Extracorporeal membrane oxygenation in severe hypoxemia: time for reappraisal?*

Oxigenação extracorpórea por membrana na hipoxemia grave: hora de revermos nossos conceitos?*

Luciano Cesar Pontes Azevedo, Marcelo Park, Eduardo Leite Vieira Costa, Edzângela Vasconcelos Santos, Adriana Hirota, Leandro Utino Taniguchi, Guilherme de Paula Pinto Schettino, Marcelo Brito Passos Amato, Carlos Roberto Ribeiro Carvalho

Abstract

In 2009, during the influenza A (H1N1) epidemic, there were many reported cases of pulmonary infection with severe hypoxemia that was refractory to the ventilatory strategies and rescue therapies commonly used to treat patients with severe acute respiratory distress syndrome. Many of those cases were treated with extracorporeal membrane oxygenation (ECMO), which renewed international interest in the technique. The Extracorporeal Support Study Group was created in order to practice ECMO and to employ it in the treatment of patients with severe hypoxemia. In this article, we discuss the indications for using ECMO and report the case of a patient with refractory hypoxemia who was successfully treated with ECMO.

Keywords: Respiratory Insufficiency; Intensive Care Units; Extracorporeal Membrane Oxygenation.

Resumo

Em 2009, muitos casos de infecção pulmonar com hipoxemia grave refratária às estratégias ventilatórias habitualmente utilizadas e às manobras de resgate para a síndrome do desconforto respiratório agudo foram relatados durante a epidemia por influenza A (H1N1). Em muitos desses pacientes, o uso de *extracorporeal membrane oxygenation* (ECMO, oxigenação extracorpórea por membrana) foi necessário, fato que fez reacender o interesse na ECMO globalmente. O Grupo De Estudos em Suporte Extracorpóreo foi criado visando a aprender a técnica e a utilizar ECMO no tratamento de pacientes com hipoxemia grave. Neste artigo, são discutidas as indicações de ECMO e é relatado o caso de uma paciente com hipoxemia refratária que foi tratada através de ECMO de forma bem sucedida.

Descritores: Insuficiência Respiratória; Unidades de Terapia Intensiva; Circulação Extracorpórea com Oxigenador de Membrana.

Introduction

From an epidemiological standpoint, the year 2009 was marked by the novel influenza A (H1N1) virus epidemic,[1] and the respiratory syndrome caused by the virus reached pandemic levels in mid-2009.[2] Mortality from influenza A (H1N1) infection was reported to be as high as 23% at that time.[3] The leading cause of death in patients with acute respiratory distress syndrome (ARDS) due to infection with the influenza A (H1N1) virus is respiratory failure that is refractory to conventional mechanical ventilation.[4] The Australian and New Zealand Intensive Care Society reported that, between June and August of 2009, 201 patients with ARDS due to influenza A (H1N1) virus infection required mechanical ventilation; of those 201, 68 (34%) required extracorporeal membrane oxygenation (ECMO) for refractory hypoxemia.[5]

* Study carried out by the Extracorporeal Support Study Group of the Intensive Care Unit of the Department of Clinical Emergencies, University of São Paulo School of Medicine *Hospital das Clínicas*; in the Intensive Care Unit of the Sírio-Libanês Hospital; and in the Respiratory Intensive Care Unit of the University of São Paulo School of Medicine *Hospital das Clínicas*, São Paulo, Brazil.
Correspondence to: Grupo de Estudos em Suporte Respiratório Extracorpóreo. Unidade de Terapia Intensiva, Disciplina de Emergências Clinicas, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Avenida Enéas de Carvalho Aguiar, 155, CEP 05403-900, São Paulo, SP, Brasil.
Tel. 55 3069-7221. E-mail: mpark@uol.com.br
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Many patients with refractory hypoxemia due to influenza A (H1N1) infection have been treated with ECMO, which has renewed interest in this life support technique. At facilities specializing in neonatal, pediatric, or adult care, ECMO is used in patients with respiratory failure, as well as in those with heart failure. The ECMO technique facilitates gas exchange, allowing the lungs to "rest" until the patient has recovered from the pathological process and minimizing the potentially deleterious effects of ventilator-induced lung injury. Therefore, ECMO can be considered the definitive rescue therapy for patients with refractory hypoxemia, given that pulmonary gas exchange can be unnecessary during ECMO use. The technique consists of removing blood by means of a pump (either a centrifugal pump or a peristaltic pump) and circulating it through an artificial lung (Figure 1). To that end, the technique that is most commonly used is the venovenous technique, by which venous blood is removed, oxygenated, and returned to the venous system of the patient, thus providing oxygenation.[6] Venoarterial access can also be used. In that case, blood is removed from the venous circulation and returned to the aorta, thus improving cardiac output and gas exchange.

Cardiorespiratory support with ECMO has been described since 1869,[7,8] although the first case of an ARDS patient whose survival was attributed to ECMO was reported in 1971.[9] The first clinical study that compared conventional mechanical ventilation with venoarterial ECMO involved 90 patients with ARDS and was published in 1979, and the mortality rate was reported to be above 90% in both groups. In the ECMO group, common adverse events included bleeding, thromboembolic events, and hemolysis.[10] A study conducted in 1986 described a venovenous CO_2 removal technique that allowed the use of mechanical ventilation with lower airway pressures and minus the adverse events associated with arterial cannulation. In that study, the mortality rate for patients with ARDS was reported to be 49%.[11] In a randomized study published in 1994 and involving 40 patients with ARDS, the CO_2 removal technique was compared with pressure-controlled ventilation; the technique was found to have no beneficial effects on mortality or on the incidence of bleeding in the ECMO group.[12] Enthusiasm for ECMO then began to wane. This was due to the apparent lack of benefits and, first and foremost, to the high incidence of complications, such as bleeding, extremity ischemia, hemolysis, and inflammatory response activation. However, in recent years, the development of new membranes and heparin-coated systems that are more biocompatible has greatly reduced the need for anticoagulation, reducing the incidence of bleeding disorders and ECMO-induced inflammatory response. Likewise, the development of next-generation centrifugal pumps reduced the incidence of ECMO-associated hemolysis.[13]

A change in the paradigm for ECMO use was recently brought about by the use of ECMO during the influenza A (H1N1) epidemic and, first and foremost, by the publication of an important study conducted in Great Britain[14] and involving patients with ARDS. That study compared the use of a protective ventilatory strategy involving low tidal volume and low airway pressure with that of venovenous ECMO and lung rest (positive end-expiratory pressure of 10-15 cmH_2O; peak airway pressure of 20-25 cmH_2O; RR of 10 breaths/min; and FiO_2 of 0.3). In the group of patients treated with ECMO, 63% survived with good functional capacity for six months, compared with 47% in the group of patients treated with the conventional protective ventilatory strategy.[14] In that study, the patients who were randomly selected for ECMO treatment were transferred to the Glenfield Hospital, in Leicester, England, which is the only center that provided ECMO.

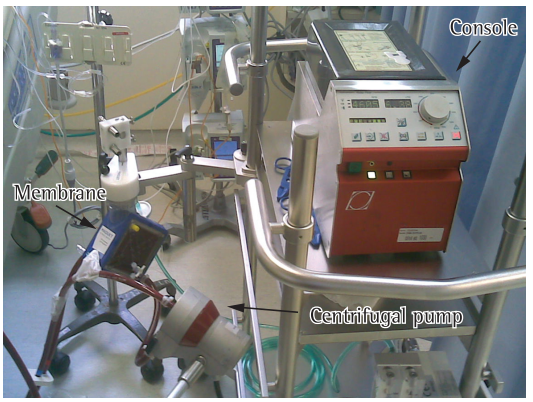

Figure 1 - Extracorporeal membrane oxygenation system. Note the membrane for gas exchange, the centrifugal pump, and the console, which regulates the blood flow.

[14] Finally, also in 2009, a study conducted in Australia and New Zealand evaluated 68 patients with severe respiratory failure due to influenza A (H1N1) infection and treated with ECMO. Of the 68 patients, 63 were treated with venovenous ECMO. The mean PaO_2 of patients at the initiation of ECMO was 55 mmHg, with an FiO_2 of 100%, and in-hospital survival was 79%.[5]

In 2010, with the objective of practicing the ECMO technique and using it routinely in patients with refractory hypoxemia, the Extracorporeal Support Study Group was created. The study group comprises health care professionals in the Clinical Emergency and Respiratory ICUs of the *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo* (HC-FMUSP, University of São Paulo School of Medicine *Hospital das Clínicas*), located in the city of São Paulo, Brazil, as well as health care professionals in the ICU of the Sírio-Libanês Hospital ICU, also in São Paulo. The physicians, nurses, and physical therapists working in those ICUs initially practiced the ECMO techniques by conducting experimental studies in pigs, with the objective of learning how to assemble the system, perform vascular cannulation, provide support to patients with severe ARDS, and manage ECMO-related complications. In Chart 1, we describe the principal criteria used by our study group in order to recommend the clinical use of ECMO.

In 2011, following the training period, we began to use ECMO in clinical settings. Below, we describe the case of a patient who presented with severe refractory hypoxemia and was treated with ECMO.

Clinical case

A 14-year-old female patient with a history of systemic lupus erythematosus had been admitted to the ICU of the HC-FMUSP Institute for Children one month prior with a profile of respiratory distress and fever. She had previously received pulse therapy with methylprednisolone and cyclophosphamide for disease control. During her ICU stay, her pulmonary function worsened, and multidrug-resistant *Acinetobacter baumannii* was isolated from her tracheal secretion. After three days, her clinical status worsened significantly. She presented with acute kidney injury, severe hypoxemia, and septic shock, for which she was treated with high doses of noradrenaline (0.8 μg • kg^{-1} • min^{-1}). Despite the use of alveolar recruitment maneuvers and paralysis with neuromuscular blocking agents, ventilation did not improve. The Extracorporeal Respiratory Support Group of the HC-FMUSP Clinical Emergency and Respiratory ICUs was brought in to determine whether the use of ECMO was feasible. The ventilation and gas exchange parameters before ECMO initiation are described in Table 1. Despite a high inspiratory pressure and positive end-expiratory pressure, the patient presented with severe hypoxemia before ECMO initiation, as evidenced by a PaO_2/FiO_2 ratio of 40.

The use of venovenous ECMO was recommended, the right femoral and left jugular veins were cannulated with 20-F catheters, and ECMO was started. After having been stabilized, the patient (with the ECMO system still in operation) was transported by ambulance to the general ICU of the HC-FMUSP. Her

Chart 1 - Criteria for the use of extracorporeal membrane oxygenation.

Mandatory criteria
Tracheal intubation and mechanical ventilation
Acute onset lung disease
Bilateral pulmonary infiltrate
PaO_2/FiO_2 ratio < 200 with positive end-expiratory pressure ≥ 10 cmH_2O
Reversible lung injury
Complementary criteria (at least one must be met)
PaO_2/FIO_2 ratio ≤ 50 with an FiO_2 = 1, for at least 1 h, with or without the use of rescue therapies (alveolar recruitment, inhaled NO, and prone position)
Hypercapnia with pH remaining ≤ 7.20 using an RR ≥ 35 breaths/min (whenever possible), a tidal volume = 4-6 mL/kg, and a plateau pressure ≤ 30 cmH_2O
Murray lung injury score > 3, with worsening of the clinical status
PaO_2/FiO_2 ratio ≤ 50 with an FiO_2 ≥ 0.8 for at least 3 h, despite the use of rescue therapies

Table 1 - Hemodynamic, respiratory, and biochemical data during extracorporeal membrane oxygenation.

Variable	Pre-ECMO	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
HR, bpm	-	141	124	129	116	130	134
MAP, mmHg	-	105	105	109	107	100	94
SpO_2, %	85	97	95	95	98	99	100
Mean ECMO blood flow, L/min	-	5.4	5.1	5.1	5.2	5.6	4.7
Mean ECMO oxygen flow, L/min	-	4.0	3.0	2.0	1.0	0.7	0.6
Mode of ventilation	PC	PS	PS	PS	PS	PS	PS
RR, breaths/min	22	32	34	41	22	27	21
Tidal volume, mL	310	200	220	350	400	350	600
Plateau pressure, cmH_2O	46	22	20	20	20	20	20
FiO_2	100	30	30	30	30	30	30
PEEP, cmH_2O	23	15	15	15	15	15	15
pH	7.51	7.39	7.39	7.42	7.48	7.34	7.29
pO_2, mmHg	40.8	68.0	50.0	45.7	50.0	83.0	85.0
pCO_2, mmHg	35	45	44	42	50	51	42
Base excess, mEq/L	5.6	1.5	1.6	2.1	11.9	10.6	6.0
SaO_2, %	81	93	85	82	88	95	95
Lactate, mg/dL	17	10	10	11	19	13	14
Hemoglobin, g/dL	-	7.6	5.6	6.4	6.8	7.2	7.9
Platelets, cells/mm^3	-	43,000	68,000	70,000	55,000	48,000	112,000

ECMO: extracorporeal membrane oxygenation; MAP: mean arterial pressure; PC: pressure-controlled; PS: pressure support; PEEP: positive end-expiratory pressure; pO_2: oxygen tension; pCO_2: carbon dioxide tension.

Simplified Acute Physiology Score 3 before ICU admission was 79, and her Sequential Organ Failure Assessment score was 15, demonstrating the severity of her clinical status and the high risk of death. Figure 2 shows a chest X-ray taken immediately after ECMO initiation. A large quantity of blood in the tracheal aspirate, together with the decreased hemoglobin concentrations and bleeding disorder (Table 1), was suggestive of a diagnosis of alveolar hemorrhage. Support with ECMO was maintained for six days, during which the patient received polymyxin and intravenous immunoglobulin for the treatment of pneumonia and the underlying disease, respectively. During that period, the patient required dialysis with continuous hemofiltration, and she was weaned from the noradrenaline. Because of her bleeding disorder, we chose to maintain the patient on ECMO without anticoagulation. No ECMO-related complications occurred. The patient presented with hypertensive pneumothorax in the left lung and therefore underwent pigtail catheter drainage (Figure 3).

During ECMO use, we performed daily autonomy tests, which consisted of attempts at maintaining gas exchange without ECMO for 1 h at the same pressures and frequencies, with an FiO_2 of 60%. For the first five days, the patient developed severe hypoxemia whenever the extracorporeal support was reduced. On the sixth day, after a satisfactory autonomy test result, ECMO was discontinued, and the ventilatory support was progressively reduced. On the eighth day, the patient was

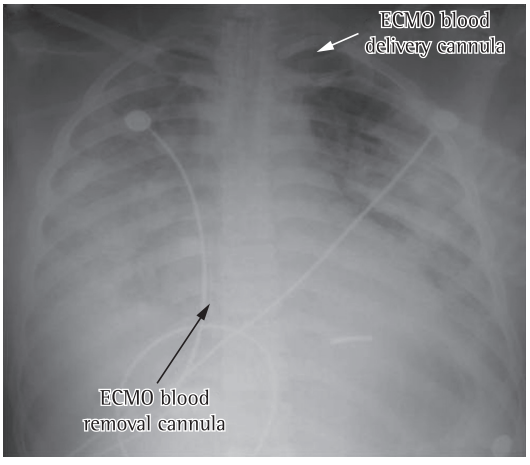

Figure 2 - Chest X-ray taken during extracorporeal membrane oxygenation use and showing the cannulas inserted into the inferior vena cava, through which blood is removed, and into the jugular vein, through which blood is returned to the patient. ECMO: extracorporeal membrane oxygenation.

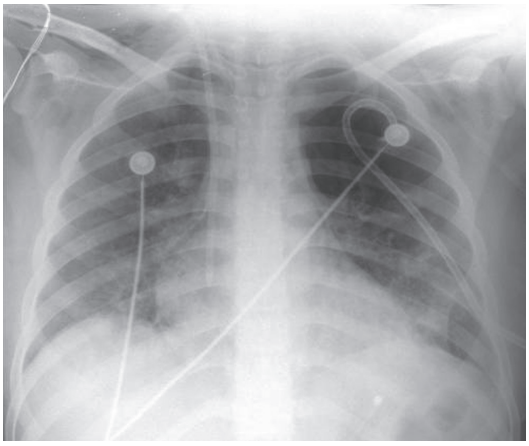

Figure 3 - Chest X-ray taken after clinical improvement and extubation.

extubated. Figure 3 shows a chest X-ray taken after extubation. On postadmission day 14, the patient was discharged to the infirmary. She was using an oxygen catheter at 2 L/min, and her SpO_2 was 98%.

In the clinical case reported here, we described the successful use of the ECMO technique, which should be progressively incorporated into the therapeutic armamentarium for patients with refractory hypoxemia but requires the use of special equipment by a properly trained team. The severity of the clinical condition of the patient, who presented with multiple organ failure and severe ARDS, is commonly associated with a high risk of death, pulmonary function being a determinant of patient evolution. The continuous use of ECMO, even while the patient is being transported from one hospital ICU to another, allows extracorporeal gas exchange in the period during which lung involvement is greatest, thus allowing the clinical condition and the prognosis to improve.

The Extracorporeal Support Study Group constitutes a pioneering project in Brazil and aims not only to treat patients with extremely severe respiratory failure but also to develop research and instruction activities related to the theme. Therefore, the objective of the group is to provide multidisciplinary teams with training in the aforementioned techniques in order to allow health care professionals at other facilities to use the method correctly.

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Sobre os autores

Luciano Cesar Pontes Azevedo
Attending Physician. Sírio-Libanês Hospital, São Paulo, Brazil.

Marcelo Park
Attending Physician. Sírio-Libanês Hospital and University of São Paulo School of Medicine *Hospital das Clínicas*, São Paulo, Brazil.

Eduardo Leite Vieira Costa
Attending Physician. Sírio-Libanês Hospital and University of São Paulo School of Medicine *Hospital das Clínicas*, São Paulo, Brazil.

Edzângela Vasconcelos Santos
Head Nurse. University of São Paulo School of Medicine *Hospital das Clínicas*, São Paulo, Brazil.

Adriana Hirota
Attending Physician. University of São Paulo School of Medicine *Hospital das Clínicas*, São Paulo, Brazil.

Leandro Utino Taniguchi
Attending Physician. University of São Paulo School of Medicine *Hospital das Clínicas*, São Paulo, Brazil.

Guilherme de Paula Pinto Schettino
Physician-Manager. Sírio-Libanês Hospital, São Paulo, Brazil.

Marcelo Brito Passos Amato
Chief Physician. University of São Paulo School of Medicine *Hospital das Clínicas*, São Paulo, Brazil.

Carlos Roberto Ribeiro Carvalho
Supervising Physician. University of São Paulo School of Medicine *Hospital das Clínicas*, São Paulo, Brazil.