

Rapid-response extracorporeal membrane oxygenation to support failed conventional cardiopulmonary resuscitation (E-CPR) in children – case reports and literature review

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ABSTRACT

The use of extracorporeal membrane oxygenation (ECMO) to support failed conventional cardiopulmonary resuscitation e.g. ECMO cardiopulmonary resuscitation (E-CPR) in children has been increasing. We report on the first three patients in whom E-CPR was used at our institution, a low volume surgical centre. Patient's diagnoses were: influenza B myocarditis, truncus arteriosus two days after complete surgical repair and cardiogenic shock during adenovirus infection with a discovered recoarctation of the aorta. The use of E-CPR rescued 1 patient (33%) out of three. Apart from high volume surgical centres, E-CPR can also be implemented in low volume centres with a trained in-house ECMO team, in selected cases.

Key words: cardiopulmonary resuscitation, child, extracorporeal membrane oxygenation, refractory cardiac arrest

Introduction

The use of extracorporeal membrane oxygenation (ECMO) to support failed conventional cardiopulmonary resuscitation (CPR), e.g. ECMO cardiopulmonary resuscitation (E-CPR) in adult and paediatric post-cardiac arrest patients, has been increasing. (1-6) E-CPR is used to support CPR in children with cardiac and non-cardiac diseases who would die without this intervention. (4) The main conditions in which E-CPR is currently used in children are: the early postcardiotomy period, operated and

non-operated congenital heart disease, myocarditis, cardiomyopathy, sepsis, paediatric and neonatal respiratory failure and trauma. (5) European Resuscitation Council Guidelines from 2010 encourage consideration of E-CPR in children with cardiac arrest refractory to conventional CPR, if the arrest occurs in a highly supervised environment and if there is available expertise and equipment. (7) Currently E-CPR in children is still instituted mainly in in-hospital paediatric cardiac arrests, (4-6) although reports of successful E-CPR in adult and paediatric out-of hospital cardiac arrests are emerging, especially with new portable ECMO systems. (8,9) The overall survival rate to hospital discharge in paediatric in-hospital cardiac

arrest post E-CPR is 33-51% (4-6,10-13) with approximately three quarters of children who survived showing good neurological outcome. (4,6,14) Children with cardiac disease showed the best survival rate, exceeding 50% in some series. (4) Another group showing good survival with E-CPR was neonates with respiratory failure. (5) In children with other medical conditions survival rates were lower. (5) Thereby E-CPR is still considered to be reserved for selected groups of paediatric patients. (15) E-CPR is well established in high-volume paediatric surgical centres with trained E-CPR teams and short activation time. However, reports from adults show that E-CPR can also be successfully used in very low-volume cardiac

surgical centres, in selected patients. (16) In our level III multidisciplinary neonatal and paediatric intensive care unit the first paediatric ECMO was done in 1994. (17,18) Since then, ECMO has been used in 45 paediatric patients. Approximately 70 open-heart surgical procedures are performed annually in neonates and children at our institution and we have had 3-5 ECMO runs per year in the last three years. Our ECMO team consists of an intensive care physician, cardiac surgeon, ECMO nurse and bedside nursing staff. Although our centre is of low-volume, we provide an in-house ECMO team 24 hours a day. Encouraged by recent progress in paediatric E-CPR, we started with our own E-CPR program in 2011. In this report we present and analyse our first three cases of E-CPR in children with different aetiologies of cardiac arrest.

Case reports

Patient 1

A 6-year old girl was admitted to our paediatric intensive care unit (PICU) with signs of shock and suspected myocarditis and myositis accompanying influenza B infection. Upon admission she was alert, complaining of generalized muscle pain, respiratory rate 24/min, oxygen saturation without oxygen supplementation 100%, heart rate 168/min, blood pressure 91/75 mmHg, capillary refill time 3-4 s, she was pale with cold extremities, body temperature 35.6 °C. Initial echocardiogram showed a structurally and functionally normal heart with a small pericardial effusion, without tamponade. Initial laboratory evaluation revealed a white blood count (WBC) $16.2 \times 10^9/L$, C reactive protein (CRP) <3 mg/L, PCT 0.10 $\mu g/L$, haemoglobin 132 g/L, lactate 3.1 mmol/L, aspartate transaminase (AST) 6.38 $\mu kat/L$, alanine transaminase (ALT) 1.61 $\mu kat/L$, creatine kinase (CK) 213 $\mu kat/L$, troponin I 6.455 $\mu g/L$, myoglobin 1891 $\mu g/L$; arterial blood gas analysis showed a pH 7.45, pCO_2 30 mm Hg, pO_2 111 mm Hg, base excess -2.6 mmol/L and bicarbonate 20.2 mmol/L. Following progressive haemodynamic deterioration she was sedated, intuba-

ted and mechanically ventilated. Her condition worsened despite volume resuscitation, inotropic support with dobutamine and epinephrine and vasopressor support with norepinephrine. Repeat echocardiogram, performed 12 hours later, showed a massive pericardial effusion with tamponade, and decreased left ventricular function. Pericardial drainage was performed and was soon followed by cardiac arrest. The patient was successfully resuscitated after 10 minutes and a left ventricular assist device (LVAD) (Levitronix) was implanted. Since her condition did not improve and she needed to be resuscitated again, we progressed to venoarterial ECMO support. After 60 minutes of CPR she was placed on ECMO (QUADROX PLS oxygenator, ROTAFLOW centrifugal pump; Maquet). Prior ECMO pH was 7.25 and lactate 10.9 mmol/L. We induced mild systemic hypothermia 33-34 °C for 48 hours, according to recent guidelines. (7) Since influenza B antigen was positive and influenza B virus RNA was present in endotracheal aspirate (polymerase chain reaction), treatment with oseltamivir was started. Renal function was not impaired despite high myoglobin levels (maximum 8776 $\mu g/L$), which tended to decrease over the following days. Haematemesis, caused by two stress gastric ulcers, was managed by endoscopic sclerotherapy on the second ECMO day. On the fourth ECMO day, improved contractility of the left ventricle was demonstrated by echocardiography. She was lightly sedated during ECMO support to allow interaction with personnel. On the fourth ECMO day sudden neurological deterioration was noticed. Pupils became dilated and cerebral function monitoring (CFM) and electroencephalography (EEG) detected decreased brain activity. Doppler ultrasound showed reduced velocities of blood flow through the right carotid artery, and computed tomography (CT) with angiography of intracranial arteries showed massive infarction of the right cerebral hemisphere with diffuse cerebral oedema. A repeat CT with angiography on the fifth ECMO day

confirmed irreversible cerebral oedema and ECMO support was discontinued. Acute viral myocarditis with aggressive mononuclear cell infiltration was histologically confirmed on autopsy as well as haemorrhagic infarction in the perfusion area of the right middle cerebral and posterior cerebral arteries with diffuse hypoxic-ischaemic injury and brain oedema.

Patient 2

A 4-month old girl was admitted to our PICU after complete primary repair of truncus arteriosus type I (cardiopulmonary bypass 95 min, circulatory arrest 73 min; unvalved pulmonary conduit). In the PICU, analgesia, sedation, muscle relaxation, mechanical ventilation and inotropic support with dopamine and milrinone was continued. Due to signs of pulmonary hypertension on transoesophageal echocardiography, nitrogen monoxide (NO) 20 ppm was started in the operating theatre. Atrial and ventricular pacemaker electrodes were inserted at the end of surgery after a short period of atrial tachycardia. During the following two days in the PICU a couple of episodes of hypotension occurred, which adequately responded to volume and calcium administration. Since pulmonary artery pressure was not monitored and there was no residual atrial septal defect after surgery, these episodes of hypotension were attributed to pulmonary hypertensive crises. In addition to NO, sildenafil was started. Due to volume overload, peritoneal dialysis was commenced on the first postoperative day. On the second postoperative day dopamine was stopped. One hour later another episode of hypotension occurred, but this one did not respond to volume, calcium or dopamine. The child became bradycardic and we started CPR. After a period of asystole ventricular fibrillation was noticed on the ECG monitor, and unsuccessful external defibrillation was attempted 6 times. After 30-minutes of CPR a resternotomy was performed and internal cardiac massage was started. Internal defibrillation turned ventricular fibrillation into

asystole again. We continued internal cardiac massage and performed surgical cannulation of the right atrium and aorta for venoarterial ECMO support. After 79 minutes of CPR the child was placed on ECMO (QUADROX PLS oxygenator, ROTAFLOW centrifugal pump; Maquet). Prior ECMO pH was 7.21 and lactate 19.0 mmol/L (figure 1). During subsequent hours, additional venous cannula was inserted into the superior vena cava and in the left atrium to unload the left atrium. A massive pulmonary haemorrhage followed resuscitation, heparinization and ECMO placement. The haemorrhage stopped gradually during the next few hours. Due to hyperkalaemia (potassium 8.8 mmol/L) and anuria, haemofiltration, with haemofilter added sequentially to the ECMO system, was started along with peritoneal dialysis. Echocardiography after ECMO placement showed akinesia of the left ventricle and minimal contractility of the right ventricle with no improvement over the following days. On the second ECMO day, pupils dilated and CFM detected no activity. EEG confirmed absence of brain activity so we started following the national brain death protocol. Brain death was determined on the third ECMO day and ECMO was discontinued. Autopsy revealed hypoxic brain injury, cerebral oedema, left parietal subdural haemorrhage, ischaemic gastroenterocolitis, massive pulmonary haemorrhage and fibrinous pericarditis.

Patient 3

A 7-week old girl was transferred by air to our PICU with signs of cardiogenic shock accompanying adenovirus infection. Before transport she was resuscitated three times for a couple of minutes. Forty-seven days before admission she had partial surgical repair of congenital heart disease (large non-restrictive muscular ventricular septal defect, bicuspid aortic valve, hypoplastic aortic arch, coarctation of aorta, smallish, apex forming left ventricle). Plasty of hypoplastic aortic arch, coarctation resection, duct closure and pulmonary artery banding was performed. On admission she

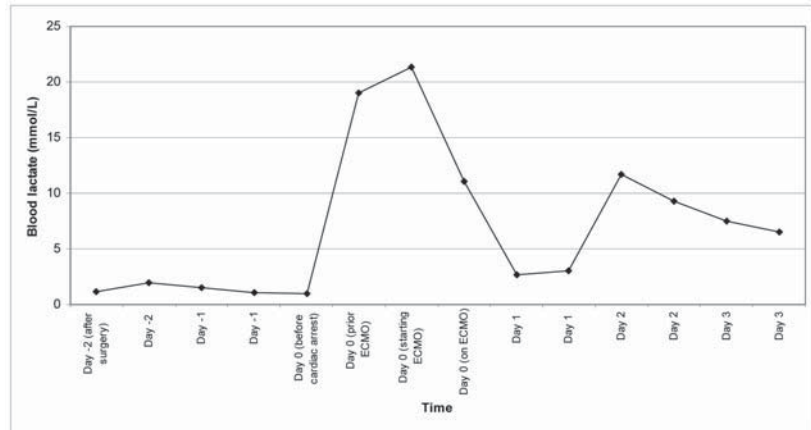


Figure 1. Blood lactate in a 4-month old girl with truncus arteriosus after cardiac surgery, before cardiac arrest, at the start of and during extracorporeal membrane oxygenation (ECMO) support.

was intubated, mechanically ventilated, placed on inotropic support with dopamine and dobutamine and vasopressor support with norepinephrine. Despite these measures she hemodynamically deteriorated and had to be resuscitated briefly, several times. Echocardiogram showed globally decreased contractility and function of both ventricles with no obvious recoarctation. During the fifth resuscitation, decision for venoarterial ECMO support was made. After 60 minutes of CPR she was placed on ECMO (QUADROX PLS oxygenator, ROTAFLOW centrifugal pump; Maquet). Prior ECMO pH 7.15 was and lactate 23.0 mmol/L. We induced mild systemic hypothermia 33-34 °C for 48 hours. Acute renal failure was managed first by haemofiltration with haemofilter added sequentially to the ECMO system and after two days by peritoneal dialysis. During two haemofilter exchanges, due to technical problems, she was resuscitated again on two consecutive days. Systemic hypothermia was prolonged to 4 days. Adenovirus DNA was confirmed in endotracheal aspirate (polymerase chain reaction) and we started treatment with cidofovir. Since adenovirus myocarditis was suspected, intravenous immunoglobulin was added. Melena, appearing on the 6th ECMO day, was managed conservatively with pantoprazole and continuous infusion of octreotide. Echocardiographically,

cardiac function improved dramatically during the following days, and she was successfully weaned from ECMO after 7 days. Her renal function gradually improved and dialysis was stopped one week after ECMO weaning. Nine days after ECMO weaning she was extubated and transferred to the general ward. During the next 10-hours she became hypertensive 120/84 mm Hg, tachypneic and tachycardic 184/min with signs of low peripheral perfusion (pH 7.26, lactate 10.6). She was transferred back to PICU. She was sedated, intubated and mechanically ventilated. Sodium nitroprusside infusion was started for blood pressure lowering. Control echocardiogram and CT angiography revealed recoarctation of aorta. Balloon catheter dilatation was performed with suboptimal results, so repeat plasty of the aortic arch was performed. The patient was discharged home with no major neurological impairment.

Discussion

We present the implementation of E-CPR as a bridge to recovery at our institution. Our first three children with cardiac arrest, in whom conventional CPR failed and ECMO was used, are described. The use of E-CPR rescued 1 patient (33%) out of three, who showed no major neurological impairment at discharge.

In all three patients there was a primary

cardiac cause of cardiac arrest: myocarditis, early postcardiotomy period, and congenital heart disease, respectively. Recently, most data about E-CPR use are from children with cardiac disease, the majority of them during the early postcardiotomy period, who experienced in-hospital cardiac arrest, mainly in the intensive care unit (ICU), and did not respond to conventional CPR. (4,5,19) There are no strict criteria for deployment of E-CPR and optimal activation time for E-CPR has not been ascertained, yet. (5,13) The decision to start E-CPR is not standardized and it is usually based on the patient's prognosis and made by the patient's primary bedside physician. (4,5) In the Children's Hospital Boston, E-CPR is activated in children with cardiac disease, who experienced an in-hospital cardiac arrest, if there is a failure of return of spontaneous circulation after 2 rounds of resuscitation drugs. (4) Other centres activate E-CPR when there is no recovery of cardiac function within 5 to 20 minutes. (11,19) Unfortunately, the activation time of E-CPR in our patients was not documented. At our institution the activation time for E-CPR is not yet strictly defined. It is based on the patient's specificity and depends on the physician's decision or in the postcardiotomy period on the surgeon's decision. The potential contraindications for E-CPR in children are pre-existing irreversible neurological injury, multi organ failure, irreversible or nonoperable primary disease, prematurity (<32-34 weeks gestation), major bleeding, and parental refusal of mechanical support. (4,19) Influence of duration of CPR before deployment of ECMO (ECMO set-up time) on outcome is still a matter of debate. Delmo Walter et al. found prolonged CPR a significant predictor of mortality. (19) A recent meta-analysis, which included 288 patients, showed that effectiveness of E-CPR is higher when implemented in the first 30 minutes after cardiac arrest. (20) On the other hand, in some series, duration of CPR was longer in patients who survived

(11), or did not predict survival. (4,6,10) Kane et al also showed that although the duration of CPR was reduced in on-going years, the survival rates in their centre did not improve. (4) Morris et al. reported that three from 6 patients who were resuscitated for more than 60 minutes survived with good neurologic function. (10) We can conclude from these data that there is no particular duration of CPR beyond which E-CPR is futile, although it seems reasonable to shorten the ECMO set-up time as much as possible. All of our three patients were receiving prolonged CPR for 60 minutes or more, but in two patients neurological function was good in the first days after ECMO placement. However, the duration of CPR before ECMO and additional time for insertion of two extra cannulas before optimization of ECMO support, was probably too long in our second postcardiotomy patient, since brain death due to hypoxic-ischemic injury occurred and cardiac function did not improve on ECMO. Delmo Walter et al. reported hypoxic-ischaemic brain injury as a cause for ECMO discontinuation in 7% of patients and persistent myocardial failure in 14% of patients. (19) Acute neurologic injury, defined as brain death, cerebral infarction or intracranial haemorrhage, was found in 22% of children undergoing E-CPR in the Children's Hospital Boston. (14) Additionally, children resuscitated and placed on E-CPR due to pulmonary hypertension have lower survival rates also in high volume centres. (4) Important predictors of mortality before ECMO in different series were: arterial pH below 7.0-7.17 (4,5), high blood lactate levels (6), high-dose inotropes before arrest (19); and during ECMO: arterial blood pH <7.2, development of end-organ injury, pulmonary haemorrhage, neurological injury, renal failure, CPR during ECMO. (4,5,6,20) All three of our patients had high serum lactate levels, but interestingly, levels of lactate were the highest in the patient who survived. This patient, who developed cardiogenic shock during an adenovirus infection and recoarctation of the

aorta discovered after ECMO weaning, survived despite several factors that increase mortality: low pre ECMO pH and high lactate, high-dose inotropes, renal failure and CPR during ECMO. We can learn from this case that final outcome cannot be predicted until it is achieved.

Common complications during E-CPR are brain injury, renal failure, sepsis, pulmonary haemorrhage, pneumothorax, arrhythmias, CPR during ECMO, gastrointestinal haemorrhage, hyperbilirubinemia, mechanical failure of ECMO circuit, thrombus in ECMO circuit and surgical site bleeding, which all occurred more often in non-survivors. (5,19) According to a recent meta-analysis complications occurred in 59% of patients. (20) In our three patients we documented: gastrointestinal haemorrhage 2, renal failure 2, brain injury 2, pulmonary haemorrhage 1, CPR during ECMO 1. The most catastrophic complication occurred in our first patient suffering from influenza B myocarditis. Her cardiac function was already improving and her neurological function was normal when a massive cerebral infarction occurred on the fourth ECMO day. Due to irreversible brain injury ECMO was discontinued and the patient died. According to other authors, complications during ECMO increase mortality and also influence survival rates after ECMO weaning. (5,20) Kane et al reported clinical and radiological evidence of CNS injury in 52% of patients receiving E-CPR. (4) Delmo Walter et al. reported ECMO discontinuation in 23% of patients due to severe neurologic injury. (19)

In conclusion, although E-CPR is still mainly reserved for high volume surgical centres, our last case shows, that it can be implemented in low volume centres with an in-house ECMO team, in selected cases. Training of all members of our team should continue to achieve shorter ECMO set-up times along with improving quality of CPR. In-hospital protocols and criteria for activation of E-CPR should be developed at our institution in the future.

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