Research Article

Venoarterial extracorporeal membrane oxygenation support for neonatal and pediatric refractory septic shock

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Abstract

Objective: To report our institutional experience of veno-arterial extracorporeal membrane oxygenation (VA ECMO) in children with refractory septic shock. **Materials and Methods:** We retrospectively reviewed our ECMO database to identify patients who received VA ECMO for septic shock from January 2004 to June 2013 at our Pediatric Intensive Care Unit in Armand-Trousseau Hospital. We included all neonates and children up to the age of 18 years who received VA ECMO for septic shock. For each patient, we collected the pre-ECMO inotrope score, clinical circulatory and ventilatory parameters, infecting organism, ECMO duration and complications, and length of hospital stay. **Main Results:** The study included 14 neonates and 8 older children (the pediatric population, with a mean age of 30 months, range: 1–113 months). Survival was 64% among newborns and 50% among pediatric patients. Multiorgan failure or severity scores did not show any correlation with mortality (Pediatric Logistic Organ Dysfunction score, $P = 0.94$; the score for neonatal acute physiology-perinatal extension II, $P = 0.34$). In the pediatric population, the inotrope score was higher in the survivor group (127.5 vs. 332.5, $P = 0.07$). Blood samples taken shortly before cannulation showed that pH ($P = 0.27$), lactate level ($P = 0.33$), PaO2/FiO2 ratio ($P = 0.49$), or oxygenation index ($P = 0.35$) showed no correlation to success or failure of ECMO. **Conclusion:** ECMO can be safely used to resuscitate and support children with refractory septic shock. We recommend that patients with oliguria whose lactate level has not decreased within 6 h of starting maximum drug therapy be transferred to an ECMO referral center.

Keywords: Extracorporeal membrane oxygenation, neonatal, pediatric, refractory, septic shock

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Introduction

Septic shock is an important cause of mortality in Pediatric Intensive Care Units (PICUs) and one of the leading causes of childhood mortality worldwide. In developed countries, mortality from pediatric septic shock ranges from 15% to 50%.[1-4] The American College of Critical Care Medicine has published guidelines to assist clinicians caring for children with septic shock.[5] These recommendations were reinforced by a section on treatment of children in the first Surviving Sepsis campaign guidelines in 2004, and regular updates thereafter.[6-8] It is recommended that venoarterial extracorporeal membrane oxygenation (VA ECMO) be considered for neonates or children with circulatory

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collapse unresponsive to all conventional treatment.[8] Overall, survival of septic patients supported with ECMO is 73% for neonates and 39% for older children.[9] Compared with these rates for conventional ECMO, the outcome for children appears better in central (also called atrio-aortic) ECMO, for which a 74% pediatric survival rate has been reported.[10]

The aim of this study was to describe our experience in the management of refractory septic shock treated with conventional ECMO.

Materials and Methods

Patients

This single-center retrospective study of our ECMO database identified patients who received conventional VA ECMO for refractory septic shock from January 2004 to June 2013, in the Armand-Trousseau Hospital PICU, a conventional ECMO referral center.

Neonates and children up to 18 years old were included if they met the following inclusion criteria: VA ECMO for circulatory collapse after the failure of fluid resuscitation and inotrope therapy, clinical signs of infection, isolation of a bacterial microorganism, and a high lactate level.

Our protocol for VA ECMO excludes children with prolonged cardiac arrest (>60 min) or a severe irreversible neurological pathology such as cranial hemorrhage or flat electroencephalogram tracing and those with secondary septic shock who required ECMO primarily for respiratory failure.

The institutional review board approved this study.

General management of septic shock

Our practices follow the guidelines published by Dellinger *et al*.[11] Children with severe septic shock admitted to our unit are given volume loading with colloid or crystalloid infusion before a vasoactive agent is started, generally dopamine in neonates and norepinephrine in children. Dobutamine is used if there is evidence of myocardial depression and low cardiac output. ECMO is instituted if shock persists, or cardiac arrest occurs.

Application of extracorporeal membrane oxygenation

VA ECMO is applied by trained vascular surgeons at bedside because hemodynamic instability makes it too dangerous to move the child. In neonates and children weighing less than 20 kg, cannulas are placed in the jugular vein and the carotid artery. In larger children, a femoral artery cannula is also placed, with an additional catheter systematically inserted distally into the femoral artery to prevent leg ischemia.

The pumps used in this study were nonocclusive pumps with distensible tubing (A100, Sofracob®) for newborns and centrifugal pumps (Rotaflow, Maquet®) for pediatric patients.

The membrane oxygenators used were the MedosHilite800LT® and MaquetQuadrox-iDpediatric®. The main difference between these two types of membrane oxygenators lies in their structure, their surface, and their cost.[12]

Patient management during extracorporeal membrane oxygenation

The pump is adjusted to obtain a blood flow of 100–150 cc/kg/min for neonates and 4–6 L/m2/min for children. Anticoagulation with intravenous unfractionated heparin is administered to maintain an activated partial thromboplastin time of twice normal. Weaning from ECMO is decided after hemodynamic parameters have remained normal for 12 h, with minimal assistance.

Data collected at Intensive Care Unit admission

Before cannulation, we recorded the following information: Age, sex, infection site, microorganism identified, Pediatric Logistic Organ Dysfunction score (PELOD),[13] pediatric index of mortality II (PIM II) score, score for neonatal acute physiology-perinatal extension II (SNAP, and SNAPPE for neonatal patients),[14] time from PICU admission to cannulation, whether ECMO began during cardiopulmonary resuscitation, the pre-ECMO inotrope score, defined as dose of dobutamine (μg/kg/min) + (dose of epinephrine [μg/kg/min] + dose of norepinephrine [μg/kg/min] × 100),[15] the PaO_2/FiO_2 ratio,[16] blood gas analyses, blood lactate, urine output, leukocyte count, C-reactive protein (CRP), procalcitonin (PCT), positive end-expiratory pressure, indexed tidal volume, and oxygenation index.

The principal outcome variables were survival to PICU discharge, time to lactate normalization, and neurologic complications. Other outcomes included the need for renal replacement therapy, the number of units of packed red blood cells and platelets transfused, capillary leak syndrome, hemorrhagic complications, days on ECMO, and time on mechanical ventilation.

Statistics

Continuous data were presented as means (standard deviation) for normally distributed variables or medians (inter-quartile-range) for skewed. A categorical variable was presented as proportions. We compared survivor and nonsurvivor population using Fisher's exact test or ANOVA tests, if appropriate. $P < 0.05$ was considered as significant.

We used Stata 13 (StatCorp, College Station, Texas, USA) for analysis.

Results

General population

We compared survivors and nonsurvivors in the entire population and separately by age group (neonates and pediatric population). This population comprised 22 patients: 14 neonates and 8 children. Eight were girls and 14 boys.

Table 1 describes the patients' characteristics at the time of connection to the ECMO circuit and the cause of their septic shock. Among the neonates, the shock was due to *Streptococcus* B infection for 57% and to *Escherichia coli* in 36%. The mean age of the pediatric population was 30 months (range: 1–113 months). All patients were intubated, ventilated and received inotropes before ECMO. Despite fluid and vasoactive drug administration, they had a progressive circulatory failure.

Two patients (9%) had cardiac arrest and were receiving chest compressions during cannulation. Conventional ECMO was placed at a mean of 12 (±13.4) h after admission in our unit.

The overall survival rate was 59.1%. Nine newborns survived to hospital discharge (64%), and 4 pediatric patients (50%). Survival was significantly better among the neonates ($P = 0.02$).

Survivors did not differ significantly from the patients who died for their inotrope score ($P = 0.77$), or for laboratory or ventilation data.

Neonatal population

Preadmission and admission data

Table 2 summarizes the clinical characteristics of the neonates before ECMO. The mean SNAPPE-II severity score on PICU admission was associated with a 15.8% risk of mortality (±17.4) and did not differ between those who did and did not survive. The average time until cannulation after arrival in our unit was 9.3 h (range: 1–21).

Table 1: Infectious disease responsible for refractory septic shock

Patients	Bacterial microorganism
Neonate 1	*P. aeruginosa*
Neonate 2	*Streptococcus* B
Neonate 3	*Streptococcus* B
Neonate 4	*Streptococcus* B
Neonate 5	-
Neonate 6	*E. Coli*
Neonate 7	*E. Coli*
Neonate 8	*Streptococcus* B
Neonate 9	*E. Coli*
Neonate 10	*E. Coli*
Neonate 11	*E. Coli*
Neonate 12	*Streptococcus* B
Neonate 13	*Streptococcus* B
Neonate 14	*Streptococcus* B
Pediatric 1	Influenza H1N1 and *S. pneumonia*
Pediatric 2	*Enterobacter*
Pediatric 3	-
Pediatric 4	-
Pediatric 5	*Streptococcus* A
Pediatric 6	*Legionella*
Pediatric 7	*Shigella*
Pediatric 8	*E. Coli*

S. pneumonia: Streptococcus pneumonia; P. aeruginosa: Pseudomonas aeruginosa; E. Coli: Escherichia coli

Table 2: Neonatal circulatory and ventilatory data immediately before cannulation for extracorporeal membrane oxygenation

Characteristics	Mean	Median	SD
Gestational weeks	39.3	40	2.09
Age (days)	1.1	1	1.23
Weight (kg)	3.3	3.4	0.45
SNAPPE II (risk of mortality %)	15.28	6.5	17.4
Inotrope score (μg/kg/min)	177.1	145	149.28
Mean arterial pressure (mmHg)	34	33	8.07
Mean pH (range)	7.13	7.11	0.12
Blood lactate (mmol/L)	7.94	6.88	4.92
Urine output (ml/kg/h)	1.8	0.5	1.9
C reactive protein (mg/L)	129.6	106.5	106.6
Tidal volume (ml/kg)	8.56	8.5	1.57
PEEP (cm H_2O)	6	6	1.83
Mean airway pressure cm H_2O	14	13	5.08
PaO_2/FiO_2 ratio	72	42	13.55
Oxygenation index	47	25	69.54
$PaCO_2$ (mmHg)	54	58	13.55

SD: Standard deviation; PEEP: Positive end-expiratory pressure; SNAPPE II: Score for neonatal acute physiology-perinatal extension II

The survivors did not differ significantly from nonsurvivors for multiorgan failure score ($P = 0.33$), inotrope score ($P = 0.2$), blood lactate level ($P = 0.11$), or pH ($P = 0.2$)

At PICU admission, 6 of the 14 neonates underwent Doppler echocardiography, with a mean left ventricular ejection fraction of 31.6% [range: 15–35]. Two patients had bradycardia during cannulation.

Postcannulation data

The mean time on ECMO was 7.43 days (range: 1–17). The mean lactate at hour 6 (H6) was 7.26 mmol/L (range: 2.4–18) and at H24 5.28 (range 1.4–11); it did not differ significantly between survivors and nonsurvivors. Six neonates (42%) had mechanical problems with the ECMO circuit. These included episodes of clotting in the circuit requiring circuitry changes, but no oxygenator pump failure or air in the circuit. One patient needed continuous hemofiltration. Of the remaining 5 deaths, 4 developed irreversible organ failure, and 3 died from failure of resuscitation while treatment was withdrawn for one. One patient was certified brain-dead.

Consumption of blood products

The average daily consumption of blood products was 0.22 units of packed red blood cells, 0.73 units of platelet concentrate, and 0.05 units of freshly active plasma. No significant difference was found between survivors and nonsurvivors for blood product consumption.

Pediatric population

Preadmission and admission data

Table 3 summarizes the clinical characteristics of the pediatric population before ECMO. At PICU admission, the mean PELOD score was 65.5% (±37.5) and the mean PIM II score 75% (±32.3) and did not differ significantly between survivors and nonsurvivors (P = 0.9 and 0.3, respectively). The mean time until cannulation after arrival in our unit was 16.9 h (±18.4; range: 0.5–48). Two children (25%) had had cardiac arrest and were receiving chest compressions immediately before cannulation. No significant difference was found between survivors and nonsurvivors regarding PELOD (P = 0.9), PIM II score (P = 0.2), or inotrope score (P = 0.07). The inotrope score was higher, but not quite statistically significant (P = 0.07), among the children who died than in survivors. The pre-cannulation blood test showed no significant differences between these two groups for blood lactate (P = 0.9), pH (P = 0.4), CRP (P = 0.1), or PCT (P = 0.2).

Table 3: Pediatric circulatory and ventilatory data prior to extra-corporeal membrane oxygenation implantation

Characteristics	Mean	Median	SD
Age (months)	30	15	37.5
Weight (kg)	11.1	10.5	6.4
PIM II (pediatric index mortality)	77.1	92.4	34.9
PELOD (risk of mortality %)	65.5	84	37.7
Inotrope score (μg/kg/min)	230	195	165
Mean arterial pressure (mmHg)	40	40	4.9
Mean pH (range)	6.97	7	0.14
Blood lactate (mmol/L)	5.2	5.3	3.5
Urine output (ml/kg/h)	1.3	0.6	1.5
Protein C-reactive (mg/L)	250.9	245.3	144.4
Tidal volume (ml/kg)	7	7.9	1.4
PEEP (cm H_2O)	8	7	4.5
Mean airway pressure cm H_2O	15	14	7.7
PaO_2/FiO_2 ratio	89.2	75.5	45.1
Oxygenation index	19	19.5	5.9
$PaCO_2$ (mmHg)	73	68	41.6

PEEP: Positive end-expiratory pressure; PELOD: Pediatric logistic organ dysfunction; PIM: Pediatric index of mortality; SD: Standard deviation

At PICU admission, seven of the eight children underwent Doppler echocardiography. Their mean left ventricular ejection fraction was 23.3% (range: 0–40).

Postcannulation data

The mean time on ECMO was 5.9 days (range: 3–10). Mean lactate at H6 was 5.18 mmol/L (range; 1.4–10) and at H24 3.23 (range: 1.4–9.5); it did not differ significantly between survivors and nonsurvivors. Three children (37%) had mechanical problems with the ECMO circuit, including episodes of circuit clotting requiring circuitry change, but no oxygenator pump failure or air in the circuit. Only one child (12%) presented severe cerebral bleeding, and two children (25%) had strokes. Three (37%) required renal replacement therapy, for a mean duration of 16 days (range: 3–16) (no significant difference between survivors and nonsurvivors for renal replacement therapy, P = 0.4). The mean duration of mechanical ventilation was 14 days (range; 4–31) and of PICU length of stay 17 days (range: 4–40). Six patients were weaned from ECMO (66%), but 2 died a few days later, one after the onset of an intracranial infarction and cerebral hemorrhage and the other after the onset of acute respiratory distress syndrome onset. Two patients died during ECMO: One was certified brain dead; treatment for other was withdrawn after the development of irreversible organ failure.

Consumption of blood products

The average daily consumption of packed red blood cells was 0.3 units per day, of platelet concentrates 1.6 units daily, and freshly active plasma 0.1 units daily. This blood product consumption did not differ significantly between survivors and nonsurvivors.

Discussion

ECMO for refractory septic shock is recognized as a useful last-resort treatment for adults,[17] neonates, and children.[10,17] Survival is better in the neonatal than the pediatric population, for all diseases combined, as reported to the Extracorporeal Life Support Organization registry (ELSO).[18]

Survival in adults varies widely, from 74% in the study by Bréchot *et al*. to 15% in that by Huang *et al*.[17,21]

Older studies report that ECMO for septic shock was associated with a survival rate greater than 80% in newborns[19,20] and 15% to 74% in older children.[10,21-23] These rates are both lower in our study. Changes over time in treatment modes and in the population of patients receiving ECMO may explain these differences.[24] The older studies do not report clinical or laboratory characteristics.[19] In 2011, MacLaren *et al*. reported a 74% survival rate in a series of 23 children with refractory septic shock treated with a new variant of VA ECMO that used central cannulation (through the right atrium and aorta). They called this central (or atrioaortic) ECMO.[10] Their preliminary data comparing the first 11 patients on central ECMO to historical controls suggested improved survival to hospital discharge in the group with central ECMO.[23,25] Their 2011 results confirm this data.[10] The patients in our study seemed to present more severe hemodynamic failure, with higher inotrope scores (230 vs. 82.2) and lower pH (6.97 vs. 7.11) than in MaLaren's cohort. The level of multiorgan failure is difficult to analyze or compare in the absence of scoring systems such as PIM II and PELOD. Our pediatric patients had a high risk of mortality before ECMO. There is, unfortunately, no scoring system for multiorgan failure for neonates.

Nevertheless, our survival rate approximates that in MacLaren's first study[23] in the children undergoing conventional ECMO (that is, with peripherally placed cannulas). It is difficult to judge the pertinence of central ECMO objective in refractory septic shock. MacLaren *et al*.[23] compared this option to results from their historical cohort with conventional ECMO. Advances in ECMO technology between the two periods include aspects of biocompatibility, monitoring, and membrane lungs.[26] Central ECMO is more invasive, and it is indicated only for left ventricular failure due to outflow obstruction. Our cohort included no patients with left ventricular failure during ECMO.

In our study, the inotrope score was higher in the children who died. This observation raises a recurring question: When can septic shock be considered refractory? The Surviving Sepsis campaign[8,11] clearly defines the 1st h of severe sepsis and septic shock but not the onset of refractory septic shock or any time period at which VA ECMO should begin. Effective lactate clearance during the first 6 h of septic shock is known to be a reliable indicator of better prognosis, and several studies have suggested that persistent lactate elevation is associated with high patient mortality and multiple organ damages.[27-30] These studies provide a reasonable basis for using serial lactate laboratory tests to monitor for prognosis and therapeutic effectiveness in pediatric septic shock.

In 2009, Brierley *et al*.[5] defined early goals of therapy for septic shock but did not specify a time course at which VA ECMO is indicated for a refractory septic shock. There is currently no time period consensually used to define when septic shock becomes refractory. We suggest here that refractory septic shock be defined as the absence of lactate clearance.[31] associated with oliguria 6 h after maximum drug therapy begins. We propose that neonates and children are meeting these criteria be transferred to a referral center for ECMO.

Conclusion

Extracorporeal membrane oxygenation can be safely used to resuscitate and support children with refractory septic shock. We propose to transfer to an ECMO referral center patients who have oliguria and no decrease of lactate level with oliguria within 6 h of maximum drug therapy.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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