

Extracorporeal membrane oxygenation support for life-threatening acute severe status asthmaticus

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Abstract

Introduction: Status asthmaticus is a life-threatening condition characterized by progressive respiratory failure due to asthma that is unresponsive to standard therapeutic measures. We used extracorporeal membrane oxygenation (ECMO) to treat patients with near-fatal status asthmaticus who did not respond to aggressive medical therapies and mechanical ventilation under controlled permissive hypercapnia.

Materials and methods: Between January 2011 and October 2015, we treated 16 adult patients with status asthmaticus (8 women, 8 men, mean age: 50.5 ± 10.6 years) with VV ECMO (13 patients) or VA (3 patients). Patients failed to respond to conventional therapies despite receiving the most aggressive therapies, including maximal medical treatments, mechanical ventilation under controlled permissive hypercapnia and general anesthetics.

Results: Mean time spent on ECMO was 300 ± 11.8 hours (range 36–384 hours). PaO₂, PaCO₂ and pH showed significant improvement promptly after ECMO initiation p=0.014, 0.001 and <0.001, respectively, and such values remained significantly improved after ECMO, p=0.004 and 0.001 and <0.001, respectively. The mean time of ventilation after decannulation until extubation was 175 ± 145.66 hours and the median time to intensive care unit discharge after decannulation was 234 ± 110.30 hours. All 16 patients survived without neurological sequelae.

Conclusions: ECMO could provide adjunctive pulmonary support for intubated asthmatic patients who remain severely acidotic and hypercarbic despite aggressive conventional therapy. ECMO should be considered as an early treatment in patients with status asthmaticus whose gas exchange cannot be satisfactorily maintained by conventional therapy for providing adequate gas change and preventing lung injury from the ventilation.

Keywords

asthma; extracorporeal membrane oxygenation

Introduction

Mortality due to asthma has been reduced in the last decades, reflecting improvements in the pharmacological and supportive management of asthmatic patients. However, at least 2000 adults die of status asthmaticus annually in USA.¹ Near fatal asthma is a serious medical condition that often results in profound hypoxemia, hypercapnia and altered mental status.² Patients with near fatal asthma breathe at high lung volumes, leading to increased mechanical load and elastic work of breathing.³ Mechanical ventilation is often required to manage asthmatic patients who deteriorate despite aggressive management; however, it may be associated with deleterious effects due to worsening dynamic hyperinflation

and increased intrathoracic pressure, with a reported mortality of 8%.¹ Mechanical ventilation causes

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increased air trapping and hyperinflation, predisposing the lungs to barotrauma. Severe bronchoconstriction, mucous plugging and air-trapping make these patients challenging to manage and optimal treatment strategies have not yet been delineated.⁴

Extracorporeal membrane oxygenation (ECMO) has shown improving survival compared to conventional management strategies in patients with potentially reversible acute respiratory failure.⁵ ECMO is an extracorporeal circuit, combining a centrifugal pump and a membrane oxygenator, which is instituted for the management of life-threatening pulmonary or cardiac failure (or both) when no other form of treatment has been or is likely to be successful. It is used as temporary support, usually awaiting recovery of the organs. ECMO can be inserted in a veno-venous (VV) configuration or can be used in a veno-arterial (VA) configuration. The term VV ECMO refers to blood being drained from the venous system and returned to the venous system. This mode only provides respiratory support and is achieved by peripheral cannulation. The term VA ECMO refers to blood being drained from the venous system and returned to the arterial system. This mode provides both cardiac and respiratory support. The goal of this therapy is to minimize ventilator-induced lung injury and allow ample time for the lung inflammatory process to subside.

Although potentially helpful, there has been little experience with ECMO in refractory asthma. Anecdotal case reports have been described in adults,⁶⁻¹³ and one case series (3 patients),¹⁴ but no extensive case review of ECMO employment in asthma exists in the literature.

We have noted an increased need for the use of ECMO in patients with status asthmaticus with failing aggressive medical and anaesthetic therapy in our intensive care unit and sought to evaluate our experience with this approach.

Materials and Methods

All patients with critical asthma admitted between January 2011 and October 2015, despite receiving the most aggressive therapies, including maximal medical treatments, mechanical ventilation under controlled permissive hypercapnia and general anesthetics, were unable to maintain adequate gas exchange, which led to asphyxia or oxygenation failure or to maintain adequate systemic circulation (near-fatal asthma) and in whom we used ECMO, were included in the study. IRB approval for this study was taken by the Institutional Ethics Committees. All the data were retrospectively evaluated.

Demographic data, including age, sex, height, weight and asthma history (including the timing of medications) are reported in Table 1. The average age in this

Table 1. Demographics and characteristics of patients with status asthmaticus (n = 16).

Age (Years)	50.5 ± 10.6
Body Surface Area (m²)	1.97 ± 0.12
Sex n° (%)	
Male	8 (50%)
Female	8 (50%)
Asthma diagnosis n° (%)	
New diagnosis	1 (6.25%)
Previous diagnosis	15 (93.75%)
Adult Asthma onset^a n° (%)	7
Known allergic exposure precipitating admission n°	
Yes	2
No	14
Recurrent episodes^b n° (%)	13
Oral corticosteroids use n° (%)	5 (31.25)
Inhaled beta agonists use n° (%)	12 (75)

^aAsthma onset after age 17 (the average age of asthma onset was 23.61 ± 16.64 years).

^bTotal of 13 recurrent episodes in 6 subjects: 2 (3 episodes), 3 (2 episodes) and 1 (1 episode).

Table 2. Medical and anesthetic therapies used in 16 patients placed on extracorporeal membrane oxygenator.

IV beta agonist n (%)	16 (100%)
IV corticosteroids n (%)	16 (100%)
IV magnesium sulfate n (%)	14 (87.5%)
IV ketamine n (%)	11 (68.75%)
Inhalational agent * n (%)	10 (62.5%)
IV neuromuscular blockade ** n (%)	3 (18.75%)

*Sevoflurane at a minimum alveolar concentration (MAC) starting at 0.5 % up to a maximum 1.0%.

**Neuromuscular blockade administered during mechanical ventilation, not for intubation.

series was 50.5±10.6 years (range 17-62), with 8 female and 8 male patients.

The pharmacologic therapies used in all 16 patients before initiation of ECMO are reported in Table 2.

Ventilatory support was typically performed using pressure-controlled ventilation. Mechanical ventilation was directed at allowing adequate expiratory effort, with relatively short inspiratory time and longer expiratory times, with respiratory rates decreased to allow for improved lung emptying based on auscultation, ventilator graphics and measurement of inspiratory plateau pressures. Lower (but not zero) positive end-expiratory pressure (PEEP) was also utilized (Table 3).

Despite these measures and many adjustments of the ventilator, the PaCO₂ remained high and respiratory acidosis persisted. The patients' conditions were near-fatal, so we believed that ECMO would provide an ideal support modality. The decision is always a collective decision between intensivist, cardiologist and cardiac surgeon.

Table 3. Mechanical ventilation setting.

	Pre-ECMO	1 hour after ECMO initiation	P-value	Post-ECMO	p-value
PaO₂/FiO₂ ratio	71 ± 12.72	351 ± 126	0.001	201 ± 13*	0.001
Respiratory rate (breaths/minute)	11 ± 1.41	13 ± 1.41	0.001	15 ± 1.41*	0.001
PIP (cmH₂O)	53.50 ± 12	18 ± 2.83	0.001	22.50 ± 0.71*	0.001
VT (mL/Kg)	245 ± 290	340 ± 85	0.22	595 ± 49.50*	0.001
Inspiratory time (seconds)	0.29 ± 0.06	0.55 ± 0.07	0.001	1.13 ± 0.66*	0.001
Peep (cmH₂O)	4 ± 0	5.5 ± 0.71	0.001	7 ± 1.41*	0.001

ECMO: extracorporeal membrane oxygenation; PIP: peak inspiratory pressure; VT: Tidal Volume; Peep: positive end-expiratory pressure.

*Significantly different versus the values 1 hour after ECMO initiation and the values pre ECMO.

All p-values are in comparison with the pre-ECMO values.

In all cases, a percutaneous cannulation procedure was carried out. Transthoracic/transesophageal echocardiography was performed to guide and to evaluate cannula positioning and definitive setting.

ECMO Circuit

A heparin-coated circuit was used that included a special intake stopcock for large volume administration (PLS System, Maquet Cardiopulmonary AG, Hirrlingen, Germany).

Depending on the patient's biometric data, we used a 21 or 23 Fr arterial cannula and a 25, 27 or 29 Fr venous cannula for VA and VV (in double cannulation setting) ECMO. For VV ECMO with a single cannula, we used a 29 or 31 Fr bi-lumen cannula. A heat exchanger device was integrated into the ECMO circuit to control the patient's temperature.

In VA ECMO cases (n=3), we adopted the femoral-femoral configuration; to prevent leg ischemia, a small shunt cannula (8-10 Fr) was inserted in the femoral artery, distal to the ECMO cannula. In femoral-jugular ECMO, we used two cannulas as the femoro-jugular setting (n=7) or a single bi-lumen cannula (and only one jugular access, n=6). In cases undergoing VV ECMO with femoro-jugular setting, we used a previously reported original technique, the χ -configuration, to optimize extracorporeal blood oxygenation (Figure 1).¹⁵

Anticoagulation was reached through heparin administration, with doses such as to maintain the activated partial thromboplastin time (aPTT) to values of 40-50 seconds.

Statistical analysis

Group statistics were expressed as mean ± standard deviation. The relationship between pre and post ECMO variables within the same group was assessed by the Student t-test (Statsoft 6-0). Significance between data was considered achieved when p<0.05.

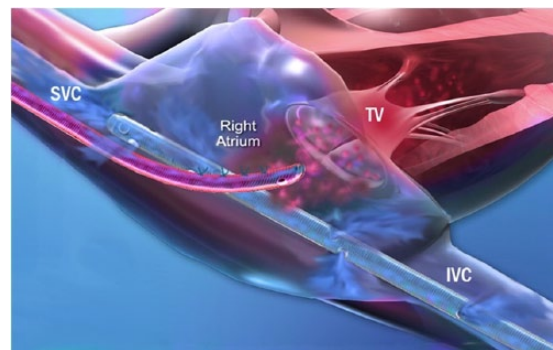


Figure 1. The χ -configuration-modified VV ECMO cannulation. Blood is drained from the two vena cavae (superior [SVC] and inferior [IVC]) by a multi-hole cannula placed through the right femoral vein to the right atrium with the tip just below on the SVC. Arterialized blood is returned to the right atrium through the self-made modified arterial cannula (23-cm long) placed through the right internal jugular vein with the tip toward the tricuspid valve (TV). A polypropylene stitch was used to make 4 consecutive bites over the distal 3-4 cm of the arterial cannula to create the desired curvature and a soft left rotation.

Results

Admission data, including precipitants and barotrauma or pneumonia evidence, are reported in Table 4. A previous diagnosis of asthma was documented in 15 patients and one was newly diagnosed during the hospitalization. The average age of asthma onset was 23.61±16.64 years. Nine patients had no previous hospital admission due to asthma. Recurrent severe asthma was noted in six other patients; two had three episodes, three had two episodes and one patient had one episode. At the time of admission, chest radiography demonstrated marked hyperinflation and air trapping without infiltrate or pneumothorax in 10 patients. The other six patients also showed signs of pneumonia with mild atelectasis on the lung basis.

Thirteen patients were cannulated by the venovenous (VV) approach; three patients underwent the

Table 4. Early clinical factors of patients with status asthmaticus (n = 16).

Precipitants admission	
Influenza A	3
Bacterial Pneumonia	6
Known allergic exposure (aspirin)	1
No specific cause	6
Chest radiography	
Hyperinflation and air trapping	10
Pneumonia signs	6

Table 5. Extracorporeal membrane oxygenation techniques, modalities and procedures.

ECMO flow (L/min)	4 ± 0.70
Mode of ECMO	
Veno-Venous*	13 (81.25%)
Veno-Arterial**	3 (18.75%)
Cannula insertion technique	
Surgical	0 (0%)
Percutaneous	16 (100%)
Hours on ECMO	300 ± 118.79
Hours of mechanical ventilation pre ECMO	53.5 ± 12.02

Legend: ECMO: extracorporeal membrane oxygenation.

*single bi-lumen cannula (only one jugular access, n =6), femoral-jugular setting (n=7) with χ -configuration (Figure 1).¹⁵

**femoral-femoral configuration, with small shunt cannula distally to prevent leg ischemia.

veno-arterial (VA) approach, but promptly converted from VA to VV as the hemodynamic conditions had stabilized. The ECMO flows were commenced with blood flow at about 4 L/min (range 3.0-4.5) and a FiO₂ of 1 (Table 5) and then adjusted to maintain a PaCO₂ between 35 and 45 mmHg and an arterial O₂ saturation >94%.

Median time from patient intubation to ECMO institution was 4.42 ± 42.45 hours (range 10 to 168). Prior to ECMO cannulation the median patient arterial pH was 6.89 ± 0.014 (range 6.82 to 7.16), PaO₂ was 71±12.7mmHg, median PaCO₂ was 111±4.24 mmHg and base excess (BE) -5±0.28 prior to cannulation (Figure 2).

Hypercapnia and hypoxemia markedly improved within an hour of initiation of ECMO (Figure 2). This enabled oxygenation to be maintained, even at dramatically reduced mechanical ventilation settings; the patients were maintained with protective ventilation, including median peak inspiratory pressure (PIP) of 18 cmH₂O (range 15 to 31 cmH₂O), respiratory rate 13 breaths/minute (range 8-25 breaths/minute) and PEEP 5.5 cmH₂O (range 5-10 cmH₂O) (Table 3). These parameters led to a tidal volume of 340±84.85mL which slowly increased with dynamic compliance.

The median time spent on ECMO was 300±118.8 hours (range 36–384 hours). Median time of ventilation after decannulation until extubation was 175 ±145.66hours (range 10-288 hours) and median time to ICU discharge after decannulation was 234±110.3 hours (range 24–420 hours) (Table 5).

Complications relating to asthma and ventilation were common prior to cannulation. Pneumothorax occurred in 5 of 16 patients. The pneumothorax resolved spontaneously during ECMO, at an interval of 4-7 days. Only in one patient was a chest tube attached to a closed underwater drainage inserted before ECMO and prompt expansion of the lung was accomplished; however, lobar atelectasis persisted. Two days after the use of ECMO, the chest tube was removed. Three patients demonstrated unilateral pupillary dilatation prior to cannulation, with concern for increased intracranial pressure and cerebral edema. Computerized tomography did not reveal intracranial abnormalities in either patient. Only one of these patients had accompanying neurological changes (seizure). Abnormalities had resolved at the time of decannulation.

Bronchoscopy with lung lavage was carried out immediately in all patients after the start of ECMO start and daily bronchofibroscope was performed securely to clear the bronchus. The chest X-ray improved significantly at 3-4 days after ECMO initiation.

No patient showed hemorrhagic or mechanical complications related to the procedure. All 16 patients were discharged alive from the ICU and the hospital.

Discussion

The management of severe asthma in the ICU has evolved in recent years despite a lack of randomized controlled trials to guide optimal therapy in these patients.¹⁻⁵

Some authors have concluded that the historically high morbidity and mortality rates associated with severe asthma were related to complications from mechanical ventilation.¹⁶ It has also been suggested that controlled hypoventilation strategies are a primary cause of improvements in clinical outcomes.¹⁷

Based on our current experience we recommend the following:

(a) Conventional therapeutic approaches to severe asthma: targeted drugs and mechanical ventilation

Dynamic hyperinflation chiefly contributes to increasing mortality in an intubated asthmatic patient.¹⁸ Recommended ventilator strategies in severe asthma and dynamic hyperinflation are focused on allowing

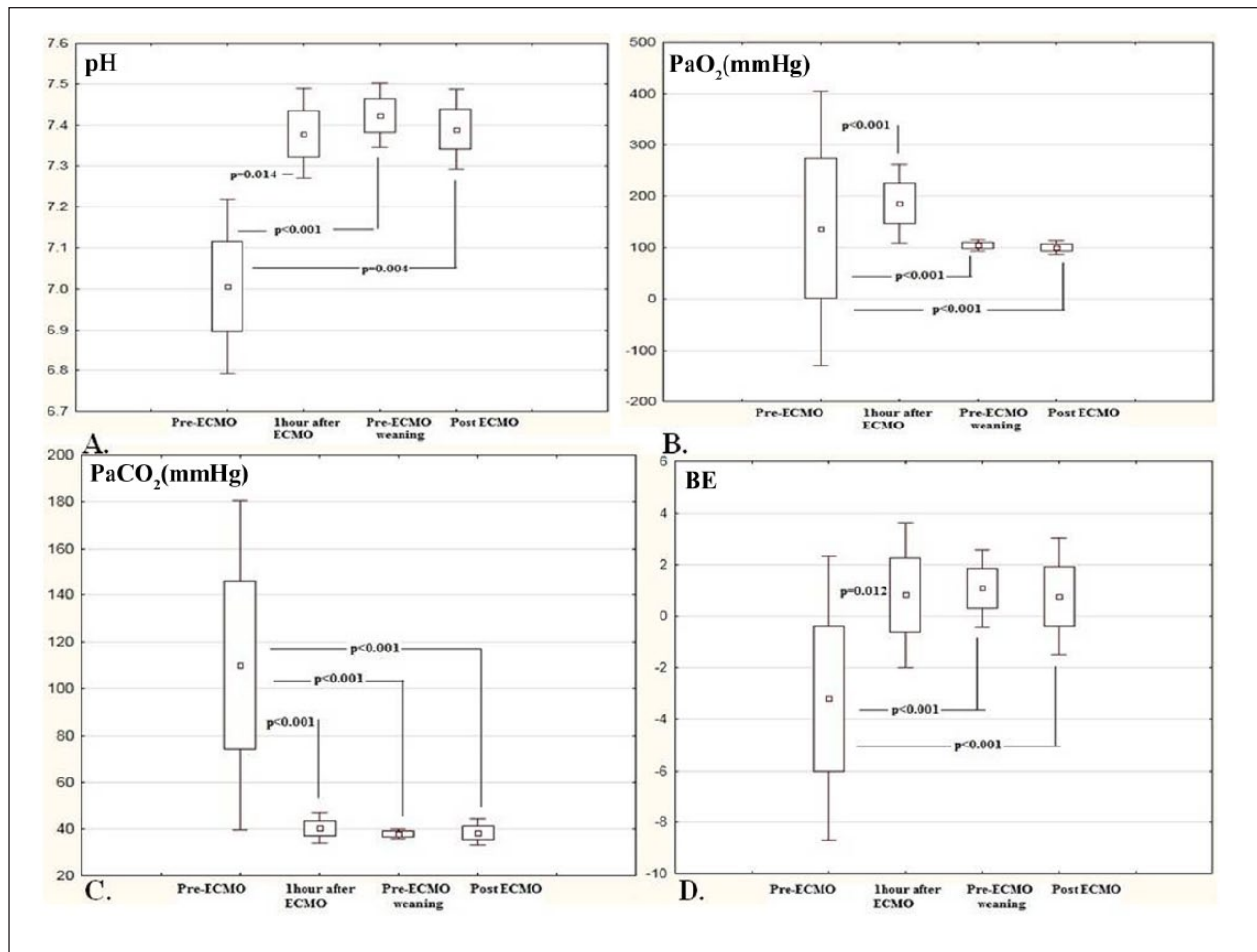


Figure 2. Distribution of mean and standard deviation in different time intervals: A) pH, B) PaO₂, C) PaCO₂ and D) Base excess.

maximal emptying times through low ventilator rates and allowing spontaneous respiration, if possible.¹⁹ The mechanism of hypoxemia and hypercapnia in acute asthmatic attack is mainly due to low ventilation perfusion, mismatch, shunting and hypoventilation.^{3,20} This is necessary to rest the lung until the inflammation causing the bronchospasm has subsided.

Ventilator strategies allowing permissive hypercapnia and limiting dynamic hyperinflation are now standard practice.

Although permissive hypercapnia has become an important strategy in ventilating asthmatic patients,¹⁹ no consensus exists regarding acceptable levels of hypercapnia. Several case reports describe diffuse cerebral oedema, subarachnoid hemorrhage, quadriplegia, hyperreflexia and extensor plantar reflexes associated with severe hypercarbia in severe asthma.

Patients with severe asthma die because their condition deteriorates or because they experience treatment-associated complications. The deterioration frequently results from severe asphyxia due to airway obstruction

rather than from cardiac arrhythmias related to the adverse effects of antiasthmatic drugs.²¹ In addition, the high airway pressure or lung hyperinflation induced by mechanical ventilation can lead to hypotension and pulmonary barotrauma.

(b) Extracorporeal membrane oxygenation

The initiation of extracorporeal carbon dioxide removal for refractory status asthmaticus should be considered when severe dynamic hyperinflation or respiratory acidosis persists for hours despite optimal conventional management. Extracorporeal carbon dioxide removal corrects respiratory acidosis and allows for reductions in respiratory rate and tidal volume, which reverse dynamic hyperinflation.²²

When the clinical situation is not stabilized with various ventilator strategies, ECMO might be a therapeutic option. The use of ECMO in asthmatic patients allows their lungs to rest, thereby, providing time for bronchiolar relaxation until the inflammation-causing bronchospasm

has subsided. ECMO allows aggressive pulmonary toilet²³ and bronchial lavage after the patient's stabilization, which were performed in all our patients, reducing the edema of the bronchial mucous membrane and gradually improving the dynamic compliance. In particular, VV support is likely to be the best choice for an asthmatic patient given the relatively low blood flows required to remove plasma carbon dioxide and the lack of need for cardiac support.²⁴

ECMO is a technique for providing support for the lung and heart, using VV or VA pumping via an artificial lung. Clinical experience has shown that this technique is an effective treatment for respiratory insufficiency and cardiopulmonary resuscitation and as cardiac assistance in patients with circulatory failure.

ECMO removes carbon dioxide from and adds oxygen to blood, diminishing the need for mechanical ventilation and preventing pulmonary barotrauma.

In a retrospective cohort study, Mikkelsen et al.²⁵ found that, among 1,257 patients treated with ECMO, 24 (1.9%) were asthmatics of whom 20 (83.3%) survived to hospital discharge compared to 1,233 (50.8%) non-asthmatics. The success of ECMO in asthma was likely due to the natural reversibility of the airflow obstruction in asthma. This is in contrast to the patient with diffuse alveolar damage due to acute lung injury, where the recovery is usually slow. Moreover, by virtue of its mechanism of action, applying ECMO allows the reduction of both the tidal volume and minute ventilation, which, subsequently, decrease dynamic hyperinflation. These further reduce the development of barotraumas and hemodynamic instability in patient, particularly those with persistent hypoxemia and acidemia who appear to have extremely severe disease.

(c) Major findings of our study

Pulmonary dysfunction improved markedly in our patients after only 21 to 86 hours of ECMO. The present results indicate that even patients with severe pulmonary dysfunction related to severe asthma may recover within a few days if they are treated with ECMO, which allows the lung to "rest", together with standard aggressive therapies.

There were no complications associated with ECMO in the present cases; however, serious complications have been reported.^{26,27} Generally, VA bypass greatly increases the risk of bleeding and of systemic thromboembolism. Thus, we believe that VV bypass should be considered before VA bypass unless severe circulatory failure exists.

ECMO complications can arise during catheter insertion or during the patient's management. In our patients, we used percutaneous cannulation and transthoracic/transesophageal echocardiography was performed to

guide and to evaluate cannula positioning. We didn't have either more or less bleeding complications and we adopted a careful monitoring of clotting time by the measurement of aPTT at the bedside. We also used Transcranial Doppler (TCD) to detect microembolic signals (MES) in real time.

Our patients failed to respond to maximal conventional therapy. An adequate level of oxygenation was only achieved by giving high inspired concentrations. The surprisingly persistent carbon dioxide retention, in the face of mechanical ventilation, probably indicated severe ventilation and perfusion imbalance from small airways occlusion. Faced with an increasing PaCO₂ and indirect evidence of raised intracranial pressure plus a rising airways pressure and evidence of early barotrauma, we resorted to extracorporeal membrane oxygenation and believe it saved the life of the patients. ECMO relieved time for the underlying pathological changes of the asthma attack to abate. Our data confirm the literature for both pediatric²⁸ and adult patients²⁵ and the international experience with ECMO use in neonates, children and adults with status asthmaticus in the Extracorporeal Life Support Organization registry. In particular, status asthmaticus, as an indication for ECMO use, appears to be associated with greater survival than other indications for ECMO.

We believe that ECMO should be considered as early as possible in the treatment of patients with severe asthma whose gas exchange cannot be satisfactorily maintained by conventional therapy.

Conclusion

In severe status asthmaticus, ECMO supported adequate gas exchange until pulmonary function improved, diminishing the need for mechanical ventilation and, probably, preventing pulmonary complications. All our patients with near-fatal severe asthma were rescued by employing ECMO. These results suggest that ECMO does have a place in the treatment of patients with severe asthma in whom cardiac arrest is imminent despite aggressive therapies after hospital admission. Further investigations are necessary to determine efficacy and timing of ECMO in severe asthma compared with standard therapies alone.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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