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CASE REPORT

Long-term extracorporeal membrane oxygenation in acute respiratory distress syndrome

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Abstract

Extracorporeal membrane oxygenation (ECMO) can be useful in patients with severe acute respiratory distress syndrome (ARDS), when refractory hypoxia and respiratory acidosis limit the possibility to apply lung protective ventilation strategies. Some patients on ECMO may have such severe lung damage that they will not improve, leading to the dilemma when to withdraw this support. We describe the case of a young woman who developed ARDS due to a *Streptococcus pyogenes* pneumonia during pregnancy. After two weeks of conventional ARDS treatment with low tidal volume ventilation, prone positioning and high-dose steroids, further deterioration occurred after difficult to treat bilateral pneumothorax, and ultimately venovenous ECMO was initiated. Treatment was complicated by *Enterococcus faecium* bacteraemia, haemolysis, pulmonary haemorrhage and haematothorax. Over a long period, the pulmonary function remained extremely poor and lung transplantation had to be considered. However, after 108 days the patient could be weaned from the ECMO. Subsequently, she was weaned from the ventilator in six further weeks. She was transferred to a revalidation centre after a hospital stay of six months. The case shows that long-term ECMO treatment for ARDS can be successful.

Introduction

Extracorporeal membrane oxygenation (ECMO) can be considered to be a rescue therapy for patients with severe acute respiratory distress syndrome (ARDS) when safe mechanical ventilation strategies fail and refractory hypoxaemia, progressive respiratory acidosis or severe air leak syndromes ensue [1,2]. After initial reluctance to use ECMO for respiratory indications due to lack of effectiveness in trials, the CESAR trial and H1N1 pandemic have renewed interest in the use of ECMO for refractory respiratory failure in ARDS [3-5]. Although the knowledge of ECMO support for this indication is increasing, no randomised controlled trials have addressed the timing of initiation and the duration of ECMO support. Early use of ECMO in ARDS seems important and in large case series ECMO is started within one week of the development of respiratory insufficiency [5]. Furthermore, prolonged ECMO can become futile due to irreversibility of lung failure when lung transplantation is not an option.

We describe the case of a young patient with severe ARDS due to community-acquired pneumonia, who recovered from prolonged severe respiratory failure requiring long-term ECMO.

Case report

A 22-year-old otherwise healthy woman was admitted to an affiliated hospital for treatment of community-acquired pneumonia and septic shock with *Streptococcus pyogenes*, for which she was treated with penicillin. At presentation, she was 18 weeks pregnant of her fourth child (G5P3). Despite receiving tocolytics, she delivered the following day, followed by manual removal of the placenta. After this procedure, her respiratory condition deteriorated, requiring high-flow oxygen therapy. Two days after admission, she was intubated for further worsening of oxygenation due to ARDS. Lung protective ventilation was initiated, together with prone positioning. She was treated with high-dose prednisone (1 mg/kg) for 12 days without improvement of the pulmonary condition. On day 12, subcutaneous emphysema revealed the existence of bilateral pneumothorax, for which chest tube placement and drainage was instituted. Despite these treatments and interventions, further respiratory deterioration occurred and on day 13 she was referred to our centre for consideration of support with ECMO.

After transfer, we were initially hesitant to initiate ECMO support because our patient was transferred relatively late in the course of ARDS and in this phase the chance of irreversible lung injury is high. No other signs of organ failure were present,

with a calculated ECMOnet (6) score of 4. A lung biopsy was considered, but we refrained from performing this procedure because the high risk of complications would not exceed the potential benefit of establishing a diagnosis with implications for treatment.

ECMO was postponed due to a temporary (slight) improvement of oxygenation and ventilation in the first days after transfer to our hospital. However, five days after transfer (15 days after initial intubation) the ventilatory support settings had returned to those at arrival in our hospital. Venovenous ECMO (hollow fibre membrane oxygenator, Maquet Quadrox D) was initiated (ratio of pressure of arterial oxygen to fraction of inspired oxygen (P/F ratio) 12 kPa^{-1}, PEEP 12 cm H_2O, inspiratory pressure (Pinsp) 36 cm H_2O, FiO_2 0.75, static compliance 11 ml/cm H_2O, tidal volume 260 ml at start of ECMO, *table 1*). Cannulas were placed in the right femoral vein (23 French cannula) and the right internal jugular vein (18 French cannula). The initial flow was 2.8 l/min (1910 rpm) with an FiO_2 of 0.6 and a sweep gas flow of 1.7 l/min. We intended to reduce the level of ventilatory support to Pinsp 20 cm H_2O and PEEP 10 cm H_2O to achieve lung protective ventilation. However, this resulted in extremely low tidal volumes. Therefore, inspiratory pressure was increased to reach tidal volumes of about 100 ml to prevent total lung collapse. Lung compliance remained extremely low (5-10 ml/cm H_2O). After initiating ECMO, the pleural drains were removed.

Seven days after initiating ECMO, the tidal volumes decreased acutely and dramatically, with deterioration of oxygenation and ventilation and need for increased ECMO support. On the chest X-ray, the pneumothorax on the left had increased and a chest drain was inserted, resulting in expansion of the lung. However, 24 hours after drain insertion, tidal volumes decreased again, accompanied by haemodynamic instability due to massive haematothorax on the left side, for which a thoracotomy had to be performed. The patient was at that time receiving anticoagulation therapy with argatroban due to presumed heparin-induced thrombopenia. aPTT levels were within the desired range (60-70 sec.).

During the following weeks, our patient experienced pulmonary haemorrhage twice which resulted in further pulmonary impairment. Bronchoscopy confirmed focal bleeding from the right lower lobe. Local treatment with xylometazoline and epinephrine was unsuccessful, but the bleeding was effectively managed with laser coagulation. Due to recurrent episodes of haemorrhage while on heparin therapy, the heparin dose was lowered to a target aPTT level of 50 sec.

The clinical course was complicated by several infectious episodes. Only three days after initiation of ECMO, blood cultures were positive for *Enterococcus faecium*. All intravascular catheters were changed, except for the ECMO cannulas, and vancomycin was administered for a prolonged period.

Table 1. Respiratory parameters, ventilator settings and ECMO support during the course of ARDS in our patient.

Parameter	Admission	Prior to ECMO	Day 1 on ECMO	Day 7 on ECMO	Day 10 on ECMO	Day 108
Arterial blood gas						
pH	7.48	7.53	7.4	7.48	7.27	7.36
pCO2 (kPa)	8.8	8.2	9.4	7.2	8	9
pO2 (kPa)	7.4	9.3	11.2	6	13.5	11.4
Ventilator settings						
Mode of ventilation	PCV	PCV	PCV	PCV	PCV	PSV
FiO2	0.60	0.75	0.60	1.00	0.80	0.45
Pinsp (cmH2O)	40	36	26	22	18	33
PEEP (cmH2O)	12	12	12	12	10	5
VT (ml)	290	260	205	80	33	350
Compliance (ml/cmH2O)	10	11	16	12	6	
ECMO settings						
ECMO flow (l/min)			2.8	4	4.3	1
FiO2			0.60	0.70	1.00	0.30
Sweepflow (l/min)			1.7	6	5	0

FiO_2 =fraction of inspired oxygen; P_{insp} = inspiratory pressure; V_T = tidal volume; PCV = pressure controlled ventilation; PSV = pressure support ventilation; PEEP = positive end-expiratory pressure.

During ECMO treatment, the respiratory tract became colonised with Pseudomonas aeruginosa and Sphingomonas koreensis. Initially, there were no signs of respiratory tract infection, such as fever, leucocytosis, purulent sputum or signs of pneumonia on chest X-rays. No respiratory deterioration occurred. After cessation of ECMO the patient was treated for tracheobronchitis (increased production of purulent sputum) with ceftazidime. After five days this antibiotic was stopped since this appeared not to be a case of pneumonia. Later on, the patient was treated for one week with colistin inhalations during a period of bronchitis.

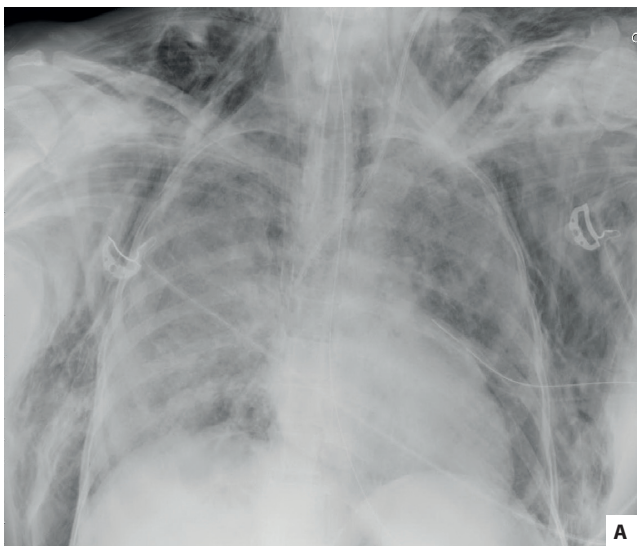
The ECMO circuit was changed five times during the 108 days of ECMO. After seven days of ECMO, the circuit was changed because of severe haemolysis due to thrombus formation in the membrane oxygenator despite adequate aPTT levels on heparin therapy (aPTT 60-70 sec). Marked haemolysis required two additional circuit changes. In addition, the ECMO circuit was changed twice due to minor thrombus formation in the membrane oxygenator, with decreased function of the oxygenator.

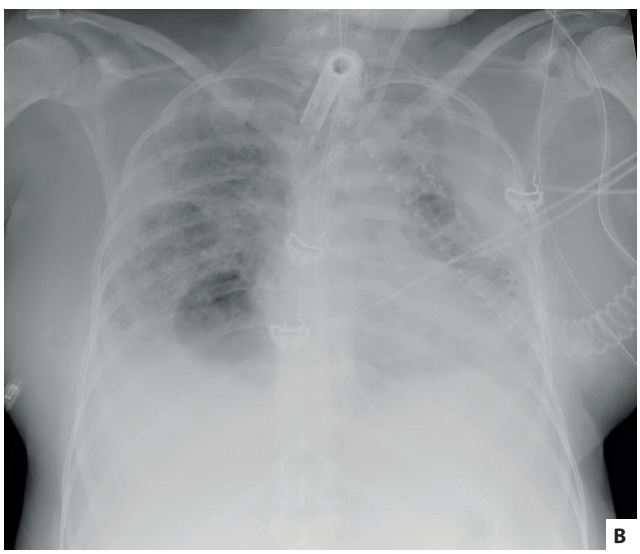
After approximately two months of ECMO and protective ventilation, there was no evident improvement in pulmonary function, with signs of extensive lung injury on X-ray and CT thorax *(figure 1)*. Although some of the lack of improvement was due to the encountered problems with bilateral pneumothorax, haemolysis and pulmonary haemorrhage, we were concerned about the irreversibility of the pulmonary injury. Lung transplantation was considered, but seemed impossible in the short term, because of shortage of donor organs with the specific blood group of the patient. We decided to focus on improving the overall condition. A tracheostomy was performed and sedative medication was reduced and subsequently stopped. With the help of the physiotherapist, the patient was able to exercise while on ECMO and to regain strength. The contribution of the patient's own respiratory effort turned out to be of such importance that ECMO support could gradually be decreased.

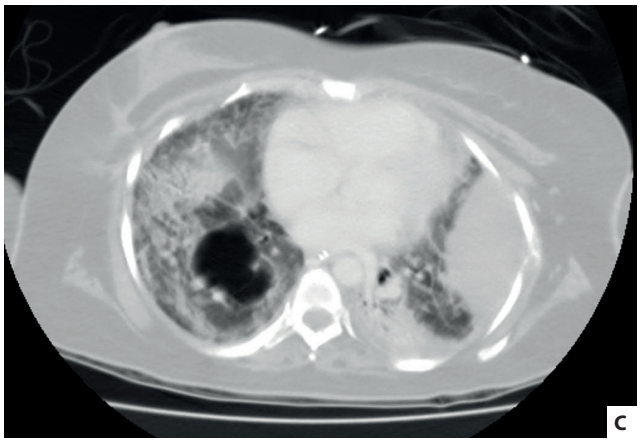
At day 108, the patient was able to breathe comfortably on pressure support ventilation; ECMO was stopped and the cannulas were removed. Unfortunately, the same day she developed fever with resulting tachypnoea. No specific cause of the fever was detected, which resolved during therapy with vancomycin and ceftazidime. Because of respiratory acidosis and exhaustion, she was supported with a single venous catheter-based extracorporeal CO2 removal device (DECAP®, Dirinco [7]) for two days, after which she was able to maintain a normal pH on low ventilator settings.

Gradually our patient was weaned from the ventilator. Her strength and general condition increased steadily through intensive training and physiotherapy; she was able to walk several metres on the ward while on the ventilator. Six weeks after ECMO decannulation, the trachea cannula was removed and she was transferred to a general ward after an ICU stay of 169 days. Six months after initial presentation, she was transferred to a revalidation centre. She improved dramatically in the weeks after ECMO treatment, but she still has respiratory insufficiency and requires additional oxygen (0.5-1.5 litres/min) four months after discharge. A pulmonary function test shows a severe restrictive pattern with a vital capacity of 0.68 l (21% of predicted) and a forced expiratory volume of 0.55 l (20% of predicted). She is able to walk 50 metres without support. Lung transplantation is still being considered.

Figure 1. Radiological appearance of the pulmonary consolidations. This chest X-ray, performed on the day of initiation of ECMO support (A), shows bilateral consolidations and subcutaneous emphysema. After 108 days of ECMO support, beside the bilateral consolidations, a pleural haematoma is visible in the left hemithorax and a bulla in the right hemithorax (B). The same changes are visible on a CT scan two months after initiation of ECMO support (C).







Discussion

We describe a 22-year-old woman with severe ARDS who was successfully weaned from venovenous ECMO after an extended period of more than 100 days. ECMO was initiated relatively late in the course of ARDS (15 days after becoming ventilator-dependent) and slow improvement of pulmonary function forced long-term ECMO.

ARDS developed after a *S. pyogenes* (group A Streptococcus, GAS) pneumonia during pregnancy. Pregnant women are at risk for developing GAS-related infections, especially during the third trimester and in the post-partum period [8].

Lung damage in ARDS results in impaired gas exchange with, in severe cases, refractory hypoxaemia and progressive respiratory acidosis. Oxygenation can be improved by increasing levels of PEEP and increasing FiO_2, although there is evidence pointing to a negative effect of a high fraction of inspired oxygen on resolution of ARDS [9]. A large randomised controlled trial has shown improved mortality when applying tidal volumes of 6 ml/kg ideal body weight versus 12 ml/kg body weight [10]. These ventilator settings can result in respiratory acidosis, which is often accepted until the pH reaches 7.20 (permissive hypercapnia). The contribution to gas exchange by ECMO allows a more lung protective ventilation strategy. Treating the respiratory acidosis with extracorporeal CO2 removal alone was not an option in our patient, due to retractable hypoxaemia. ECMO should only be initiated when lung damage is considered reversible. Earlier trials and case series concerning venovenous ECMO for respiratory failure describe initiation of ECMO support in an early phase of ARDS, preferably not later than seven days after onset of mechanical ventilation [5, 11-13]. The rationale for this decision lies in the described pathophysiological phases of ARDS. A phase of increased capillary permeability, pulmonary oedema and an inflammatory process (exudative phase) is followed by a proliferative stage, with resolution of oedema and proliferation of alveolar cells and fibroblasts. This initial phase has a duration of approximately 7-10 days. In some patients, ARDS then resolves, with reconstitution of normal pulmonary parenchyma. Others progress to a phase with fibrosing alveolitis, with hypoxia, decreased pulmonary compliance and the development of pulmonary hypertension [14,15]. The window of opportunity for treatment of ARDS therefore seems to lie in the first two weeks of mechanical ventilation, and the effect of low tidal volume ventilation will probably be greatest in this period. Our patient was initiated on ECMO after 15 days of mechanical ventilation, but still could be weaned from ECMO and mechanical ventilation.

We continued ECMO for a long period of time: 108 days before decannulation was possible. Case series and trials have described maximum periods of around 50 days [3], although one case report describes a similar length of ECMO [16]. This indicates that at least partial resolution of pulmonary fibrosis after ARDS might be possible.

The complications that occurred during ECMO therapy have protracted the course of this patient. Pneumothorax on both sides, haematothorax after chest drain insertion for which thoracotomy was performed, and multiple episodes of pulmonary haemorrhage complicated the first eight weeks of treatment. After this period, improvement was evident, but slow. This improvement may be due to two different effects. After treating the complications, we were able to ventilate with very low tidal volumes (2-3 ml/kg) compared with 6 ml/kg described in the trial by Amato [10] and the ARDS network [17], due to the support in gas exchange by ECMO. It has been described in other studies [18] that treatment with these low tidal volumes might improve the resolution of ARDS. The other reason for further improvement was the decision to place a tracheostomy and stop sedative medication. This enabled the patient to exercise while on ECMO treatment, increasing strength and endurance and thus augmenting respiratory performance.

Scoring systems have been developed to estimate which patients will benefit from ECMO support. The ECMOnet score [6] has been developed in patients undergoing venovenous ECMO for ARDS due to influenza A (H1N1) pneumonia. As our patient had no signs of organ failure other than respiratory failure, her ECMOnet score was below the described cut-off point, indicating support with venovenous ECMO could be useful. This scoring system gives information about the mortality risk, not about the clinical condition after ECMO support. Although our patient could be weaned from ECMO support and mechanical ventilation, her respiratory condition remains impaired and lung transplantation is still being considered.

Our case shows that even after 108 days of ECMO recovery can occur, making it difficult to take the decision to stop treatment when no obvious improvement occurs in the first weeks.

Conclusion

We describe a case of a 22-year-old woman with severe ARDS complicating a community-acquired pneumonia with *Streptococcus pyogenes*, who was supported with venovenous

ECMO for intractable hypoxia and respiratory acidosis under lung-protective ventilation strategy. ECMO was initiated late in the course of the disease (15 days after initiation of mechanical ventilation) and was maintained for an extensive period (108 days). The patient could be completely weaned from ECMO and mechanical ventilation. As little is known about when to initiate ECMO and how long to proceed this support in ARDS, further research into the use of venovenous ECMO for respiratory failure in ARDS is warranted.

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