The approach to extracorporeal cardiopulmonary resuscitation (ECPR) in children: a narrative review by the paediatric ECPR working group of EuroELSO

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The approach to extracorporeal cardiopulmonary resuscitation (ECPR) in children. A narrative review by the paediatric ECPR working group of EuroELSO

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Abstract

Extracorporeal Cardiopulmonary Resuscitation (ECPR) has potential benefits compared to conventional Cardiopulmonary Resuscitation (CCPR) in children. Although no randomised trials for paediatric ECPR have been conducted, there is extensive literature on survival, neurological outcome and risk factors for survival. Based on current literature and guidelines, we suggest recommendations for deployment of paediatric ECPR emphasising the requirement for protocols, training, and timely intervention to enhance patient outcomes. Factors related to outcomes of paediatric ECPR include initial underlying rhythm, CCPR duration, quality of CCPR, medications during CCPR, cannulation site, acidosis and renal dysfunction. Based on current evidence and experience, we provide an approach to patient selection, ECMO initiation and management in ECPR regarding blood and sweep flow settings, unloading of the left ventricle, diagnostics whilst on ECMO, temperature targets, neuromonitoring as well as suggested weaning and decannulation strategies.

Keywords

extracorporeal cardiopulmonary resuscitation (ECPR), paediatric, children, Extracorporeal life support organization (ELSO), ECMO, survival rate, outcome, EuroELSO, review

Introduction

Extracorporeal cardiopulmonary resuscitation (ECPR) is defined by the Extracorporeal Life Support Organization (ELSO) as veno-arterial (V-A) ECMO which is instituted during conventional cardiopulmonary resuscitation (CCPR), delivered with manual or mechanical compressions, or within 20 minutes of the return of spontaneous circulation (ROSC) without ongoing compressions.[1] Patients cannulated after 20 minutes of sustained ROSC are classified as receiving V-A ECMO, not as ECPR. The main goal of ECPR is to restore systemic circulation whilst allowing identification and treatment of the aetiology of the cardiac arrest (CA) and facilitating recovery of the heart and vital organs. Following ECPR, mechanical support can also be a bridge to organ transplantation if candidacy is ascertained (bridge to bridge in the form of durable mechanical support), long-term mechanical support or palliative care.

In children, in contrast to adults, no randomised controlled trials examining the role of ECPR have been published and ELSO guidance on paediatric ECPR is based on the available, mostly retrospective, evidence. In this review, we describe the background, selection criteria, practical aspects, and outcomes of ECPR in children and provide recommendations for patient population and indications for considering ECPR based

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on current knowledge, conventional resuscitation guidelines, literature, and expert opinion.

Conventional CPR

Conventional CPR (CCPR) for paediatric out-of-hospital cardiac arrest (OHCA) is associated with poor survival and poor neurological outcomes. After CCPR for OHCA, only 2%–11% survive to hospital discharge, and 2%–5% survive with good functional status.[2]

Outcomes of CCPR for paediatric in-hospital cardiac arrest (IHCA) are better and have improved over time. The last decades survival rates for paediatric IHCA have increased. Survival to hospital discharges are reported between 37%–54%.[3–5] Despite the significant increase of both ROSC and hospital survival,[6,7] only between 39 and 58% of patients in whom ROSC is achieved survive to hospital discharge.[4,7] In a paediatric intensive care setting a multicentre study has shown that approximately one quarter of the children who achieved ROSC, developed multiple CPR events, with only 25% survival to hospital discharge.[4] Mortality after ROSC is often caused by withdrawal of life sustaining support because of anoxic brain damage and/or renal failure.[6] In a recent analysis of 1100 children with IHCA, medical cardiac patients had lower odds of survival with favourable neurologic outcomes compared to non-cardiac and surgical cardiac patients.[8]

Potential benefits of ECMO in CPR

Lasa et al compared 591 ECPR patients with 3165 CCPR patients (CCPR >10min) using the American Heart Association Get With the Guidelines Registry (GWTG-R).[9] After adjusting for covariates, patients receiving ECPR had higher odds of survival to discharge [OR 2.80, 95% CI 2.13–3.69, $p < .001$] and survival with favourable neurologic outcome [OR 2.64, 95% CI 1.91–3.64, $p < .001$] compared to patients who received CCPR. Hospital mortality despite ROSC after CCPR may therefore be reduced by the judicious use of ECPR for specific patient populations and within a highly practiced environment, as stated in the current AHA guidelines.[10]

Compared to CCPR, ECPR may give better outcomes for several reasons. The most important factor is possibly the ability to fully "rest the heart" after a period of hypoperfusion and chest compressions, allowing the maximum opportunity for end-organ recovery. Providing adequate systemic perfusion is extremely important to prevent secondary damage of other organs including the brain, kidneys and intestines. Optimising ventilator pressures and limiting oxygen exposure minimises associated lung injury. The timely deployment of ECMO in a CPR setting often makes it possible to limit or stop inotropic and vasopressor support, reducing myocardial oxygen consumption whilst providing luxuriant coronary perfusion. This can theoretically permit myocardial recovery whilst maintaining good systemic perfusion. And finally, the ECMO system can be used to minimise secondary damage by hyperthermia through tight temperature regulation.

Survival

There are many publications about outcomes of paediatric ECPR, however, no RCT's have been conducted and evidence is limited to case series, single centre cohort studies, ECMO registry reports and some (systematic) reviews, mainly related to IHCA in children with cardiac disease. Therefore, all the available knowledge is based on experience in children in whom the decision to proceed with ECPR had been made by the treating team based on their experience and their local protocols.

The two largest cohorts in children include two ELSO registry studies describing survival to hospital discharge of 43% in 3005 patients and a more recent cohort (2011-2019) with survival 48% in 2289 patients.[11,12] Between 2009 and 2022, 5704 paediatric ECPR and 2142 neonatal ECPR cases were registered in the ELSO-registry with 41 and 44% survival to hospital discharge.[13] Several GWTG-R studies report a survival of 31%–51% in different patient populations.[9,14–18] Survival in smaller cohort studies vary from 14 to 80% depending on the study population.[19,20] A meta-analysis of 28 studies showed combined hospital survival of 46% in 1348 patients.[21]

Most ECPR is performed in children with cardiac disease who suffer an in-hospital cardiac arrest.[15,18,22] Survival in some subpopulations is notably lower, for example in the ELSO-registry, ECPR survival was only 14% in meningococcal sepsis and 30% for children with neoplasms.[19,23] In contrast, in certain situations survival can be higher, for example ECPR during cardiac catheterisation, survival to discharge was 79%.[24]

Neurological outcome

Multiple studies have evaluated neurological outcome after paediatric ECPR. However, the neurodevelopmental assessment tools utilised often vary between studies making comparison of outcomes challenging. Most studies have used the Paediatric Cerebral Performance Category (PCPC) or Paediatric Overall Performance Category (POPC) and the

outcomes vary widely. In interpreting these results, one should be aware that some studies report favourable neurological outcome in survivors whilst others report favourable neurological outcomes in relation to the entire group of ECPR patients. Bembea et al combined ELSO and GWTG-R outcomes and reported favourable outcome (normal or mild disability; PCPC 1-2) in 93% of the survivors.[25] These results seem encouraging; however, scoring is subjective and most studies had significant missing data on neurological outcome. In a more recent analysis of the GWTG-R registry, only 31% of ECPR patients who experienced >10 min of CPR had a favourable neurologic outcome.[15] This is similar to results found in the paediatric resuscitation quality (PediRes-Q) registry where 31% of all ECPR patients which reflects 67% of survivors, had a favourable neurological outcome.[18] Some studies undertook a more detailed long-term prospective follow-up. Joffe et al reviewed 14 IHCA ECPR cohort studies with total of 762 cardiac patients and reported an average survival of 49%. Neurological follow-up (varying between months to years after ECMO) of the survivors showed a favourable outcome, defined as normal neurology or a mild disability (PCPC 1-2), in 79%.[26] A report from Lasa et al analysed 3756 patients (cardiac and non-cardiac) of which 16% received ECPR. Survival to hospital discharge was 27% for CCPR patients compared to 40% in the ECPR group.[9] Survival with favourable neurologic outcome occurred in 18% of the CCPR patients and 27% of all the ECPR patients. In a secondary analysis of the Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) In-Hospital trial, approximately one-third of patients survived to 12-month with good neurobehavioral status, using the Vineland adaptive Behaviour Scales.[27]

Risk factors

When reviewing current literature in paediatric ECMO, several risk factors for mortality and neurological outcome may be identified, as well as protective factors which may improve outcomes. The described risk factors are summarised in Table 1 and will be discussed in more detail below as together they provide important clues and targets on how to approach paediatric ECPR. We have divided these factors into categories. The first are basic patient characteristics 'before ECPR', that can mostly not be modified (such as underlying chromosomal abnormalities, or underlying cardiac anatomy), but do play an important role in patient selection. The second category relates to the cardiac arrest and subsequent resuscitation. Many of these factors, such as quality of resuscitation, can be influenced by the resuscitation team and should be a focus of protocols and training in order to help improve survival. The third category involves factors that may influence outcomes while on ECMO and many may be influenced by the way we approach the support of these children, such as providing adequate blood flow. The last category is focussed on factors after decannulation from ECMO and the effect on long-term neurological outcomes.

ECPR for IHCA

The American Heart Association (AHA) resuscitation guidelines state that ECPR can be considered in children with underlying cardiac disease with a witnessed in-hospital cardiac arrest in centres with established ECMO programs.[10] The European resuscitation Counsel (ERC) recommends to consider ECPR for children with emergency department CA or IHCA with a presumed or confirmed reversible cause where CCPR does not promptly lead to ROSC.[53] ELSO suggests that combining high-quality ECPR with high-quality CCPR may be considered if the CA is witnessed and is associated with a reversible condition.[40] To achieve the best possible outcomes for ECPR it is important to be prepared, have ECPR protocols in place, identify patients at risk, and select patients carefully.

Anticipation and preparedness

To improve outcomes for CPR it is essential to have protocols and training for every step in the paediatric chain of survival. The Paediatric Extracorporeal Cardiopulmonary Resuscitation ELSO Guidelines provide an important resource in preparation for and establishing an ECPR program.[40] Prevention of cardiac arrest is still the best way to reduce hospital mortality.[54] On paediatric wards this can be achieved by implementation of early warning scores and rapid response teams. For children in intensive care, identifying those at greatest risk of cardiac arrest and ensuring timely team discussion and timely ECMO cannulation before cardiac arrest ensues will improve patient outcomes. In some children in ICU, vascular access may be difficult because of vessel patency related to their underlying disease and/or previous history, in those patients it can be helpful to assess vessel patency with ultrasound to determine which vessels could be cannulated if ECPR were to become a reality. Training of the team for ECPR will reduce the interruptions to chest compressions (CC) and significantly improve time to cannulation.[55] The ELSO ECPR guidelines include a valuable task list and task assignment for ECPR team members.[40] Outcome after cardiopulmonary resuscitation (CPR) is influenced

Table 1. Factors associated with outcomes of ECPR. CA: cardiac arrest, CHD: congenital heart disease, AKI: acute kidney injury, RRT: renal replacement therapy, IHCA: in-hospital cardiac arrest, OHCA: out-of-hospital cardiac arrest, CCPR: conventional cardiopulmonary resuscitation. The factors 'after ECPR' are not risk factors for mortality or survival, but essential components to ECPR care.

	Adverse Risk Factors for mortality and/or poor neurological outcome	Protective factors for improved survival
Before ECMO (baseline characteristics)	Single-ventricle physiology[28–31] Non-cardiac disease[32,33] Acquired heart disease[27] Higher complexity of CHD[28] Prematurity[33] Younger age (<12 months)[34] Chromosomal abnormalities[35] Neurologic comorbidity[17] Trauma[36] Obesity[36] Gastro-intestinal comorbidity[27] Technology dependence[27]	Two-ventricle physiology[28–31] Cardiac disease [17,37,38] White race[36,39] Post-cardiac surgery[27]
Cardiac arrest and CPR	OHCA Unwitnessed CA[40] Long duration of CCPR[41] CCPR interruptions[42] CCPR location outside ICU[27] High lactate[27,43] Acidosis, pH <7.01[28] Hypercarbia[44] Sodium bicarbonate bolus[32] Calcium[45] Blood-primed ECMO circuit[35]	IHCA Short duration of CCPR[41] Open-chest compressions[27] CA in catheterisation lab[24] PH >7.17[39] Neck/RCA cannulation[28,38]
During ECPR	Time to normal lactate[43] Normalization of lactate[27] AKI/Renal failure[28,32,33,35,38,39,46] RRT[31,34] Fluid overload[47] ECMO duration[30] Neurologic complications[28,31,34,35,38,39,48]	Early diagnosis and management of underlying cause[49–52]
After ECPR	Transition of care	Neurodevelopmental follow-up

by the resuscitation team response. Prior simulation training improves individual overall CPR performance and assisting early calls for help for the resuscitation.[56]

Patient selection

There is a high level of heterogeneity in ECPR initiation practice worldwide.[57] To further improve outcomes and reduce time consuming decision making it is important to establish local agreements over inclusion and exclusion criteria for ECPR. Most important is to select patients with a reasonable chance of recovery which may be difficult to ascertain at the time of cardiac arrest. Decision-making should therefore be supported by predetermined in- and exclusion criteria. Multiple studies have shown that cardiac patients, and especially post-cardiac surgery patients, have better outcomes than non-cardiac patients.[27,32,33] However, in other reports within the cardiac population, the medical-cardiac patients (e.g. myocarditis) have better outcomes, whereas the patients with single ventricle physiology (versus two-ventricle physiology) or very complex heart disease (RACHS 6) have worse outcomes.[28–31] In the recent multicentre analysis of 1100 children with IHCA 11% died, 69% achieved ROSC >20 min, and 20% were transitioned to ECPR.[8] Of these 217 ECPR patients, 35% were medical cardiac, 50% were surgical cardiac, and 14.7% were non-cardiac patients. There was no data on the specific outcome of the ECPR groups.

Based on the limited outcomes in non-cardiac patients it might be reasonable to limit ECPR to children with witnessed IHCA, to exclude those with known cerebral damage or no chance to bridge to recovery or

transplant, and to be critical in cases of pneumonia, sepsis, oncology and severely impaired immunology.

Initial underlying rhythm

As mentioned before, ECPR is mostly performed in children with underlying cardiac disease. In adults sudden cardiac arrest due to an arrhythmia carries better outcomes than asystole at ECMO-initiation.[58] In children the most common underlying rhythm is bradycardia with poor perfusion or asystole/pulseless electrical activity (PEA), and not a primary arrhythmia.[8,15,27] This is probably due to their prolonged pathway towards cardiac arrest. The outcomes in asystole versus an arrhythmia vary in the paediatric literature and asystole has been described as a risk factor for mortality.[33] In a recent meta-analysis survivors had a shockable rhythm more often compared to non-survivors.[41] However, an analysis of the GTWG-R registry could not identify a difference in survival between an initial shockable versus a non-shockable rhythm.[15] In an ELSO-registry analysis of ECPR in children without congenital heart disease, PEA was a predictor of mortality.[36] In the secondary analysis of the THAPCA trial approximately 60% of patients presented with bradycardia, 20% with PEA, 13% with VF/VT, and 5% with asystole. Survival was 23%, 40%, 56% and 0% respectively.[27] More studies are needed in specific patient populations, but a non-shockable rhythm in itself is not a contra-indication to ECPR in children at this time.

CPR duration pre ECMO

Of course, "time is brain", and therefore the time from arrest to ECMO flow is ideally as short as possible, probably preferably less than 60 min, the so-called golden hour. Theoretically, the shorter the period of CPR pre-ECMO, the better the survival and neurological outcomes. However, many studies do not show a correlation between duration of CPR and death and/or neurologic outcome.[22] Based on a systematic review, Mandigers et al created a model in which a weak negative linear relationship between survival and CPR duration in ECPR was found.[59] In a recent meta-analysis, the pooled data from 17 paediatric studies reported that the duration of CPR was negatively associated with survival.[41] Survivors received an average of 37 +/− 25 min of CPR compared to 48 +/− 38 min in non-survivors. Multiple cases of ECPR after longer CPR duration (up to 176 min) before ECMO flow with favourable neurological outcomes have been reported, therefore it is hard to define a CPR duration cut-off after which ECMO is futile.[60–62] The overall expert consensus is to aim for initiation of ECMO-flow within 40–60 min after the onset of cardiac arrest.[40] In the secondary analysis of the THAPCA trial, the highest survival was seen in children who had had 31–45 min of CCPR prior to cannulation.[27] Recently, early ECPR (<70.5 min CPR) was compared with late ECPR (>70.5 min CPR) in infants suffering IHCA in a single-center.[29] Early ECPR had a hospital survival of 45.5% compared to 17.2% in the late ECPR group. Early activation of the ECPR team and reducing time to ECMO flow by team training and organisation remains important to increase survival. Where possible, staff should anticipate and plan for possible ECPR for high-risk patients on the intensive care units in terms of candidacy, cannulation strategies and priming the circuit in advance.

Quality of CPR

Probably more important than CPR duration is the prompt initiation and the quality of CPR. A witnessed arrest and subsequent direct start of CPR is likely to improve outcomes to keep the no-flow state as short as possible before irreparable damage occurs. The quality of CPR mostly relates to the time from CA to initiation of chest compressions (CC), the rate and depth of CC, the duration of CC interruptions, ventilation rate, or intra-arrest maintenance of target blood pressure and end-tidal CO_2.[8] A longer pause in CC has been shown to be related to lower survival with favourable neurologic outcome.[42] High quality cardiopulmonary resuscitation (CPR) improves outcomes, but what constitutes the best possible CPR for an individual patient is still based on limited evidence and probably differs between patients and aetiologies.[63] Real-time monitoring during CPR may allow staff to modify CPR itself (for example, adjust rate and depth). Potential bedside tools to monitor CPR effectiveness include invasive or non-invasive arterial blood pressure, end-tidal CO_2 ($ETCO_2$), near-infrared spectroscopy (NIRS) and focused echocardiography.[64] A recent analysis of the PediRes-Q collaborative was not able to show a relationship between the quality of CPR and outcomes.[18] However, quality overall was below recommended by the AHA and thus provided room for improvement. The secondary analysis of the THAPCA-trial showed that open-chest compressions were independently associated with greater 1-year survival, possibly due to the shorter duration between start of chest compressions to initiation of ECMO.[27] Experimental models also suggest that open-chest compressions may be haemodynamically superior to closed-chest compressions by generating greater arterial pressure, cardiac output, coronary perfusion pressure, and cerebral blood flow.[65]

Medication during CPR

Epinephrine dosing during CCPR (also prior to ECPR) is subject of discussion. Based on experience and expert opinion some centres are cautious with adrenaline resuscitation dosing once decided to cannulate for ECMO in an attempt to limit increased afterload which may reduce ECMO flows.[66] In adult ECPR, a limitation of epinephrine dosing may have contributed to an increase in neurologically intact survival.[67] However, a recent single-centre study in paediatric ECPR failed to find a relationship between epinephrine dosing and blood pressure on ECMO or the need of vasodilators.[68] A retrospective analysis of 191 cases of paediatric ECPR in 5 centres, showed that epinephrine is dosed less frequently and guidelines for epinephrine dosing are followed less rigidly compared to CCPR. They did not show a decreased ECMO-flow with increased use of epinephrine, but the authors did find an increased use of vasodilators.[33] Together with the finding that survivors had received fewer epinephrine doses and continuing epinephrine beyond 10 min of resuscitation did not improve survival, it is suggested that limiting epinephrine dosing may be beneficial and at least not harmful, but further research is needed. Furthermore, the dosing of bicarbonate and calcium during CPR should also be further researched as both are associated with decreased survival.[32,45]

Cannulation

The site of cannula insertion is based on patient characteristics (e.g. age, diagnosis, comorbidities) and local experience. Following cardiac surgery central cannulation is commonly chosen in an ECPR situation, especially in those with an open chest. In all other cases peripheral cannulation is often preferred because it may diminish interruption of CPR and is less invasive. A single centre retrospective study showed no difference in survival between different cannulation sites.[69] Other studies are in favour of peripheral cannulation, but this may be biased by the fact that the more unstable patients have their chest left open after cardiac surgery and are cannulated centrally.[28,38] In some children, peripheral vascular access may be problematic due to their anatomy or vascular thrombosis. Therefore, it is wise to assess vascular patency in children at risk of cardiac arrest early in their treatment course. When high flows need to be achieved, for example in a patient with sepsis, central cannulation might be necessary. Percutaneous cannulation has been shown to be related to fewer complications and shorter cannulation time, potentially improving outcomes in patients undergoing ECPR.[70] It should be considered, where appropriate, in older children and young adolescents. In a large, multicentre, international registry of adult cardiac arrest patients who received percutaneous or surgical cannulation for femoro-femoral ECPR, percutaneous cannulation was associated with lower rate of severe neurological complications, and similar rates of in-hospital mortality, limb ischaemia and cannulation site bleeding.[71] In addition, in adults, bilateral femoral cannulation compared to unilateral femoral cannulation, was associated with a reduced risk for compartment syndrome/fasciotomy, lower rates of bleeding and vessel repair during ECMO, and lower in-hospital mortality.[72]

Hypercarbia and hyperoxia

Following ECMO flow initiation, a rapid decline in $PaCO_2$ (compared to $paCO_2$ level prior to cannulation – delta $PaCO_2$) and thereby reduced perfusion of an already compromised brain by CCPR can result in secondary damage. In paediatric V-A ECMO patients, an ELSO-registry analysis showed that hypercarbia in itself, but also a relative decrease in $PaCO_2$ greater than 30% were associated with a higher risk of neurologic complications including death by neurological criteria.[73] In neonates respiratory ECMO a significant decrease in $PaCO_2$ after ECMO initiation is associated with acute neurological events. Cautious $PaCO_2$ decrease should be the aim after initiation of any ECMO run.[74] In a retrospective observational study with 201 paediatric ECMO patients improved survival was associated with smaller changes of $PaCO_2$ at the time of ECMO initiation.[75] An ELSO-registry report showed that hypercarbia prior to initiation of ECMO was associated with death due to neurological criteria in paediatric ECPR.[44] Furthermore, hyperoxia should be avoided because of the possible harmful effects of oxygen free radicals.[76] Hyperoxia after ROSC has been associated with increased mortality and poor neurologic recovery.[77,78] Possible mechanisms include increased reactive oxygen species with a consequent increase in brain lipid-per-oxidation, impaired cerebral oxidative energy metabolism, and accelerated neuronal degeneration.[79]

We recommend that institutions develop a strategy of initiating ECMO with low FiO_2 of 21% on the blender and a low sweep flow (ratio of sweep gas to ECMO flow of 0.5–0.7) and monitor patient's arterial blood gases in the first hour to avoid hyperoxia and a rapid decrease in $PaCO_2$. We suggest performing after establishing ECMO flow to check $PaCO_2$ (and thereby assessing delta PaCO2) and PaO_2 and adjust sweep gas and blender FiO_2 accordingly. Target normoxia and avoid both hypoxia and hyperoxia post return of ECMO circulation (ROEC).

Acidosis

Acidosis pre-ECMO and on ECMO are both associated with higher mortality.[28,31,35,39,44] Pre-ECPR pH <7.01 is associated with worse outcome and should be taken into account with other risk factors before deploying ECPR. An initial high lactate and the peak lactate are a reflection of the severity of the arrest and are risk factors for mortality.[35,43] Administering sodium bicarbonate during CPR to correct acidosis does not protect and may actually decreases the chance of survival.[32] There are also suggestions that giving high doses of calcium may be associated with poor outcome.[45]

ECMO flow

Providing adequate ECMO flow and adequate oxygen delivery is essential. A persistent (lactic) acidosis on ECMO is probably caused by severe organ damage or inability to provide sufficient ECMO-flow and is also prognostic for poor outcomes.[27,43,80] ECMO flow should therefore be titrated to deliver adequate systemic blood flow aiming at normalisation of haemodynamics, including normalisation of lactate levels, resolution of acidosis and restoration of urine output.[40] If lactate levels cannot be normalised within 24–48 hours despite optimal ECMO blood flow, then one should consider other pathologies including intestinal or brain ischaemia or an undiagnosed metabolic pathology.

Unloading the left ventricle

After V-A ECMO cannulation, in children without adequate intra-cardiac shunts, cardiac stun can occur due to the imposed afterload of the ECMO circuit. In this situation the left ventricle (LV) is unable to open the aortic valve and empty. Consequently, severe LV dilatation can occur, eventually leading to compromised coronary perfusion and further ventricular dilatation. Cardiac stun can lead to cardiac thrombus formation and pulmonary haemorrhage due to elevated left atrial pressures and the resultant pulmonary oedema. This should be closely monitored by following pulse pressure on arterial pressure curve, assessment of left ventricle and aortic valve on echocardiography, and signs of pulmonary oedema on chest x-ray.

Several strategies to prevent or treat cardiac stun are available. First, as long as there is sufficient systemic perfusion, slightly reducing ECMO flow can be tried which may reduce afterload which the LV might then be able to overcome. However, this is hardly ever possible as providing adequate systemic blood flow is essential. Another strategy is to support the LV by low-dose adrenaline (0.05–0.1 ug/kg/min) and/or milrinone (0.5 ug/kg/min). In all patients, but especially in case of systemic hypertension, vasodilators (e.g., sodium nitroprusside, milrinone) should be used to reduce the afterload imposed on the LV. Generally, a pulse-pressure of 10–15 mmHg is targeted. If the aortic valve still does not open despite these aforementioned measures, further emergent intervention is warranted. Percutaneous left atrial decompression can be done using one of three possible techniques: balloon-atrioseptostomy (Image 1), atrial stent placement, or insertion of an LA vent connected to the venous limb of the circuit.[81] Alternatively, one can surgically place an extra cannula in the left atrium, a so called 'left vent' which is connected to the venous limb of the ECMO circuit. But this (often) requires sternotomy. In older children, an intra-aortic balloon pump or Impella should be considered to unload the left ventricle as proven successful in adult literature.[82] Placing a vent directly into LV can be considered but is uncommon.

Diagnostics

Attempts should be made to identify the reason for the cardiac arrest as soon as possible once ECMO flows are established. Cardiac catheterisation or CT scan to diagnose the cause of cardiac arrest, such as unexpected residual lesions have been associated with better outcome in children post-cardiotomy.[49–52] Other reasons for cardiac collapse could be arrhythmias and/or myocarditis/cardiomyopathy which may benefit from anti-arrhythmic medication or other specific therapies.

Hypothermia

The ELSO paediatric ECPR guidelines suggest hypothermia (33–34°C) for 24–48 h post-arrest to optimise neurologic outcomes and to avoid hyperthermia despite no comparative evidence of improved survival.[40] More recent literature does not support therapeutic hypothermia for paediatric ECPR. Sanford et al analysed 2289 paediatric patients from the ELSO-registry and found no survival or neurological benefit for patients kept <34.0°C for >24 h.[12] The THAPCA trial for IHCA, with more than half of patients on ECMO, did not find a significant benefit for therapeutic hypothermia compared to normothermia.[83]

In the absence of any RCTs, maintaining normothermia (36.0–37.5°C) seems reasonable, but avoiding hyperthermia should be considered as an important recommendation. Patient temperature can often be very well controlled by the temperature regulation of the ECMO circuit.

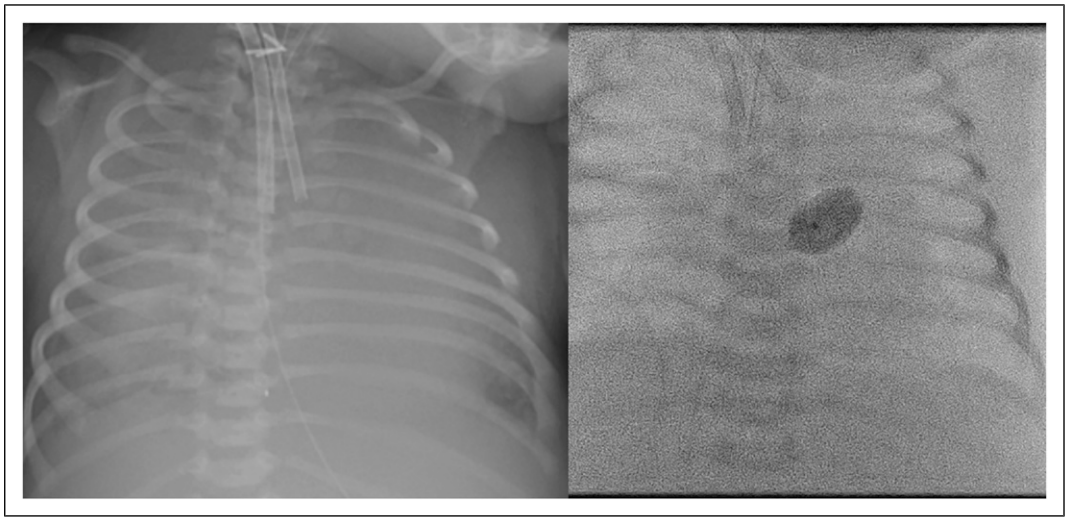

Image 1. Example of an atrial balloonseptostomy in a neonate with normal cardiac anatomy and cardiac stun after ECPR and cannulated in neck. Left: Signs of pulmonary oedema. Right: Fluoroscopy image during atrial balloon septostomy.

Renal dysfunction

In the ELSO-registry, renal replacement therapy is the most reported complication in neonatal and paediatric ECPR.[13] Renal dysfunction and fluid-overload pre-ECMO and during ECMO are both associated with worse outcomes.[28,32,33,35,38,39,46] However, one multivariate analysis found that AKI/RRT is no longer a risk factor for mortality when correcting for fluid overload at ECMO discontinuation, suggesting that AKI/RRT might not be associated with worse outcome when fluids can be withdrawn by RRT.[47] The negative impact of RRT on survival is probably not due to the actual RRT itself, but more a reflection of the underlying disease and/or event that lead to renal dysfunction and the concomitant requirement of RRT.[31,34]

Neuromonitoring

Whilst on V-A ECMO it is important to perform neuromonitoring like near-infrared spectroscopy (NIRS), (amplitude integrated) EEG and routine brain ultrasound in neonates, however this practice is highly variable amongst ECMO programs in Europe.[84] In children on ECMO-support neurologic complications are frequently seen, especially in ECPR patients.[16,85] In these patients, intracranial haemorrhage, hypoxic ischaemic injury, ischaemic stroke, cerebral oedema, and seizures are a frequent cause of death or severe functional impairment.[30,44] With appropriate neuromonitoring and neuroprotective measures neurologic injury can be minimised or detected early.[86] The ELSO guidelines on neuromonitoring recommend frequent cranial ultrasound in infants with an open fontanelle, cranial CT-scan in case of clinical suspicion for neurological complications or abnormal findings on neuromonitoring, to consider continuous cerebral oximetry monitoring with NIRS in all patients undergoing ECMO, and to consider continuous EEG monitoring within 12–24 h of ECMO cannulation for a duration of at least 24–48 h.[87] The use of plasma biomarkers for neurologic injury is appealing, but requires further investigation before it can be clinically applied.[88]

Duration of ECMO

Median ECMO duration after ECPR varies between 3 and 7 days, but is generally 3–5 days in the larger studies.[17,29–31,33,44,48,89] In the ELSO-registry median duration is 3.5 and 4 days for paediatric and neonatal ECPR respectively.[13] In V-A ECMO in general and also in ECPR patients, increased duration of ECMO is associated with a greater risk of mortality and a poor neurologic outcome.[30,31,41,45,90] This is likely related to the inability of the heart and the body to heal from the insult of cardiac arrest or due to complications that may arise with increased time on ECMO.[25] In a large single-centre study of ECPR in children with congenital heart disease, survivors with acceptable neurology had a median ECMO duration of 3 [2-5] days compared to 7 [2-12] days in non-survivors and survivors with severe neurologic dysfunction.[30] Interestingly, in an ELSO-registry study of ECPR in children without congenital heart disease with a survival to discharge of 41%, the median ECMO duration was 5 days in survivors compared to 2 days in non-survivors.[36] The authors did

not comment on the reason for this observed significant difference, probably due to the nature of the ELSO-registry where no distinction is made between death or poor neurologic prognosis as a reason for ECMO discontinuation. In a meta-analysis of 30 ECPR studies of cardiac and non-cardiac patients, the mean ECMO duration in survivors was 97 [+/− 120] hours compared to 119 [+/− 116] hours in non-survivors ($p < .01$).[41]

Weaning/decannulation

Signs of recovery include improving pulse pressure with limited inotrope support, increasing end-tidal CO_2, and improved cardiac function on assessment with echocardiography. Weaning from ECPR follows the principles of weaning of V-A ECMO for paediatric cardiac failure, with the purpose to determine if the patient is ready to decannulate ECMO.[91] The weaning process varies according to institutional and patient factors but would commonly occur over 4–8 h with a gradual decrease in ECMO flows while optimising lung ventilation strategy, intravascular volume status, and vasoactive medications. Once the patient has demonstrated satisfactory haemodynamics on minimum ECMO support, typically around 50 mL/kg/min, it is reasonable to trial the patient off ECMO and then decannulate if successful. Detailed description of weaning techniques is beyond the scope of this review and described in more detail in the ELSO Red Book.[92] Prior to ECMO wean and decannulation, it is important to have a team discussion on strategies of further management should the ECMO wean not succeed.

Follow-up and outcomes

Centres that deploy paediatric ECPR, and ECMO in general, are advised to maintain a standardized follow-up program to diagnose and support neurodevelopmental issues as soon as possible. A recent ELSO guideline advises robust longitudinal follow-up with early intervention. Uniform collection of data for developmental, psychological, neurological assessment and other somatic aspects like kidney function for adequate short- and long-term follow-up is essential.[93]

In case of no recovery

In the ECPR patient, V-A ECMO is deployed as a bridge to recovery, heart transplant, or a bridge to decision. On initiation of ECPR and during the entire ECMO run, parents should be well informed on the risks and possible outcomes. In reality approximately 50% of ECPR patients do not survive and when recovery fails, ECMO should be discontinued after careful discussion and team agreement as well as family discussion. In case of clinically severe neurologic concerns further neurologic evaluation can be indicated, including cranial CT or EEG, to help aid in the decision to continue or withdraw life support.[44] In case of brain death in some countries organ donation procedure is possible.[94] After decision to discontinue treatment, end-of-life care is indicated for these children and their families. Together with parents a careful plan is made for end-of-life care for the patient. Religious and other (psychological, social, bereavement) support should be offered where appropriate.

ECPR for OHCA

In children, there are insufficient data to support the recommendation for the use of ECPR for out-of-hospital cardiopulmonary arrest.[10,40] In the ELSO-registry, only 3% of ECPR is OHCA.[11] In an OHCA situation often a combination of risk factors for worse outcome are present (i.e. delayed start of CPR, suboptimal quality CPR, asystole, non-cardiac causes, long pre-arrest phase, or unwitnessed arrest).[53] Following the current evidence and guidelines, ECPR for OHCA should probably be limited to specific protocols in more experienced centres, preferably in research settings. Exceptions can be made for children with hypothermia without asphyxia, in which the brain is protected by hypothermia before going into cardiac arrest. Adults with hypothermic cardiac arrest due to non-asphyxial hypothermia have improved neurologic outcomes when treated with ECPR compared to patients with asphyxia hypothermic cardiac arrest.[95] In cases of drowning, water temperature, body temperature and heart rhythm should be considered before deciding for ECPR. In an ELSO-registry analysis of 247 patients receiving ECMO following a drowning event, only 23% of patients who were cannulated during CPR survived to hospital discharge, in patients who did not experience a cardiac arrest the survival was 71%.[96]

Future directions

Preventing ECPR by timely identifying those at risk for cardiac arrest and early intervention is the best method to improve hospital survival.[54] In the future, carefully selected randomised-controlled trials are necessary to aid in patient selection, pre-ECPR practice, and post-ECPR practice.[97] The use of artificial intelligence to predict cardiac arrest in children has been studied and seems promising.[98,99] Further research and

development is needed to deploy these algorithms in daily practice.

To further improve outcomes in paediatric ECPR secondary injury to the brain and other organs while recovering from the circulatory arrest should be minimised. Brain damage and kidney failure are both associated with an increase in morbidity and mortality. A promising development could be administration of hydrogen gas either through the ventilator or through the oxygenator of the ECMO system which decreases brain and kidney injury in a pig model of global ischaemic injury by reducing the oxygen radical to water and thus mitigating oxygen radical mediated tissue injury.[100] Inhaled hydrogen has been proven safe in mice and healthy adults[101,102] and its feasibility and safety in paediatric ECPR is currently being studied [clinical trial NCT05574296]. Potentially H_2 Administration in ECPR might improve both neurological outcomes and survival.

Conclusion

ECPR has become an established modality in many centres for children with cardiac disease who experience prolonged IHCA and carries approximately 50% survival to hospital discharge depending on the underlying cause of cardiac arrest. Both the system and skilled staff are key to ECPR program success. In order to achieve and improve on these outcomes it is important to be well prepared and have local protocols in place that help with inter-professional team training, patient selection, resuscitation, timing and location of cannulation, careful decrease in $PaCO_2$, prevention of hyperoxia, prevention of hyperthermia, achieving adequate flow, investigating and treating the cause of the cardiac arrest, minimise complications, minimise time on ECMO, good neurological assessment and follow-up and provide excellent end-of life care for those that do not survive.

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References

1. Conrad SA, Broman LM, Taccone FS, et al. The extracorporeal life support organization maastricht treaty for nomenclature in extracorporeal life support. A position paper of the extracorporeal life support organization. *Am J Respir Crit Care Med* 2018; 198: 447–451. DOI: 10.1164/rccm.201710-2130CP.
2. Idrees S, Abdullah R, Anderson KK, et al. Sociodemographic factors associated with paediatric out-of-hospital cardiac arrest: a systematic review. *Resuscitation* 2023; 192: 109931. DOI: 10.1016/j.resuscitation.2023.109931.
3. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2022 update: a report from the American heart association. *Circulation* 2022; 145: e153–e639. DOI: 10.1161/cir.0000000000001052.
4. Berg RA, Nadkarni VM, Clark AE, et al. Incidence and outcomes of cardiopulmonary resuscitation in PICUs. *Crit Care Med* 2016; 44: 798–808. DOI: 10.1097/ccm.0000000000001484.
5. Martinez PA, Totapally BR. The epidemiology and outcomes of pediatric in-hospital cardiopulmonary arrest in the United States during 1997 to 2012. *Resuscitation* 2016; 105: 177–181. DOI: 10.1016/j.resuscitation.2016.06.010.
6. Hamzah M, Othman HF, Almasri M, et al. Survival outcomes of in-hospital cardiac arrest in pediatric patients in the USA. *Eur J Pediatr* 2021; 180: 2513–2520. DOI: 10.1007/s00431-021-04082-3.
7. Berg RA, Sutton RM, Holubkov R, et al. Ratio of PICU versus ward cardiopulmonary resuscitation events is increasing. *Crit Care Med* 2013; 41: 2292–2297. DOI: 10.1097/CCM.0b013e31828cf0c0.
8. Federman M, Sutton RM, Reeder RW, et al. Survival with favorable neurologic outcome and quality of cardiopulmonary resuscitation following in-hospital cardiac arrest in children with cardiac disease compared with non-cardiac disease. *Pediatr Crit Care Med* 2024; 25: 4–14. DOI: 10.1097/pcc.0000000000003368.
9. Lasa JJ, Rogers RS, Localio R, et al. Extracorporeal cardiopulmonary resuscitation (E-CPR) during pediatric in-hospital cardiopulmonary arrest is associated with improved survival to discharge: a report from the American heart association's get with the guidelines-resuscitation (GWTG-R) registry. *Circulation* 2016; 133: 165–176. DOI: 10.1161/circulationaha.115.016082.20151203.
10. Topjian AA, Raymond TT, Atkins D, et al. Part 4: pediatric basic and advanced life support: 2020 American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2020; 142: S469–s523. DOI: 10.1161/cir.0000000000000901.20201021.
11. Barbaro RP, Paden ML, Guner YS, et al. Pediatric extracorporeal life support organization registry international report 2016. *Asaio j* 2017; 63: 456–463. DOI: 10.1097/mat.0000000000000603.

12. Sanford EL, Bhaskar P, Li X, et al. Hypothermia after extracorporeal cardiopulmonary resuscitation not associated with improved neurologic complications or survival in children: an analysis of the ELSO registry. *Resuscitation* 2023; 188: 109852. DOI: 10.1016/j.resuscitation.2023.109852
13. Tonna JE, Boonstra PS, MacLaren G, et al. Extracorporeal life support organization registry international report 2022: 100,000 survivors. *Asaio J* 2024; 70(2): 131–143. DOI: 10.1097/mat.0000000000002128.
14. Matos RI, Watson RS, Nadkarni VM, et al. Duration of cardiopulmonary resuscitation and illness category impact survival and neurologic outcomes for in-hospital pediatric cardiac arrests. *Circulation* 2013; 127: 442–451. DOI: 10.1161/CIRCULATIONAHA.112.125625.20130122.
15. Perry T, Bakar A, Bembea MM, et al. First documented rhythm and clinical outcome in children who undergo extracorporeal cardiopulmonary resuscitation for in-hospital cardiac arrest: a report from the american heart association get with the guidelines® – resuscitation registry (GWTG-R). *Resuscitation* 2023; 193: 110040. DOI: 10.1016/j.resuscitation.2023.110040.
16. Kobayashi RL, Gauvreau K, Alexander PMA, et al. Higher survival with the use of extracorporeal cardiopulmonary resuscitation compared with conventional cardiopulmonary resuscitation in children following cardiac surgery: results of an analysis of the get with the guidelines-resuscitation registry. *Critical care Medicine* 2023; 8.
17. Lasa JJ, Guffey D, Bhalala U, et al. Critical care unit characteristics and extracorporeal cardiopulmonary resuscitation survival in the pediatric cardiac population: retrospective analysis of the virtual pediatric system database. *Pediatr Crit Care Med* 2023; 24: 910–918. DOI: 10.1097/pcc.0000000000003321.
18. Brown SR, Frazier M, Roberts J, et al. CPR quality and outcomes after extracorporeal life support for pediatric In-Hospital cardiac arrest. *Resuscitation* 2023; 189: 109874. DOI: 10.1016/j.resuscitation.2023.109874.
19. Henry BM, Benscoter A, Perry T, et al. Outcomes of extracorporeal life support in children with meningococcal septicemia: a retrospective cohort study. *J Pediatr Intensive Care* 2023; 12: 337–343. DOI: 10.1055/s-0042-1750302.
20. Aharon AS, Drinkwater DC, Churchwell KB, et al. Extracorporeal membrane oxygenation in children after repair of congenital cardiac lesions. *Ann Thorac Surg* 2001; 72: 2095–2101. DOI: 10.1016/S0003-4975(01)03209-X.
21. Farhat A, Ling RR, Jenks CL, et al. Outcomes of pediatric extracorporeal cardiopulmonary resuscitation: a systematic review and meta-analysis. *Crit Care Med* 2021; 49: 682–692. DOI: 10.1097/ccm.0000000000004882.
22. Esangbedo ID, Brunetti MA, Campbell FM, et al. Pediatric extracorporeal cardiopulmonary resuscitation: a systematic review. *Pediatr Crit Care Med* 2020; 21: e934–e943. DOI: 10.1097/pcc.0000000000002373.
23. Suzuki Y, Cass SH, Kugelmann A, et al. Outcome of extracorporeal membrane oxygenation for pediatric patients with neoplasm: an extracorporeal life support organization database study (2000–2019). *Pediatr Crit Care Med* 2022; 23: e240–e248. DOI: 10.1097/pcc.0000000000002915.
24. Allan CK, Thiagarajan RR, Armsby LR, et al. Emergent use of extracorporeal membrane oxygenation during pediatric cardiac catheterization. *Pediatr Crit Care Med* 2006; 7: 212–219. DOI: 10.1097/01.Pcc.0000200964.88206.B0.
25. Bembea MM, Ng DK, Rizkalla N, et al. Outcomes after extracorporeal cardiopulmonary resuscitation of pediatric in-hospital cardiac arrest: a report from the get with the guidelines-resuscitation and the extracorporeal life support organization registries. *Crit Care Med* 2019; 47: e278–e285. DOI: 10.1097/ccm.0000000000003622.
26. Joffe AR, Lequier L, Robertson CMT. Pediatric outcomes after extracorporeal membrane oxygenation for cardiac disease and for cardiac arrest: a review. *Am Soc Artif Intern Organs J* 2012; 58: 297–310. DOI: 10.1097/MAT.0b013e31825a21ff.
27. Meert KL, Guerguerian A-M, Barbaro R, et al. Extracorporeal cardiopulmonary resuscitation: one-year survival and neurobehavioral outcome among infants and children with in-hospital cardiac arrest. *Crit Care Med* 2019; 47: 393–402. DOI: 10.1097/ccm.0000000000003545.
28. Chan T, Thiagarajan RR, Frank D, et al. Survival after extracorporeal cardiopulmonary resuscitation in infants and children with heart disease. *J Thorac Cardiovasc Surg* 2008; 136: 984–992. DOI: 10.1016/j.jtcvs.2008.03.007.
29. Yoo BA, Yoo S, Choi ES, et al. Extracorporeal cardiopulmonary resuscitation in infants: outcomes and predictors of mortality. *J Chest Surg* 2023; 56: 162–170. DOI: 10.5090/jcs.22.138.
30. Sperotto F, Saengsin K, Danehy A, et al. Modeling severe functional impairment or death following ECPR in pediatric cardiac patients: planning for an interventional trial. *Resuscitation* 2021; 167: 12–21. DOI: 10.1016/j.resuscitation.2021.07.041.
31. Melvan JN, Davis J, Heard M, et al. Factors associated with survival following extracorporeal cardiopulmonary resuscitation in children. *World J Pediatr Congenit Heart Surg* 2020; 11: 265–274. DOI: 10.1177/2150135120902102.
32. Raymond TT, Cunnyngham CB, Thompson MT, et al. Outcomes among neonates, infants, and children after extracorporeal cardiopulmonary resuscitation for refractory inhospital pediatric cardiac arrest: a report from the National Registry of Cardiopulmonary Resuscitation. *Pediatr Crit Care Med* 2010; 11: 362–371. DOI: 10.1097/PCC.0b013e3181c0141b.
33. Ortmann LA, Reeder RW, Raymond TT, et al. Epinephrine dosing strategies during pediatric extracorporeal cardiopulmonary resuscitation reveal novel impacts on survival: a multicenter study utilizing time-stamped

epinephrine dosing records. *Resuscitation* 2023; 188: 109855. DOI: 10.1016/j.resuscitation.2023.109855.
34. Shakoor A, Pedroso FE, Jacobs SE, et al. Extracorporeal cardiopulmonary resuscitation (ECPR) in infants and children: a single-center retrospective study. *World J Pediatr Congenit Heart Surg* 2019; 10: 582–589. DOI: 10.1177/2150135119862598.
35. Kane DA, Thiagarajan RR, Wypij D, et al. Rapid-response extracorporeal membrane oxygenation to support cardiopulmonary resuscitation in children with cardiac disease. *Circulation* 2010; 122: S241–S248. DOI: 10.1161/CIRCULATIONAHA.109.928390.
36. Beni CE, Rice-Townsend SE, Esangbedo ID, et al. Outcome of extracorporeal cardiopulmonary resuscitation in pediatric patients without congenital cardiac disease: extracorporeal life support organization registry study. *Pediatr Crit Care Med* 2023; 24: 927–936. DOI: 10.1097/pcc.0000000000003322.
37. Morris MC, Ittenbach RF, Godinez RI, et al. Risk factors for mortality in 137 pediatric cardiac intensive care unit patients managed with extracorporeal membrane oxygenation. *Crit Care Med* 2004; 32: 1061–1069. DOI: 10.1097/01.Ccm.0000119425.04364.Cf.
38. Tajik M, Cardarelli MG. Extracorporeal membrane oxygenation after cardiac arrest in children: what do we know? *Eur J Cardio Thorac Surg* 2008; 33: 409–417. DOI: 10.1016/j.ejcts.2007.12.018.
39. Thiagarajan RR, Laussen PC, Rycus PT, et al. Extracorporeal membrane oxygenation to aid cardiopulmonary resuscitation in infants and children. *Circulation* 2007; 116: 1693–1700. DOI: doi:10.1161/CIRCULATIONAHA.106.680678.
40. Guerguerian A-M, Sano M, Todd M, et al. Pediatric extracorporeal cardiopulmonary resuscitation ELSO guidelines. *Am Soc Artif Intern Organs J* 2021; 67: 229–237. DOI: 10.1097/mat.0000000000001345.
41. Sood N, Sangari A, Goyal A, et al. Predictors of survival for pediatric extracorporeal cardiopulmonary resuscitation: a systematic review and meta-analysis. *Medicine (Baltim)* 2022; 101: e30860. DOI: 10.1097/md.0000000000030860.
42. Lauridsen KG, Lasa JJ, Raymond TT, et al. Association of chest compression pause duration prior to E-CPR cannulation with cardiac arrest survival outcomes. *Resuscitation* 2022; 177: 85–92. DOI: 10.1016/j.resuscitation.2022.05.004.
43. de la Llana RA, Marsney RL, Gibbons K, et al. Merging two hospitals: the effects on pediatric extracorporeal cardiopulmonary resuscitation outcomes. *J Pediatr Intensive Care* 2021; 10: 202–209. DOI: 10.1055/s-0040-1715853.20200831.
44. Joye R, Cousin VL, Wacker J, et al. Death by neurologic criteria in children undergoing extracorporeal cardiopulmonary resuscitation: retrospective extracorporeal life support organization registry study, 2017–2021. *Pediatr Crit Care Med* 2023; 20. DOI: 10.1097/pcc.0000000000003406.
45. Anton-Martin P, Moreira A, Kang P, et al. Outcomes of paediatric cardiac patients after 30 minutes of cardiopulmonary resuscitation prior to extracorporeal support. *Cardiol Young* 2020; 30: 607–616. DOI: 10.1017/S1047951120000591.
46. Huang S-C, Wu E-T, Chen Y-S, et al. Extracorporeal membrane oxygenation rescue for cardiopulmonary resuscitation in pediatric patients. *Crit Care Med* 2008; 36: 1607–1613. DOI: 10.1097/CCM.0b013e318170b82b.
47. Gist KM, Misfeldt A, Sahay RD, et al. Acute kidney injury and fluid overload in pediatric extracorporeal cardiopulmonary resuscitation: a multicenter retrospective cohort study. *Am Soc Artif Intern Organs J* 2022; 68: 956–963. DOI: 10.1097/mat.0000000000001601.
48. Ozturk Z, Kesici S, Ertugrul İ, et al. Resuscitating the resuscitation: a single-centre experience on extracorporeal cardiopulmonary resuscitation. *J Paediatr Child Health* 2023; 59: 335–340. DOI: 10.1111/jpc.16295.
49. Howard TS, Kalish BT, Wigmore D, et al. Association of extracorporeal membrane oxygenation support adequacy and residual lesions with outcomes in neonates supported after cardiac surgery. *Pediatr Crit Care Med* 2016; 17: 1045–1054. DOI: 10.1097/pcc.0000000000000943.
50. Agarwal HS, Hardison DC, Saville BR, et al. Residual lesions in postoperative pediatric cardiac surgery patients receiving extracorporeal membrane oxygenation support. *J Thorac Cardiovasc Surg* 2014; 147: 434–441. DOI: 10.1016/j.jtcvs.2013.03.021.
51. Soynov IA, Kornilov IA, Kulyabin YY, et al. Residual lesion diagnostics in pediatric postcardiotomy extracorporeal membrane oxygenation and its outcomes. *World J Pediatr Congenit Heart Surg* 2021; 12: 605–613. DOI: 10.1177/21501351211026594.
52. Kato A, Lo Rito M, Lee K-J, et al. Impacts of early cardiac catheterization for children with congenital heart disease supported by extracorporeal membrane oxygenation. *Cathet Cardiovasc Interv* 2017; 89: 898–905. DOI: 10.1002/ccd.26632.
53. Van de Voorde P, Turner NM, Djakow J, et al. European resuscitation council guidelines 2021: paediatric life support. *Resuscitation* 2021; 161: 327–387. DOI: 10.1016/j.resuscitation.2021.02.015.
54. Marino BS, Tabbutt S, MacLaren G, et al. Cardiopulmonary resuscitation in infants and children with cardiac disease: a scientific statement from the American heart association. *Circulation* 2018; 137: e691–e782. DOI: 10.1161/CIR.0000000000000524.
55. Whitmore SP, Gunnerson KJ, Haft JW, et al. Simulation training enables emergency medicine providers to rapidly and safely initiate extracorporeal cardiopulmonary resuscitation (ECPR) in a simulated cardiac arrest scenario. *Resuscitation* 2019; 138: 68–73. DOI: 10.1016/j.resuscitation.2019.03.002.
56. MacGloin H, Lofton L, Sanz D, et al. 7 the impact of in-situ simulation training on individual and team performance during real cardiopulmonary resuscitations on a paediatric intensive care unit (picu). *BMJ Simulation &*

Technology Enhanced Learning 2016; 2(Suppl 1): A17–A18.
57. Nguyen D-A, De Mul A, Hoskote AU, et al. Factors associated with initiation of extracorporeal cardiopulmonary resuscitation in the pediatric population: an international survey. *Am Soc Artif Intern Organs J* 2022; 68: 413–418. DOI: 10.1097/mat.0000000000001495.
58. Mørk SR, Stengaard C, Linde L, et al. Mechanical circulatory support for refractory out-of-hospital cardiac arrest: a Danish nationwide multicenter study. *Crit Care* 2021; 25: 174. DOI: 10.1186/s13054-021-03606-5.
59. Mandigers L, Boersma E, den Uil CA, et al. Systematic review and meta-analysis comparing low-flow duration of extracorporeal and conventional cardiopulmonary resuscitation. *Interact Cardiovasc Thorac Surg* 2022; 35: ivac219. DOI: 10.1093/icvts/ivac219.
60. Alsoufi B, Al-Radi OO, Nazer RI, et al. Survival outcomes after rescue extracorporeal cardiopulmonary resuscitation in pediatric patients with refractory cardiac arrest. *J Thorac Cardiovasc Surg* 2007; 134: 952–959. DOI: 10.1016/j.jtcvs.2007.05.054.
61. Ghez O, Fouilloux V, Charpentier A, et al. Absence of rapid deployment extracorporeal membrane oxygenation (ECMO) team does not preclude resuscitation ECMO in pediatric cardiac patients with good results. *Am Soc Artif Intern Organs J* 2007; 53: 692–695. DOI: 10.1097/MAT.0b013e318151412f.
62. Kelly RB, Porter PA, Meier AH, et al. Duration of cardiopulmonary resuscitation before extracorporeal rescue: how long is not long enough? *Am Soc Artif Intern Organs J* 2005; 51: 665–667. DOI: 10.1097/01.mat.0000171596.39362.7a.
63. Kleinman ME, Brennan EE, Goldberger ZD, et al. Part 5: adult basic life support and cardiopulmonary resuscitation quality: 2015 American heart association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015; 132: S414–435. DOI: 10.1161/cir.0000000000000259.
64. Kool M, Atkins DL, Van de Voorde P, et al. Focused echocardiography, end-tidal carbon dioxide, arterial blood pressure or near-infrared spectroscopy monitoring during paediatric cardiopulmonary resuscitation: a scoping review. *Resusc Plus* 2021; 6: 100109–20210330. DOI: 10.1016/j.resplu.2021.100109.
65. Alzaga-Fernandez AG, Varon J. Open-chest cardiopulmonary resuscitation: past, present and future. *Resuscitation* 2005; 64: 149–156. DOI: 10.1016/j.resuscitation.2004.06.022.
66. Lasa JJ, Jain P, Raymond TT, et al. Extracorporeal cardiopulmonary resuscitation in the pediatric cardiac population: in search of a standard of care. *Pediatr Crit Care Med* 2018; 19: 125–130.
67. Lamhaut L, Hutin A, Puymirat E, et al. A Pre-Hospital Extracorporeal Cardio Pulmonary Resuscitation (ECPR) strategy for treatment of refractory out hospital cardiac arrest: an observational study and propensity analysis. *Resuscitation* 2017; 117: 109–117. DOI: 10.1016/j.resuscitation.2017.04.014.
68. Kucher NM, Marquez AM, Guerguerian A-M, et al. Epinephrine dosing use during extracorporeal cardiopulmonary resuscitation: single-center retrospective cohort. *Pediatr Crit Care Med* 2023; 24: e531–e539. DOI: 10.1097/pcc.0000000000003323.
69. Torres-Andres F, Fink EL, Bell MJ, et al. Survival and long-term functional outcomes for children with cardiac arrest treated with extracorporeal cardiopulmonary resuscitation. *Pediatr Crit Care Med* 2018; 19: 451–458. DOI: 10.1097/pcc.0000000000001524.
70. Conrad SA, Grier LR, Scott LK, et al. Percutaneous cannulation for extracorporeal membrane oxygenation by intensivists: a retrospective single-institution case series. *Crit Care Med* 2015; 43: 1010–1015. DOI: 10.1097/ccm.0000000000000883.
71. Wang L, Li C, Hao X, et al. Percutaneous cannulation is associated with lower rate of severe neurological complication in femoro-femoral ECPR: results from the Extracorporeal Life Support Organization Registry. *Ann Intensive Care* 2023; 13: 77. DOI: 10.1186/s13613-023-01174-1.
72. Simons J, Di Mauro M, Mariani S, et al. Bilateral femoral cannulation is associated with reduced severe limb ischemia-related complications compared with unilateral femoral cannulation in adult peripheral venoarterial extracorporeal membrane oxygenation: results from the extracorporeal life support registry. *Crit Care Med* 2024; 52: 80–91. DOI: 10.1097/ccm.0000000000006040.
73. Shah N, Li X, Shanmugham P, et al. Early changes in arterial partial pressure of carbon dioxide and blood pressure after starting extracorporeal membrane oxygenation in children: extracorporeal life support organization database study of neurologic complications. *Pediatr Crit Care Med* 2023; 24: 541–550. DOI: 10.1097/pcc.0000000000003216.
74. Joram N, Rozé JC, Tonna JE, et al. Association between early change in arterial carbon dioxide tension and outcomes in neonates treated by extracorporeal membrane oxygenation. *Asaio J* 2023; 69: 411–416. DOI: 10.1097/mat.0000000000001838.
75. Bembea MM, Lee R, Masten D, et al. Magnitude of arterial carbon dioxide change at initiation of extracorporeal membrane oxygenation support is associated with survival. *J Extra Corpor Technol* 2013; 45: 26–32.
76. Cornet AD, Kooter AJ, Peters MJL, et al. The potential harm of oxygen therapy in medical emergencies. *Crit Care* 2013; 17: 313. DOI: 10.1186/cc12554.
77. Wang CH, Chang WT, Huang CH, et al. The effect of hyperoxia on survival following adult cardiac arrest: a systematic review and meta-analysis of observational studies. *Resuscitation* 2014; 85: 1142–1148. DOI: 10.1016/j.resuscitation.2014.05.021.20140602.
78. Roberts BW, Kilgannon JH, Hunter BR, et al. Association between early hyperoxia exposure after resuscitation from cardiac arrest and neurological disability: prospective multicenter protocol-directed cohort study. *Circulation* 2018; 137: 2114–2124. DOI: 10.1161/circulationaha.117.032054.

79. Vereczki V, Martin E, Rosenthal RE, et al. Normoxic resuscitation after cardiac arrest protects against hippocampal oxidative stress, metabolic dysfunction, and neuronal death. *J Cerebr Blood Flow Metabol* 2006; 26: 821–835. DOI: 10.1038/sj.jcbfm.9600234.
80. Kramer P, Mommsen A, Miera O, et al. Survival and mid-term neurologic outcome after extracorporeal cardiopulmonary resuscitation in children. *Pediatr Crit Care Med* 2020; 21: e316–e324.
81. Eastaugh LJ, Thiagarajan RR, Darst JR, et al. Percutaneous left atrial decompression in patients supported with extracorporeal membrane oxygenation for cardiac disease. *Pediatr Crit Care Med* 2015; 16: 59–65. DOI: 10.1097/pcc.0000000000000276.
82. Ezad SM, Ryan M, Donker DW, et al. Unloading the left ventricle in venoarterial ECMO: in whom, when, and how? *Circulation* 2023; 147: 1237-1250. DOI: 10.1161/CIRCULATIONAHA.122.062371.
83. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after in-hospital cardiac arrest in children. *N Engl J Med* 2017; 376: 318–329. DOI: 10.1056/NEJMoa1610493.
84. Cvetkovic M, Chiarini G, Belliato M, et al. International survey of neuromonitoring and neurodevelopmental outcome in children and adults supported on extracorporeal membrane oxygenation in Europe. *Perfusion* 2023; 38: 245–260. DOI: 10.1177/02676591211042563.
85. Polito A, Barrett CS, Wypij D, et al. Neurologic complications in neonates supported with extracorporeal membrane oxygenation. An analysis of ELSO registry data. *Intensive Care Med* 2013; 39: 1594–1601. DOI: 10.1007/s00134-013-2985-x.
86. Lorusso R, Taccone FS, Belliato M, et al. Brain monitoring in adult and pediatric ECMO patients: the importance of early and late assessments. *Minerva Anestesiol* 2017; 83: 1061–1074. DOI: 10.23736/s0375-9393.17.11911-5.20170622
87. Pandiyan P, Cvetkovic M, Antonini MV, et al. Clinical guidelines for routine neuromonitoring in neonatal and pediatric patients supported on extracorporeal membrane oxygenation. *Am Soc Artif Intern Organs J* 2023; 69: 895–900. DOI: 10.1097/mat.0000000000001896.
88. Bembea MM, Rizkalla N, Freedy J, et al. Plasma biomarkers of brain injury as diagnostic tools and outcome predictors after extracorporeal membrane oxygenation. *Crit Care Med* 2015; 43: 2202–2211. DOI: 10.1097/ccm.0000000000001145.
89. Bezuska L, O'Doherty JP, Ali B, et al. Extracorporeal membrane oxygenation in paediatric cardiac surgery: 5-year single centre experience. *J Cardiothorac Surg* 2023; 18: 314. DOI: 10.1186/s13019-023-02440-w.
90. Taka H, Kotani Y, Kuroko Y, et al. Risk factors and outcomes of pediatric extracorporeal membrane oxygenation. *Asian Cardiovasc Thorac Ann* 2021; 29: 916–921. DOI: 10.1177/0218492321997379.
91. Brown G, Moynihan KM, Deatrick KB, et al. Extracorporeal life support organization (ELSO): guidelines for pediatric cardiac failure. *Am Soc Artif Intern Organs J* 2021; 67: 463–475. DOI: 10.1097/mat.0000000000001431.
92. Brogan TV, Lequier L, MacLaren G, et al. *Extracorporeal life support: the ELSO red Book*. 6th ed. Ann Arbor, MI: Extracorporeal Life Support Organization, 2022.
93. Ijsselstijn H, Schiller RM, Holder C, et al. Extracorporeal life support organization (ELSO) guidelines for follow-up after neonatal and pediatric extracorporeal membrane oxygenation. *Am Soc Artif Intern Organs J* 2021; 67: 955–963. DOI: 10.1097/mat.0000000000001525.
94. Fainberg NA, Morrison WE, West S, et al. Organ donation from patients on extracorporeal membrane oxygenation at the time of death. *Crit Care Explor* 2022; 4: e0812. DOI: 10.1097/cce.0000000000000812.
95. Sawamoto K, Bird SB, Katayama Y, et al. Outcome from severe accidental hypothermia with cardiac arrest resuscitated with extracorporeal cardiopulmonary resuscitation. *Am J Emerg Med* 2014; 32: 320–324. DOI: 10.1016/j.ajem.2013.12.023.
96. Burke CR, Chan T, Brogan TV, et al. Extracorporeal life support for victims of drowning. *Resuscitation* 2016; 104: 19–23. DOI: 10.1016/j.resuscitation.2016.04.005.
97. Olson T, Anders M, Burgman C, et al. Extracorporeal cardiopulmonary resuscitation in adults and children: a review of literature, published guidelines and pediatric single-center program building experience. *Front Med* 2022; 9: 935424. DOI: 10.3389/fmed.2022.935424.
98. Matam BR, Duncan H, Lowe D. Machine learning based framework to predict cardiac arrests in a paediatric intensive care unit : prediction of cardiac arrests. *J Clin Monit Comput* 2019; 33: 713–724. DOI: 10.1007/s10877-018-0198-0.
99. Yu P, Skinner M, Esangbedo I, et al. Predicting cardiac arrest in children with heart disease: a novel machine learning algorithm. *J Clin Med* 2023; 12: 2728. DOI: 10.3390/jcm12072728.
100. Cole AR, Perry DA, Raza A, et al. Perioperatively inhaled hydrogen gas diminishes neurologic injury following experimental circulatory arrest in swine. *JACC Basic Transl Sci* 2019; 4: 176–187. DOI: doi:10.1016/j.jacbts.2018.11.006.
101. Cole AR, Raza A, Ahmed H, et al. Safety of inhaled hydrogen gas in healthy mice. *Med Gas Res* 2019; 9: 133–138. DOI: 10.4103/2045-9912.266988.
102. Cole AR, Sperotto F, DiNardo JA, et al. Safety of prolonged inhalation of hydrogen gas in air in healthy adults. *Crit Care Explor* 2021; 3: e543. DOI: 10.1097/cce.0000000000000543.