Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome: single-centre experience with 1-year follow-up†

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Abstract

OBJECTIVES: During 2009, pandemic influenza A (H1N1) affected France and several patients developed influenza A (H1N1)-associated acute respiratory distress syndrome. The use of extracorporeal membrane oxygenation (ECMO) could be advocated as therapeutic solution. We present our experience with ECMO utilized in patients with influenza A (H1N1)-associated respiratory failure.

METHODS: We conducted a retrospective observational analysis of our experience with veno-venous ECMO for 2009 influenza A (H1N1)-associated respiratory failure. We have excluded from our study all not confirmed cases of influenza A (H1N1). Veno-venous ECMO was always instituted using a percutaneous cannulation technique. Mechanical circulatory support was maintained until respiratory function recovery.

RESULTS: Between October 2009 and February 2010, we performed veno-venous ECMO support in 12 patients with influenza A (H1N1)-associated respiratory failure. Mean age was 33 ± 12 years (14–63 years) and there was a prevalence of female sex. Median time from influenza A (H1N1) onset to mechanical ventilation (MV) initiation was 6 days (1–17 days); median time from MV to veno-venous ECMO support was 3 days (1–20 days). Six patients (50%) suffered ventilator-associated pneumonia during ECMO support. Eight patients (66.6%) suffered significant haemorrhage requiring transfusion of more than 2 packed red cells. In two patients (16.6%), there was a thrombosis of the inferior vena cava and one of them experienced pulmonary embolism. Mean duration of ECMO support was 23 ± 14 days (3–47 days); mean duration of mechanical ventilatory support was 24 ± 21 days (6–70 days). ECMO was weaned in 10 patients (83.3%) and all these patients are still alive after a period of follow-up of 13.8 ± 1.12 months (11.03–14.83 months). Two patients (in-hospital mortality of 16.6%) died under ECMO support for refractory septic shock.

CONCLUSIONS: Veno-venous ECMO for 2009 H1N1-associated respiratory failure gives good results with a very low mortality rate. The use of a mobile unit is a safe procedure and may improve survival of patients who might not be otherwise eligible for transfer to our institution. Larger studies are however required in order to optimize and refine the best treatment strategy in this subgroup of patients.

Keywords: Acute respiratory distress syndrome • Influenza A H1N1 • Extracorporeal membrane oxygenation

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a serious clinical condition which compromises progressively lung function and finally culminates in severe hypoxaemia or hypercapnia. Despite aggressive medical management and new insights in the pathophysiology of this disease, mortality rate due to ARDS is still high [1]. In this setting, the use of extracorporeal membrane oxygenation (ECMO) could be advocated as extreme and life-saving therapeutic solution. Originally applied to support the respiratory function of paediatric patients with good results [2], the use of ECMO has been progressively extended to adult population [3]. As outlined in the CESAR trial, ECMO treatment in the setting of severe adult respiratory failure is associated with significant improvement in survival at 6 months compared with conventional ventilation treatment [4]. During 2009, pandemic influenza A (H1N1) began in Mexico during March and also affected France during northern hemisphere winter and several
patients developed H1N1-associated ARDS. Here, we present our experience with ECMO support utilized in patients with H1N1-associated ARDS.

MATERIALS AND METHODS

We performed a retrospective observational analysis of our experience with ECMO support for 2009 H1N1-associated ARDS. In this setting, veno-venous (V-V) ECMO was indicated in two situations: the first is a PaO2/FiO2 ratio <50 mmHg despite FiO2 > 80% and positive end-expiratory pressure (PEEP) adjusted to obtain a plateau pressure (P-plate) <32 cmH2O; the second is a P-plate >35 mmHg, despite a reduction in PEEP to 5 mmHg and tidal volume (V-t) to 4 ml/kg. Absolute contraindication to V-V ECMO is short life expectancy linked to neoplastic or other medical conditions. Any contraindications to anticoagulation, age over 70 years, multi-organ failure, duration of mechanical ventilation (MV) >7 days, Sequential Organ Failure Assessment (SOFA) [5] score >15 or Simplified Acute Physiology Score (SAPS) [6] >90 are considered relative contraindications. We have also calculated the APACHE II score for every patient [7]. Every patient had a transthoracic echocardiography to estimate cardiac function before V-V ECMO institution. In the case of severe hypotension (mean arterial pressure <60 mmHg) and preserved cardiac function, before ECMO initiation, we preferred to manage first volaemia (target central venous pressure of 10–12 mmHg) and then to start vasopressor support in order to maintain a mean arterial pressure of >70 mmHg and to avoid implantation of veno-arterial (V-A) ECMO. V-V ECMO was then instituted using the percutaneous Seldinger technique. Venous drainage site was preferably the femoral vein, preferably with a 24 Fr cannula (Edwards Lifesciences, Irvine, CA, USA), and the reinfusion site was mainly the right jugular vein, with a 16–18 Fr cannula (Edwards Lifesciences). In cases in which the right jugular vein was not available for cannulation (venous thrombosis, previous surgery, etc), reinfusion cannula was introduced either in the subclavian vein or in the contralateral femoral vein. After cannulation of the vessels, we systematically performed a chest X-ray or a transthoracic echocardiography in order to check the correct position of the inflow cannula at the inferior vena cava-right atrium junction. V-V ECMO system consists also of venous (drainage) and arterial (reinfusion) tubing, a membrane oxygenator (Quadrox Bioline, Jostra-Maquet, Orléans, France), a centrifugal pump (Rotaflow, Jostra-Maquet, Orléans, France) and an oxygen/air blender (Sechrist Industries, Anaheim, France) and a centrifugal pump (Rotaflow, Jostra-Maquet, Orléans, France) and an oxygen/air blender (Sechrist Industries, Anaheim, France), a centrifugal pump (Rotaflow, Jostra-Maquet, Orléans, France) and an oxygen/air blender (Sechrist Industries, Anaheim, France). In the case of ECMO institution in a remote hospital, after commencement of mechanical respiratory support and stabilization of the patient, we transferred all the patients to our medical intensive care unit (ICU) by means of our Mobile Unit of Mechanical Circulatory Support. ECMO management encompassed centrifugal pump flow between 4.5 and 6.5 l/min, gas flow between 4 and 5 l/min and FiO2 set between 40 and 100% depending on oxygenation capacity of artificial membrane. Ventilator setting was usually as less aggressive as possible with volume-controlled ventilation using V-t of 2–4 ml/kg, PEEP at 5–10 mmHg, P-plate <20–23 cmH2O, respiratory rate of 8–10/min and FiO2 < 50% adjusted to obtain more than 85% in arterial oxygen saturation (SaO2). Anticoagulation management was obtained with continuous heparin infusion maintaining activated clotting time at 150–180 s. Criteria for changing ECMO circuit were: massive deposition of fibrin, severe hypoxaemia despite oxygenation at 100% FiO2, severe thrombocytopenia without other aetiology, significant haemolysis, membrane rupture and pump, motor or controller dysfunction. In our experience, we used to systematically change the circuit every 7–10 days. Renal failure (3-fold increase in the upper threshold of creatinine value, urine output <0.5 ml/kg over 24 h or anuria for 12 h) was managed by continuous V-V haemofiltration. In the case of persistent respiratory failure requiring long-lasting MV, percutaneous tracheotomy was usually performed. Rapid diagnosis of influenza A was made with quantitative real-time polymerase chain reaction assays on nasal swabs and we excluded from our study all non-confirmed cases. Once the results of nasal swabs were available, we began an antiviral treatment with Oseltamivir (150 mg per day). V-V ECMO support was maintained until respiratory function recovery. We considered good criteria for V-V ECMO weaning a PaO2/FiO2 ratio >200 mmHg with 21% FiO2 on ECMO, centrifugal pump flow <1 l/min and gas flow <1 l/min and, concerning MV setting, P-plate <18 mmHg, FiO2 <60% and PEEP <7 mmHg. Demographics, haemodynamic and respiratory pre- and post-implantation data, complications associated with V-V ECMO support and causes of death were retrieved and collected. Main outcome variables were survival to V-V ECMO weaning, survival to hospital discharge and 1-year survival. Every patient discharged from hospital has been contacted to confirm vital status at 1 year. This study has been conducted in accordance with the ethical committee of our hospital. Written informed consent for every data analysis was not obtained according to French legislation because this observational study did not modify existing diagnostic or therapeutic strategies [8]. Continuous variables were expressed as means ± standard deviation or medians. Categorical data were expressed as counts. Comparisons used pair bilateral t-test for continuous variables. A P-value of <0.05 was considered significant.

RESULTS

Between October 2009 and February 2010, we performed V-V ECMO in 12 patients with a confirmed diagnosis of H1N1-associated ARDS. The mean age was 33 ± 12 years (range 14–63 years) and there was a prevalence of females (male to female ratio is 1:2). Patients’ data before V-V ECMO implantation are summarized in Table 1. In particular, the most frequent co-morbidities were: obesity (body mass index ≥30 kg/m2) in seven patients (58.3%), asthma in two patients (16.6%), immunodeficiency in two patients (16.6%) and infection from hepatitis B and C virus in one patient (8.3%). Pregnancy or post-partum condition was present in four patients (33.3%, with 16.6% ongoing pregnancy). Pregnancy was, respectively, 25th and 31st week. In the first case, it was necessary to perform an emergency Caesarean delivery because of foetal death the day before ECMO commencement. In the second case, respiratory support with ECMO has lasted 8 days and the pregnancy was carried to the end of 9 months. Eight patients (66.6%) had no relevant past medical history or risk factors for respiratory disease. Median time from influenza A onset to MV initiation was 6 days (range 1–17 days) and median time from MV initiation to V-V ECMO support was 3 days (range 1–20 days). We implanted femoro-jugular V-V ECMO in all patients but two, for whom outflow cannula was inserted in the contralateral femoral vein or in the subclavian vein. Mean pump flow was 4.4 ± 1.3 l/min (range 2.2–6.5 l/min). We never switched a V-V ECMO support to a V-A
ECMO support. No events occurred while transferring patients on ECMO to our institution for the 11 patients implanted in a remote hospital. As shown in Table 2, blood gas parameters after ECMO initiation: three patients (25%) requiring norepinephrine infusion (mean dosage 4.7 ± 5.5 mg/h, range 1–13 mg/h), two patients (16.6%) epinephrine (mean dosage 8.4 ± 10.2 mg/h, range 0.5–20 mg/h) and one patient (8.3%) requiring both. At admission to our ICU, mean SAPS II score was 41.6 ± 18.5 (range 22–77), mean SOFA score was 9.8 ± 5.1 (range 3–21), mean APACHE II score was 18.9 ± 7.2 (range 11–35) and mean Glasgow score was 8.6 ± 4.4 (range 3–15). At admission, four patients (33.3%) had secondary bacterial pneumonia. The most common organisms involved were methicillin-sensitive Staphylococcus aureus (MSSA) in two patients and Streptococcus pneumoniae in two patients. One patient (8.3%) experienced a septic shock due to MSSA carrying Pant−Valentine leukocidin genes. After initiation of V-V ECMO support, a decrease in blood lactate (mean 1.9 ± 0.7 mmol/l, range 0.5–3 mmol/l) and PCO2 (mean 37.2 ± 6.7 mmHg, range 26.4–47.5 mmHg) and improvement in SaO2 (mean 92.5 ± 7.9%, range 88–100%), pH (mean 7.38 ± 0.14, range 6.99–7.50) and PO2 (mean 89.0 ± 42.5 mmHg, range 46–189 mmHg) reflected improvement of oxygenation and cellular metabolism. Table 2 shows blood gas data 1 h after ECMO initiation. As shown in Fig. 1, all ventilation parameters were significantly improved.

Six patients (50%) suffered ventilator-associated pneumonia (VAP) during V-V ECMO support and ICU stay. Pathogens were Escherichia coli (one patient, three episodes), high-concentration cephalosporinase-producing E. coli, Pseudomonas aeruginosa, association of P. aeruginosa and Klebsiella pneumoniae, MSSA and association of MSSA and Enterobacter cloacae. Two of these patients (both of them with infection due to MSSA) already had, at the moment of admission to our ICU, secondary bacterial pneumonia. Five patients (41.6%) experienced bacteraemia related to Acinetobacter baumannii (n = 1), high-concentration cephalosporinase-producing E. cloacae (n = 2) and Enterococcus faecalis (n = 2). Eight patients (66.6%) experienced significant haemorrhage requiring transfusion of more than 2 packed red blood cells. Five patients (41.6%) required continuous V-V hemofiltration for acute renal failure; two of these patients finally died and the remaining three completely recovered a normal renal function. Four patients (33.3%) experienced pneumothorax, which was bilateral in two cases. All were treated with a chest tube. There were no occurrence of major neurologic events; one patient experienced a flaccid quadriplegia related to long-term ICU stay and totally recovered. With respect to complications of
and in good performance status.

months (range 11.0–23.7). In 10 patients (83.3%) and all these patients survived to ICU discharge. Two patients died on ECMO support was 24 ± 21 days (range 6–70 days). ECMO was weaned in 10 patients (83.3%) and all these patients survived to ICU discharge and to hospital discharge. Two patients died on ECMO (in-hospital mortality of 16.6%) and both died from septic shock: one patient died from early-onset E. coli VAP 24 h after ECMO initiation and one patient died from septic shock due to P. aeruginosa VAP. After a mean period of follow-up of 13.8 ± 1.12 months (range 11.03–14.83 months), 10 patients were still alive and in good performance status.

**DISCUSSION**

In our experience, we utilized V-V ECMO in 12 cases of confirmed H1N1-associated ARDS. After a mean period of support of 23 days, 10 patients were weaned from ECMO and were finally discharged alive from our hospital. Therefore, hospital mortality was 17% and these data are comparable with the results of other published series with similar populations [9, 10]. In fact, H1N1-associated ARDS carries a high morbidity and mortality rate and ECMO support helps to face this life-threatening disease. Moreover, data obtained at follow-up show an excellent 1-year survival rate. These good and encouraging results can be partially explained by the nature of the ECMO indication itself. Indeed, it has already been understood that ECMO support for ARDS secondary to H1N1 (as other viral pneumonia) have better results than for other causes of ARDS [11]. H1N1 concerns, in most cases, young patients with no or few comorbidities and, even if the respiratory failure could be severe, it is a disease with rapid onset and very high potential of recovery.

Moreover, in our experience, the rate of complications directly associated with venous vessels percutaneous cannulation is acceptable. We did not experience venous vessels laceration or infections at the site of cannulas insertion. Haemorrhagic complications did not require immediate surgical intervention but only packed red blood cells transfusions. Despite optimal antithrombotic treatment, two patients experienced deep venous thrombosis (both of them at the level of the inferior vena cava) and one of them finally developed acute pulmonary embolism. Transportation from the referring hospital to our ICU was uneventful and, as previously described [12], it is a safe procedure in experienced team.

From a practical standpoint, our general experience with V-V ECMO support shows that it is mandatory to have a good pump flow in these patients in order to reach a satisfactory oxygenation. This allows to set up the MV parameters to so-called ‘protective ventilation’ trying to limit MV-related lung damages. Indeed, these lesions can be partially or even totally irreversible, thus limiting the possibilities of pulmonary function recovery, and are directly due to the absence of a protective ventilation without ECMO [13]. So, it is worthy to stress the attention over two aspects of V-V ECMO support: first, the assistance must be initiated early in the natural history of the pathology, before instauration of irreversible lesions, and secondly, V-V ECMO must be the most effective as possible. In our opinion, the most effective configuration of this mechanical respiratory support is the femoro-jugular V-V ECMO. The venous drainage cannula is inserted in the femoral vein and its tip is placed at the inferior vena cava–right atrium junction; indeed, this cannula drains only deoxygenated blood to avoid requirement of high flow. The infusion cannula is inserted in the right jugular vein and its tip is placed at the level of the superior vena cava. This configuration has the lowest risk of shunt effect.

The main limitations of our study are the small numbers of patients and the fact that it is a retrospective observational study.

In conclusion, the results of this observational study show that the use of V-V ECMO in the setting of 2009 H1N1-associated ARDS gave good results with acceptable complications and mortality rate. This study also confirms that the use of a mobile unit is a safe procedure, allowing ECMO implantation and commencement in the referring hospital and then transportation to our ECMO experienced unit. A larger, multicentre study is however required in order to optimize and refine the best treatment (medical, ventilatory and mechanical) strategy in this subgroup of patients with respiratory failure.

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