of a mild obstructive disorder ($FEV_1 < 80\%$) was observed in nine of 21 patients (43%), in combination with a mild restrictive pattern ($TLC < 80\%$) in three patients. Long time on ECMO was associated with reduced TLC ($P < 0.05$).

The exercise tests also showed mean performance values in the lower normal interval with nine patients (43%) performing $< 80\%$ of predicted. Sixteen patients interrupted the exercise due to leg fatigue and only five due to dyspnea. A slight drop in SpO_2 after work was noted in seven patients. DL_{CO} was reduced in 13 of 20 patients (65%). However, the most consistent abnormality was a delayed outwash of inhaled isotope during radiospirometry seen in all patients, with mean $T\frac{1}{2}$ from the right lung 44 s and left lung 48 s (normal < 30 s)

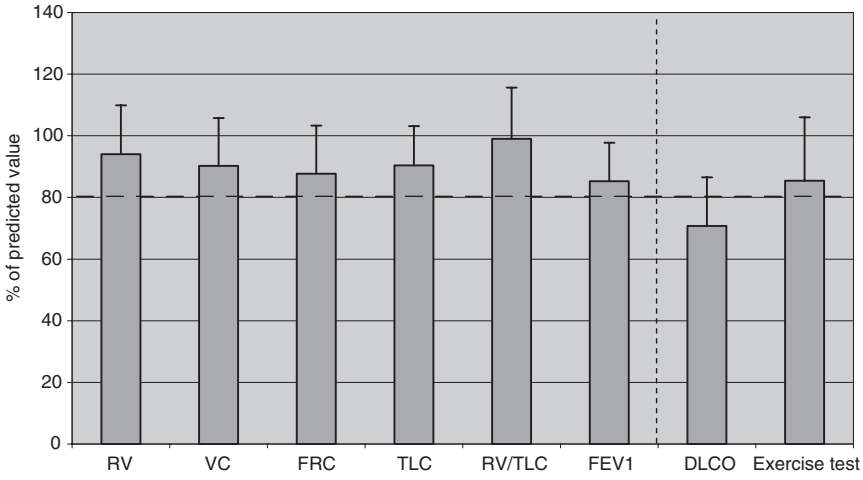

Fig. 1. Results on pulmonary function and exercise tests expressed as percentage of predicted value (mean ± SD). Broken line = 80% of predicted value.

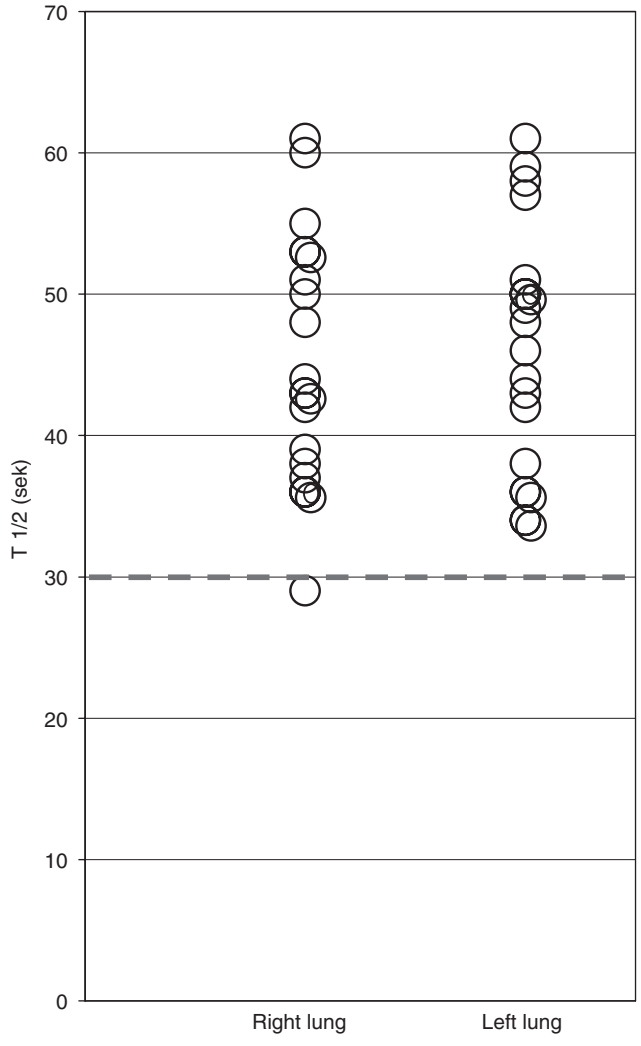

Fig. 2. $T\frac{1}{2}$ for outwash of isotope from lungs during radiospirometry for 19 of the follow-up patients. The graph shows each lung separately. Broken line indicates limit for normal value (<30 s).

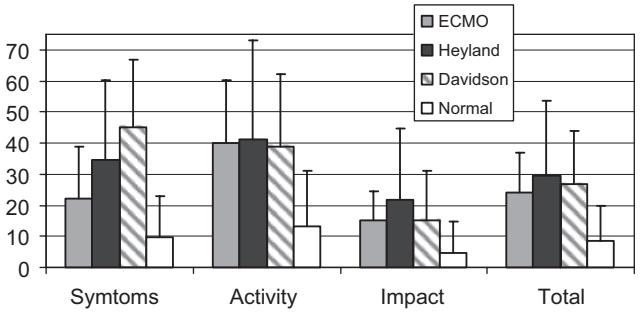

Fig. 3. Results on St Georges Respiratory Questionnaire. Scores (mean ± SD) for extracorporeal membrane oxygenation (ECMO) patients in comparison with two previous studies in conventionally treated ARDS patients, by Heyland (performed 12 months after discharge) and Davidsson (median 23 months after discharge), respectively. Normal values according to the SGRQ manual.

(Fig. 2). Both a lowered DL_{CO} ($P<0.05$) and an increased $T\frac{1}{2}$ for wash out of inhaled isotope ($P<0.05$) correlated to long ECMO treatment times.

HRQoL according to SGRQ

Fifteen of the 21 patients completed the questionnaire. Three were unable to complete the form due to a complicated social situation, one chose not to participate and two patients stated difficulties in differentiating pulmonary problems from their underlying disease. The results are shown in Fig. 3. The mean scores were generally higher than normal values in all domains, indicating subjective respiratory problems with an impact on daily life. Old age was associated with higher scores in all domains of the SGRQ ($P<0.05$).

Discussion

Follow-up studies after conventionally treated ARDS have revealed that many patients have residual morphologic lung injury as in chronic pulmonary fibrosis, reduced pulmonary function and diminished HRQoL years after hospital discharge.[6–13] Severe disease and prolonged mechanical ventilation are factors of high risk for persistent abnormalities.[2] ECMO is used in severe ARDS, resistant to conventional therapy.[4] Patients, who require ECMO, probably have a more severe ARDS, which theoretically may result in more serious long-term respiratory sequelae. However, the gentle ventilation strategy that comes with ECMO today may contribute to minimize the ventilator-induced lung injury and shorten the recovery phase. Because there are few follow-up studies in ECMO-treated patients after severe ARDS[10,17,18] and little is known of the long-term lung function, it is important to evaluate the extent of residual pulmonary injury as well as the HRQoL.

Time aspects

Previous studies in long-term survivors of conventionally treated ARDS have been performed at various time intervals, range 3–115 months, from discharge to follow-up.[9] Abnormalities in pulmonary function and HRQoL seemed to have stabilized after 12 months.[12,13,17] However, pulmonary dysfunction was still found after more than 5 years.[26] In our study, we chose a follow-up time later than 12 months and the median time interval from discharge from ECMO to follow-up was 26 months (range 12–50 months).

Lung parenchymal abnormalities

HRCT showed some degree of reticular pattern and ground-glass opacities, presumed to represent fibrosis, in a majority of our patients. However, the extension of morphologic abnormalities was limited and the anterior predominance of parenchymal pathology previously described in conventionally treated ARDS patients was not seen.[3,7,8,27] A reason for this might be that ECMO treatment, with gentle ventilation, spares or protects the lungs from ventilator-associated damage.

Pulmonary dysfunction

Pulmonary function tests performed in patients late after ARDS point to a variable degree of persistent lung function impairments consisting of obstructive and/or restrictive ventilatory defects, bronchial hyperreactivity and impaired oxygen transfer.[7,9,11,12]

The most sensitive test for residual impaired pulmonary function in our study, post-ARDS and -ECMO, was radiospirometry. All patients had prolonged wash out durations, 50% longer compared with healthy individuals, consistent with a subclinical obstructivity (Fig. 2). Radiospirometry reflects air trapping in the peripheral airways, which is thought to be one of the most important reasons for permanent and unspecific pulmonary symptoms after ARDS.[2] Radiospirometry has, to our knowledge, not been used previously to evaluate patients after ARDS.

A residual impaired oxygen transfer, expressed as reduced DL_{CO}, was seen in 65% of our patients. In a previous follow-up study of ECMO-treated ARDS patients, DL_{CO} was abnormal in all patients.[17] Reduced DL_{CO} is also the most common residual impairment described in conventionally treated ARDS patients with frequencies most often between 40% and 80% of the patients.[7,11]

Most lung function values had normalized in our study group, with mean values for all lung spirometry tests in the lower normal interval (Fig. 1). However, a number of patients had signs of persistent mild restrictive or obstructive disorders consistent with previous studies of conventionally treated ARDS patients[11,12] and the few studies post-ARDS and –ECMO.[10,17,18]

Exercise tests have rarely been used in follow-up studies of ARDS patients. A few studies have claimed that exercise testing is very sensitive in detecting minor abnormalities in pulmonary gas transfer.[9] Our study demonstrated test values in the lower normal interval for two-thirds of the patients and most interrupted due to leg fatigue. This is in agreement with a previous study of ECMO-treated ARDS patients in which results for normal but untrained individuals were revealed.[17]

In our study, long time on ECMO was associated with more extensive CT changes, restrictive pulmonary function tests and impaired lung diffusion. This might be explained by a more severe underlying disease in patients requiring longer ECMO runs. Theoretically, the ECMO procedure itself could result in further pulmonary damages. However, this is more unlikely because ECMO therapy was not correlated to any specific effect on pulmonary morphology in a material of non-surviving ARDS patients, after ECMO and conventional treatment, respectively.[6]

Reduced HRQoL

The overall HRQoL, an important secondary outcome for both physical and mental health, has been measured in several investigations in patients late after ARDS, mainly with the Medical Outcomes Study Short Form 36 (SF 36), while pulmonary symptoms, as measured by SGRQ, are included in just a few follow-up studies.[12,13,26] All studies show some residual impairment in QoL due to breathing problems late after conventionally treated ARDS. Our patients had mean scores in the SGRQ, which in all domains were higher than normal values,[24,25] indicating subjective respiratory problems. The problems were most often described as 'shortness of breath' even during light exercise. However, our patients had an overall tendency for lower scores compared with conventionally treated ARDS patients (Fig. 3). Scores in the *symptom* domain were significantly lower ($P < 0.05$) compared with one of the earlier studies after conventional treatment of ARDS.[13] In our study, older patients had significantly higher SGRQ scores overall, which might reflect the more difficult recovery from severe injuries in elderly.

Majority of our patients (76%) were back in their former occupation after ECMO-treated ARDS. None was in need of extra oxygen supply and they all returned home after being discharged from hospital. These findings are important from a socio-economic point of view. Also in two earlier studies, the majority of long-time survivors of ARDS and ECMO therapy were reported to have good physical and social functioning and a high rate of employment.[17,18]

Limitations of our study were the small number of patients, the non-uniform time intervals between discharge and follow-up and the design as an uncontrolled study. However, there are only about 30 adult survivors after ARDS and ECMO annually reported to the worldwide ELSO registry[28] and just a few previous follow-up studies in this group are available.[10,17,18]

Strength was the extensive follow-up program that included HRCT of the lungs, several pulmonary function tests, as well as a dedicated questionnaire for evaluation of respiratory problems. To our knowledge, no previous study of ARDS patients has included all of the above mentioned tests.

Our recommendation is a follow-up program for adult survivors of ARDS and ECMO, including HRCT of the lungs, exercise test, DL_{CO}, radiospirometry and SGRQ. A future collaboration between all ECMO centers in follow-up studies after ARDS would be most desirable.

In conclusion, lung parenchymal changes on HRCT suggestive of fibrosis and minor pulmonary function abnormalities remain common and can be detected for more than 1 year after ECMO-treated severe ARDS. Furthermore, these patients experience a reduction in HRQoL due to the pulmonary sequelae. However, the impairments are most often mild and the majority of adult ARDS and ECMO survivors have good physical and social functioning and a high rate of employment.

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