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Improving Resuscitation and Extracorporeal Membrane Oxygenation Outcomes in Critically Ill Pediatric Cardiac Patients: from big data, to bench, to bedside

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Anyone, anywhere, can now initiate
cardiac resuscitative procedures.
All that is needed are two hands.

Kouwenhoven WB et al.
JAMA, 1960

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Abstract

Introduction: Despite an undeniable improvement in knowledge and care over time, resuscitation in cardiac patients remains one of the most relevant challenges for cardiologists and intensivists.

Objectives: We aimed to provide insight into resuscitation and outcomes of critically ill pediatric cardiac patients, exploring different knowledge opportunities - from big data, to bench, to bedside. We performed 6 individual projects, aiming *to define*, *predict,* and *treat* resuscitation events and ultimately improve the associated outcome.

Methods: We performed:

1. a systematic review and meta-analysis on the incidence, risk factors, and outcome of CA in pediatric cardiac patients;
2. a *big data* analysis to determine whether novel mathematically computed variables as shock index (SI), coronary perfusion pressure (CPP), and rate pressure product (RPP) may predict resuscitation events;
3. a retrospective analysis of ELSO Registry data on patients resuscitated with ECMO after failure to wean (FTW) from cardiopulmonary bypass (CPB);
4. a review of extracorporeal CPR (ECPR) events and their outcomes at our center (BCH), modeling prediction of severe functional impairment or death;
5. a propensity-weighted analysis to define the benefits of left atrial (LA) decompression in patients with biventricular physiology supported with ECMO;
6. a prospective Phase1 study for the safety evaluation of a new FDA-approved drug, the inhaled hydrogen (H2), which has shown potential in prevention/treatment of ischemia-reperfusion injury in animal models.

Results: We have shown:

1. Among 126,087 critically ill cardiac patients, 5% (CI 4-7%) experienced CA, and21% (CI 15-28%) underwent ECPR. Overall, 35% of patients (CI 27-44%) did not reach ROSC, and 54% died before discharge (CI 47-62%);
2. 7% (296/4,161) of patients who underwent cardiac surgery had CPR/ECPR, need for ECMO/VAD, unplanned surgery, heart transplant, or death within 7 postoperative days. In a multivariable regression model adjusted for age, surgical complexity, inotropic and respiratory support, and organ dysfunction, SI>1.83 was significantly associated with the adverse outcome (OR 6.6 [CI 4.4-10.0]), and CPP>35mmHg was protective against the outcome (OR 0.5 [0.4-0.7]);
3. 55% of the 2,322 patients who FTW from CPB died before discharge. Non-cardiac congenital anomalies, comorbidities, pre-operative CA, pre-operative mechanical ventilation>24h, pre-operative bicarbonate administration, longer CPB time, complex surgical procedures, longer ECMO duration, and ECMO complications were all independently associated with in-hospital mortality. Age>26 days (OR 0.56 [CI 0.42-0.75]) reduced the odds of mortality;
4. 52% of the 182 patients who underwent ECPR at BCH died before discharge. The median Functional Status Scale (FSS) among survivors was 8 (IQR 6-8), and only one survivor had severe functional impairment. Predictive models identified FSS at admission, single ventricle physiology, ECMO duration, mean PELOD-2, and worst mASPECTS as independent predictors of severe functional outcome at discharge (AUC=0.931) and at 6 months (AUC=0.924);
5. 18% of the 1,508 cardiac patients with biventricular physiology supported with ECMO underwent LA decompression (LA+). Covariates were well-balanced after propensity-weighting. In-hospital adverse outcome rate was 47% in LA+ patients vs 51% in LA-. Propensity-weighted multivariable logistic regression showed LA decompression to be protective for in-hospital adverse outcome (OR 0.77 [CI 0.64-0.93]);
6. H2 inhalation is safe in adult healthy volunteers, with no significant adverse events. This lays the foundation of a future trial for the use of H2 for the prevention/treatment of ischemia-reperfusion injury.

Conclusion: The incidence of resuscitation events in pediatric cardiac patients is not negligible, but there is a trend of improvement overtime. Prediction and prevention of resuscitation events is essential, and *big data*-derived hemodynamic indices may serve as additional support tool. Overall, outcomes after resuscitation in pediatric cardiac patients remain poor. However, there are multiple opportunities to act, including better identification of modifiable risk factors and targeted intervention as LA decompression in patients with biventricular physiology, and the application of novel translational researches as the use of inhaled H2 for the improvement of the neurologic outcome. Future steps will include a randomized trial on the use of inhaled H2 to improve neurologic outcomes in cardiac ECPR pediatric patients.

Background

Resuscitation can be defined as the therapy aiming to preserve the integrity of vital organs when the circulation is ineffective, and a cardiac arrest (CA) is ongoing or impending. Critically ill pediatric cardiac patients are individuals at high risk of ineffective circulation, heart failure, arrhythmias, CA, and death. Despite an undeniable improvement in knowledge and care over time, resuscitation in cardiac patients remains one of the most relevant challenges for pediatric intensivists, who are constantly researching new strategies to prevent and predict the resuscitation event, and improve its outcomes (1).

Cardiac arrest and cardiopulmonary resuscitation in patients with cardiac disease

Hospitalized children with cardiovascular disease are at higher risk for CA (2). A recent study involving a total of 3,739 hospitals in 38 states participating in the Kids' Inpatient Database showed that cardiopulmonary resuscitation (CPR) occurred in 0.74% of hospitalizations of children with cardiovascular disease, compared with 0.05% of those of children without cardiovascular disease. In terms of risk, these data may be translated in a 13-fold higher risk of CA (OR 13.8, CI 12.8–15.0) in hospitalized patients with cardiovascular disease compared to those without cardiac disease (2). The frequency of CA among patients with cardiovascular disease admitted to the cardiac intensive care unit (CICU) or general pediatric intensive care unit (PICU) is higher and ranges from 2.6 to 10% (3–14), up to 12.7% in single-ventricle patients during their post-operative Stage 1 palliation period (15). This percentage differs significantly from the one reported for the general PICU population (0.9-1.4%) (16, 17). A detailed systematic review and meta-analysis of studies that focused on the incidence of CA, associated risk factors, and outcomes in patients with cardiac disease admitted to the CICU or PICU is reported as Project 1 of this Thesis.

Multiple reasons may explain the higher likelihood of patients with cardiovascular disease to experience CA. The vast majority of children with cardiac disease have a congenital heart disease (CHD), thus blood pathway may be abnormal. These patients requires either surgical correction or palliation, and may therefore have residual lesions, different circulation physiology, or develop new lesions, flow problems or complications over time. In fact, this population is at higher risk of myocardial dysfunction, arrhythmias, and – in case of single ventricle patients – unbalanced systemic and pulmonary circulation. Additionally, cardiorespiratory interactions may have more impact on the hemodynamics, especially in the setting of invasive mechanical ventilation. Finally, but not less importantly, the anatomical and physiological substrates of CHD can influence the response and effectiveness of resuscitation, especially in neonates and single ventricle patients (1).

One of the most unique examples of high-risk cardiac patient is the patient with single ventricle physiology. Single ventricle patients typically undergo a series of staged operations. For patients with hypoplastic left heart syndrome (HLHS), the pathognomonic single ventricle CHD, the first step of palliation is the Stage 1 operation, which allows to provide an adequate systemic flow (reconstruction of the aorta and systemic outflow), adequate removal of any atrial restriction, and adequate pulmonary blood flow (using a Sano

shunt or Blalock-Taussig shunt). The associated increased myocardial work and oxygen demand and the risk of imbalances between the pulmonary and systemic blood flow (Qp/Qs) given the parallel circulations make these patients at significant increased risk of CA. Also, occlusion of the shunt may rapidly cause cardiovascular collapse with need for resuscitation (1, 18). The rate of in-hospital CA in Stage 1 patients has been reported to be up to 12% (14), and – interestingly - significantly lower after placement of a Sano shunt compared to a BT-shunt (19). Finally, the Single Ventricle Reconstruction Trial reported a 12-month 31% rate of death between Stage 1 and the Glenn operation, highlighting the unique liability of these patients (19). Given their unique physiology, resuscitation in these patients is a significant challenge. In fact, while chest compressions in a structurally normal heart will result in separate provision of theoretically equal pulmonary and systemic blood flow from the right ventricle (RV) and left ventricle (LV) respectively, in a single ventricle the same compression will provide flow to the parallel circulations with a Qp/Qs balance or imbalance dependent on the pulmonary and systemic resistances (PVR and SVR, respectively) (1).

The following palliation stage is a bidirectional Glenn or hemi-Fontan operation which aim to create a superior cavopulmonary anastomosis, ensuring pulmonary blood flow from the superior vena cava. The third and last palliative step is the Fontan operation, in which all the systemic return is baffled to the pulmonary circulation, making the two circulations in series. Therefore, chest compression will results in systemic flow, and pulmonary flow will depend on both SVR and PVR. Further, the presence of associated ventricular dysfunction and/or significant atrioventricular valve regurgitation may compromise the oxygen delivery, representing an additional risk factor for CA. Patients with Glenn or Fontan physiology in the prearrest phase may benefit from afterload reduction or gentle positive pressure ventilation (1, 20, 21). Overall, the survival after cardiac arrest in these patients is poor and, among survivals, the risk of end-organ injury is increased. As a result, it is important for providers to recognize and intervene when prearrest low cardiac output and impaired oxygen delivery develop (1).

Low cardiac output secondary to a baseline myocardial disease (as cardiomyopathy or myocarditis) or in the setting of transient endothelial dysfunction, inflammation, myocardial ischemia/reperfusion injury, or changes in ventricular loading conditions (known as low cardiac output syndrome), is often a leading condition for CA (1). In patients with cardiomyopathy or chronic myocarditis, intercurrent illness or procedural sedation may be enough to further decrease the cardiac output and induce significant clinical deterioration and CA. Thus, prevention is certainly the most important action for these patients. Conversely, patients with myocarditis may present with relatively preserved systolic function and absence of cardiomegaly at chest X-ray, but will have rapid deterioration. Although the myocardial recovery is excellent in this population, prevention of CA and support of any rapidly evolving myocardial dysfunction is mandatory, including early initiation of mechanical circulatory support to allow full myocardial recovery.

Low cardiac output status is a well described complication following cardiac surgery, and is thought to be secondary to a variable combination of transient endothelial dysfunction, inflammation, myocardial ischemia and reperfusion injury, or changes in ventricular loading conditions (1, 22, 23). Once more, careful monitoring of hemodynamics parameters by continuous arterial and central venous tracing, oximetry (venous or near-infrared spectroscopy), lactate levels, core-temperature, and telemetry may predict any impending deterioration (1, 24–26). Inotropic support should be started to improve systolic function, and pacing may help to optimize cardiac output. Sedation, analgesia and temperature control will decrease the oxygen demand. Mechanical ventilation should be targeted on the baseline physiology considering the cardio-respiratory interactions. In

patient with RV dysfunction or pulmonary hypertension, the use of pulmonary vasodilators will improve RV output and LV preload. All these factors may prevent a low cardiac output state from progressing to CA (1). Finally, in case of failing of these treatments, mechanical support should be considered.

Cardiac patients are also at higher risk of arrhythmias (1). Although arrhythmias in children is generally better tolerated than in adults, in the setting of CHD, baseline ventricular dysfunction or in the presence of after factors that decrease the oxygen delivery, arrhythmias may represent the cause of acute decompensation. Children after cardiac surgery may be at higher risk of acquired complete heart block, which can be not well tolerated especially in the setting of low cardiac output. Temporary pacing is currently used when the arrhythmia is not tolerated, and a permanent pacemaker is considered especially in patients whose sinus rhythm has not recovered in the first postoperative week. Other significant arrhythmias that may induce rapid circulatory failure and CA are junctional ectopic tachycardia (JET), supraventricular tachycardia (SVT) with rapid conduction, torsades de pointe in patients with long QT syndrome, as well as ventricular tachycardia (VT) or fibrillation (VF). Dedicated antiarrhythmic drugs, decrease of the oxygen demand using sedation and temperature control in the case of JET, as well as isoproterenol or magnesium sulfate for torsade the pointe, must be rapidly considered. VT and VF are mainly secondary to coronary ischemia, which is less common in children compared with adults. Data from adult registries showed that the use of lidocaine in VF or pulseless VT was associated with increased return to spontaneous circulation (ROSC) and 24-hours survival, while amiodarone was not (27). However, neither drugs were significantly associated with increased survival to hospital discharge; thus, both of them are currently used in the pediatric cardiac population.

Given all these peculiar characteristics, survival after resuscitation can be low in infants and children with cardiac disease (1). Despite an overall improvement of the survival rate after in-hospital CA in the general pediatric population in the last decade (3-fold improvement), the mortality rate for cardiac patients remains high (30 to 65%) (1, 3–6, 11, 12, 16, 28–30). A detailed analysis of mortality data in cardiac critically ill patients is reported in Project 1 of this Thesis. In 2010, the American Heart Association (AHA) officially recognized the pediatric cardiac patient as a peculiar high-risk patient for CA in its official Resuscitation Guidelines, with particular reference to the single-ventricle patient (31). Further, in the 2015 guidelines, the AHA strongly supported the consideration of Extracorporeal Membrane Oxygenation (ECMO) as part of the Resuscitation protocol in cardiac patients - named as extracorporeal cardiopulmonary resuscitation (ECPR) - when ECMO expertise and equipment are available (32). Finally, in 2018, the AHA published a new Statement entirely dedicated to the resuscitation of the pediatric cardiac patient (1).

Extracorporeal Membrane Oxygenation

Veno-arterial (VA) Extracorporeal Membrane Oxygenation (ECMO) provides mechanical circulatory support for resuscitation in children who experienced severe acute cardiac failure (33). ECMO may be used to support failed conventional CPR (i.e. ECPR), but also to support patients in cardiogenic shock or impending CA that may otherwise die, such as in a contest of low-cardiac output, combined cardiac and respiratory failure, or failure to wean (FTW) from cardiopulmonary by-pass (CPB) after pediatric surgery (1, 34–38).

The primary purpose of VA-ECMO in the setting of a failing heart is to restore end-organ perfusion. Once the end-organ perfusion is restored, every effort must be taken to identify the underline cause of heart failure, so that appropriate intervention and treatment may take place or be administered. For example, in the setting of post-cardiotomy ECMO, the identification and subsequent correction of a residual lesion may represent the key strategy for the recovery of the patient's hemodynamics and later ECMO decannulation.

Indications for VA-ECMO support in the cardiac patient may be categorized as surgical and medical. Within the surgical indications, ECMO may be used as pre-operative support in both neonates and children with profound cyanosis, shock, or end-organ dysfunction. Examples of the use of pre-operative ECMO in neonate are the neonate with Ebstein's malformation and functional pulmonary atresia with shock secondary to circular shunt, or the D-transposition of the great arteries with significant cyanosis and pulmonary hypertension (37). Similarly, critically ill children in shock with very high operative risk, as the Stage 1 palliation patient with thrombosis of the shunt, may benefit from pre-operative stabilization with mechanical support. However, VA-ECMO in surgical cardiac patients is most often used in the acute postoperative period. Main indications in this setting are FTW from CBP, low cardiac output state secondary to ventricular dysfunction, pulmonary hypertension or intractable arrhythmias, or CA.

Failure to wean from CPB may result from severe post-CPB cardiac and/or pulmonary dysfunction, or hemodynamically significant residual lesions. In these patients, transition to VA-ECMO can provide longer duration of cardiopulmonary support while awaiting cardiac and/or pulmonary recovery, bridge to a surgical or catheter-based intervention aimed at correcting a residual lesion, or bridge to transplantation (39, 40). In a two-center report of post-operative ECMO use in children with biventricular CHD undergoing cardiac surgery, Chaturvedi et al. reported improved survival in patients in whom ECMO was initiated in the operating room, some of whom failed to wean from CPB, compared to ECMO initiated in the intensive care unit (64% vs. 29%) (41). In this report, the authors suggested that avoiding prolonged exposure to inadequate cardiac output and cardiac arrest in post-operative period improved outcomes for these children. Overall, previous reports of children supported with ECMO for failing to wean from CPB documented variable in-hospital mortality, which ranges from 23 to 60% (42–45). Unfortunately, these single-institution reports are limited by small sample size and generalizability (3-15). A detailed summary of studies that have addressed FTW patients, their risk factors, and outcomes is reported within Project 3. Overall, VA-ECMO remains one of the most important strategies to improve outcome in cardiac patients who FTW from CBP.

As mentioned above, a postoperative low cardiac output state may result from ventricular dysfunction, pulmonary hypertension, or intractable arrhythmias, and may lead rapidly to CA and death (22, 55). Following complex cardiac surgery requiring cardiopulmonary bypass (CPB), a predictable decline in cardiac performance occurs as systemic and pulmonary afterload increase, while relative myocardial contractility decreases (22, 23). Low cardiac output state is a multifactorial process. Implicated factors include certain preoperative factors, myocardial dysfunction associated with CPB, ischemia-reperfusion injury, arrhythmias, and residual cardiac lesions, as well as altered loading conditions, increased metabolic demands, temperature instability, systemic inflammation, and derangements of the neurohormonal axis(22, 55). Clinical manifestations include a compensatory response with tachycardia and elevated systemic vascular resistance, as well as signs reflecting inadequate tissue perfusion as oliguria, increased arterial-venous O2 content difference, elevated lactate, and

metabolic acidosis (22, 55). Low cardiac output state is significantly associated with increased morbidity and mortality, especially in neonates and in high-surgical risk patients (22, 55). In this setting, ECMO may restore oxygen delivery and allow myocardial rest and recovery. Also, it may offer more time to treat life-threatening arrhythmias and pulmonary hypertension. Finally, it may bridge to a surgical or catheter-based intervention aimed at correcting a residual lesion, as well as to other forms of mechanical support strategies as VADs, or, ultimately, to heart transplantation.

Multiple studies have highlighted the importance of identifying residual lesions to facilitate timely ECMO decannulation in postoperative patients. Prior reports on ECMO support following cardiac surgery for CHD have reported a high frequency (up to 25%) of residual lesions in children requiring post-operative ECMO (48). Thus, patients unable to be weaned off VA-ECMO should undergo a detailed evaluation for residual lesions, by echocardiography and possibly cardiac catheterization (48). Multiple reports have also shown that prompt diagnosis and correction of residual lesions is essential to improve ECMO survival (48, 56, 57).

Medical indications for VA-ECMO in pediatric cardiac patients include myocarditis, cardiomyopathy, intractable arrhythmias, and sepsis. The clinical outcome of children who required ECMO for fulminant myocarditis are promising, with survival to hospital discharge being between 54 and 83% (58). Sub-acute and chronic myocarditis, as well as cardiomyopathy, with significant myocardial damage and very poor systolic function, may have significant lower chances of survival if not supported with mechanical support. In this setting, ECMO is used mostly as a bridge for VAD or heart transplantation (37, 59). Although the use of ECMO for intractable arrhythmia is rare, arrhythmias associated to a failing heart, as in the case of myocarditis and cardiomyopathy, is certainly more common. Finally, sepsis represents a more recent - and challenging - indication for ECMO support. In fact, the presence of a failing heart is associated with presence of significant peripheral vasoplegia, such that flow requirements may be significantly high. However, the use of ECMO in septic patients is increasing worldwide, with rates of survival at discharge ranging from 41% (60) to 74% (this last percentage refers to cases with central cannulation only (61)).

The use of ECMO as a support of CPR is becoming increasingly frequent, both in surgical and medical cardiac patients, specifically for in-hospital cardiac arrest (1, 33, 37, 38). In a wide study comparing cardiac patients who did or did not undergo ECPR, Lasa et al. demonstrated increased survival and survival with good neurologic outcome at hospital discharge in the ECPR cohort compared to the CPR-only cohort (40% vs 27%, and 27% vs 18%, respectively). After adjustment for covariates, patients receiving ECPR had higher odds of survival to discharge (OR 2.80; CI 2.13-3.69) and survival with favorable neurological outcome (OR 2.64; CI 1.91-3.64) than patients who received CPR only. This association persisted when analyzed by propensity score-matched cohorts (OR, 1.70; CI 1.33-2.18; and OR 1.78; CI 1.31-2.41, respectively) (62). Interestingly, 59% of patients who underwent ECPR were post-surgical patients (62). A recent meta-analysis of adult and pediatric studies on ECPR patients showed ECPR increased the odds of survival from 2.5 to 3.8 times compared to CPR alone (63). Overall, the use of extracorporeal strategies to ensure a return to circulation has quickly reached a consensus and their utilization is increasing consistently over time. However, mortality rate and level of neurologic and functional dysfunction remain high following ECPR (4, 35, 64–66). Among children with heart disease, the in-hospital mortality rate after ECPR ranges from 44 to 65% (4, 64–69). Additionally, survivors

often experience organ failure and adverse neurologic outcome with different degrees of neurologic dysfunction (1, 4, 64–66). In the future, intense efforts must be placed in improving these outcomes.

Multiple strategies has been investigated to improve outcomes in patients with cardiac disease supported with ECMO. A special consideration should be made for patients with biventricular physiology and a failing heart. In fact, while ECMO ensure organ perfusion, it may have detrimental effects on the left ventricle (LV). ECMO increases LV afterload, thus the LV end-diastolic volume and pressure increase reducing transmural myocardial perfusion and impairing myocardial function and recovery. In this setting, left atrial (LA) decompression, either transcatheter or surgical, has been described as a successful strategy for decreasing the left heart pressure in adults and pediatric patients by reducing the LV distension, decreasing the LV wall stress facilitating myocardial rest and recovery (69–75). Furthermore, LA decompression may protect from lung injury secondary to cardiogenic pulmonary edema or pulmonary hemorrhage when severe LA hypertension is present (69, 70, 72, 74).

Different techniques have been described to decompress the left heart in patients supported with ECMO. In patients with central cannulation, addition of a LA cannula through one of the pulmonary veins (or less frequently addition of a pulmonary artery cannula) is the most diffused approach (76–78). In patients with peripheral ECMO or when LA cannulation is not anatomically possible, transcatheter or surgical atrial septostomy are the preferred options (73, 74, 76, 77). Finally, in appropriately sized patients, a synergic combination of ECMO with a temporary, minimally invasive, percutaneously implanted intracorporeal left ventricular assist device (i.e. Impella) has been recently described as a valuable alternative (76, 77). Since the LA decompression is not universally performed in children on ECMO, and procedure can be associated with adverse events, (73, 76, 77) the benefits of LA decompression still need to be clearly defined. However, data to date suggest that specific cohorts of patients may benefit from this intervention(69).

Neurologic outcome after resuscitation

Brain ischemia and injury develop when the cellular demand for oxygen is not met by the oxygen delivery. Oxygen delivery to the brain is proportional to cerebral blood flow and systemic oxygen saturation. Thus, when either one or both of these components (i.e. cerebral blood flow and systemic oxygen saturation) are deficient, brain ischemia will rapidly occur (1). Moreover, injury will develop not only during the ischemic time, but also in the phase of reperfusion (i.e. ischemia-reperfusion injury) after resuscitation.

It is well known that ischemia-reperfusion injury has a major impact on neurologic outcomes. For example, the measured degree of cerebral hypoxia that occurs during cardiac arrest (79) or during cardiopulmonary bypass (80) significantly affects neurologic outcomes. Similarly, the duration of CPR (during which ischemia occurs) is inversely related to survival and subsequent end-organ injury (81).

Neurologic outcome after resuscitation varies among studies (1, 82). In a recent retrospective analysis of pediatric cardiac patients undergoing ECPR, Kramer et al. showed that, among the 72 patients who underwent ECPR in their institution in the previous decade, 36% survived and 73% of them had favorable neurologic outcome (defined as a change in the Pediatric Cerebral Performance Category -PCPC- less $\leq$1 compared to the prearrest PCPC) (82). Other reports showed a favorable outcome at discharge ranging from 64% to 95% of survivors. However, outcome definitions and assessment methods highly differ among studies (62, 82–85).

Effective prediction of neurologic outcome after resuscitation remains challenging. Previous studies have attempted to predict poor neurologic outcome including death in adult populations after cardiac arrest or ECPR, while limited modeling attempts exist in the pediatric population. Adult models have shown to successfully predict a CPC ≥3 at discharge with a prediction accuracy based on AUC ranging from 0.700 to 0.877 (86–89). Notably, Youn included both neuroimaging and EEG details in their predictive model, reaching a prediction accuracy of 0.855 (90). A similar approach was used by Yang following pediatric cardiac arrest, including blood gas analysis and specific CT findings (gray to white matter ratio and ambient cistern effacement) in a model predicting PCPC >3 at discharge, reaching an AUC of 0.897 (91). Brain MRI has been shown to be predictive of unfavorable neurologic outcome in pediatric patients after in-hospital or out-of-hospital cardiac arrest (92–94). However, data modeling of death or severe neurologic impairment using models that include neuroimaging in the pediatric CPR and ECPR population are currently missing.

Therapies to directly address the ischemia reperfusion injury and improve neurologic recovery following hypoxic ischemic insult are limited. One notable exception is the use of targeted temperature management, a standard of care in comatose survivors following cardiac arrest (95). Although initial clinical trials suggested survival benefits with therapeutic hypothermia (96, 97) subsequent studies led to targeted temperature management (i.e. normothermia) to become standard following resuscitation from cardiac arrest (1, 98). However, outcomes following cardiac arrest and other ischemic insults remain poor, and the need for new therapies to treat the ischemia-reperfusion injury is pressing. In this Thesis, we will explore a novel potential therapy for the prevention/ treatment of ischemia reperfusion injury after resuscitation that has shown promising results on animal models (99, 100), i.e. the hydrogen gas (H2) (Project 6).

Despite considerable progress in knowledge and care in the last decade, a lot remains to be understood in the field of resuscitation in critically ill pediatric cardiac patients, and outcomes remain poor. Future researches are needed to prevent and predict resuscitation events, as well as to predict and treat patients who face the most adverse outcomes.

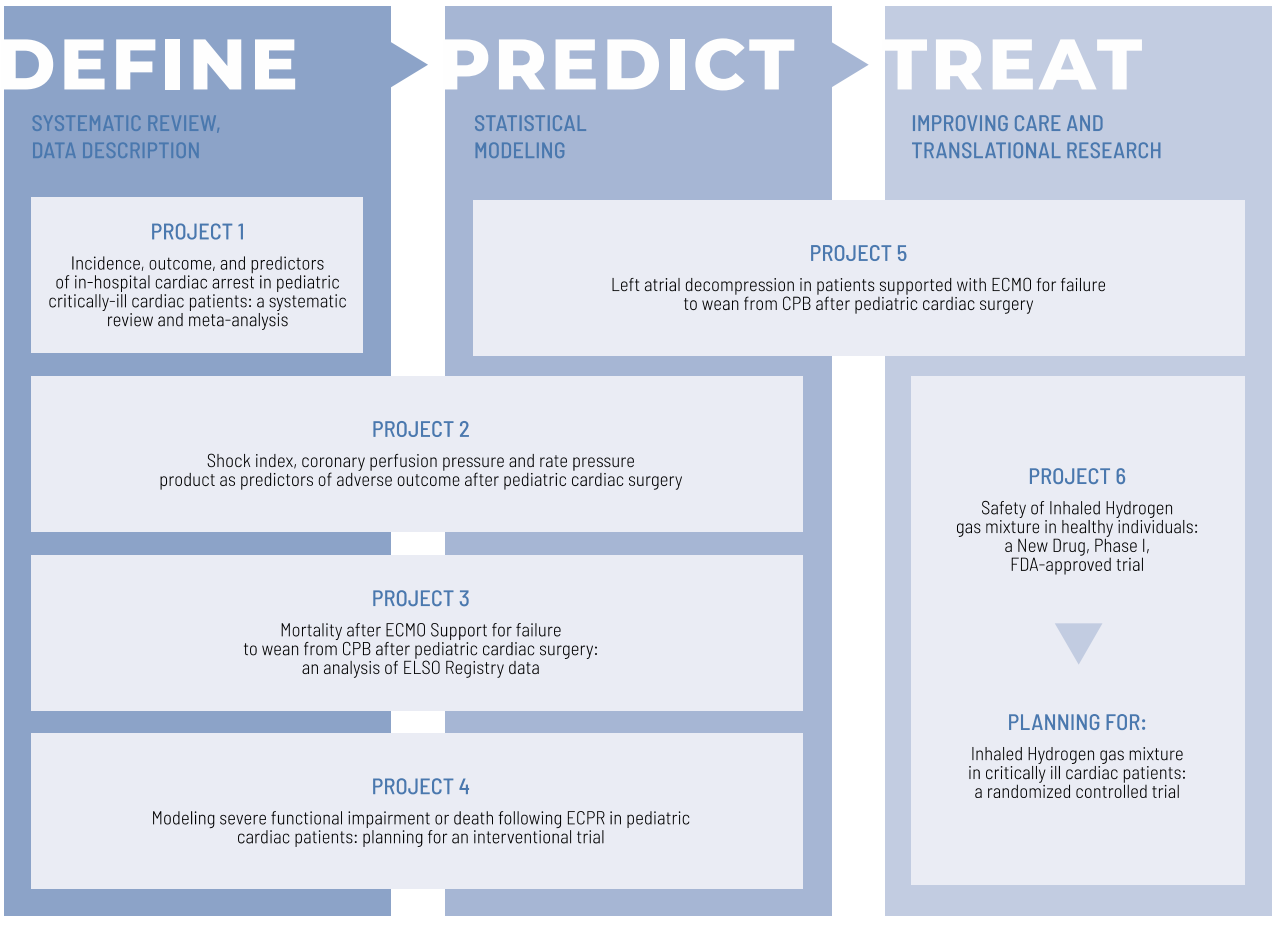
Objectives

The core objective of this Ph.D. Project is to provide insight into the resuscitation and outcomes of critically ill cardiac patients, exploring different opportunities of knowledge - from big data, to bench, to bedside. Particularly, we aim to explore new techniques of data analysis to predict clinical deterioration, mortality and functional outcome after resuscitation. Further, we aim to explore new therapeutic strategy, some of them significantly innovative, with the ultimate goal to improve the patients' outcome.

The aims of our Project can be summarized as follows (**Figure 1**):

- **Aim 1. To define**: to define and describe the incidence, characteristics, risk factors and outcome of critically ill pediatric cardiac patients who underwent resuscitation. For this aim, we will describe different populations, from patients who experienced CA, underwent ECPR, to those who had low cardiac output post cardiac surgery and required ECMO as a form of resuscitation.
- **Aim 2. To predict:** to investigate new predictors and to model factors associated with resuscitation events and their outcome; for this aim, we will explore both monocenter and multicenter large datasets, applying different statistical techniques to model the likelihood of resuscitation or its outcome.
- **Aim 3. To treat:** to investigate new therapies to improve care and outcome. Particularly, we will explore the role of the left atrial decompression in children supported with ECMO, and a new innovative potential therapy for the prevention of neurologic damage in patients who experienced ECPR.

Figure 1. Structure of the Ph.D. Project.



Projects

Project 1

Define

Incidence, outcome, and predictors of in-hospital cardiac arrest in pediatric critically ill cardiac patients: a systematic review and meta-analysis

Registered in PROSPERO - ID CRD42020156247, 2020

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Manuscript in writing phase

Abstract

Aim: We aimed to systematically review data on the incidence of in-hospital cardiac arrest (CA), associated mortality, and risk factors in pediatric patients with cardiac disease admitted to the pediatric or cardiac intensive care unit (PICU/CICU).

Methods: We performed a systematic review and meta-analysis by searching Pubmed, Cochrane, Web of Science, Embase, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), from inception to September 2021. Random effects meta-analysis was used to compute the pooled proportions of patients who experienced CA, underwent ECPR, were not able to achieve ROSC, and the pooled in-hospital mortality.

Results: Of the 2,574 studies identified, 25 were included in the systematic review (126,087 children, 5,185 CA), and 18 studies in the meta-analysis (123,736 patients, 4,173 CA). Overall, 5% (CI95%: 4-7%) of patients admitted to the PICU/CICU experienced at least one CA. In studies conducted before 2010, 8% (CI95%: 7-9%) of patients experienced CA, while in more recent studies only 3% (CI95%: 3-4%). In centers with ECMO expertise, a pooled proportion of 21% (CI95%: 15-28%) of patients underwent ECPR. Thirty-five percent of patients (CI95%: 27-44%) did not reach ROSC. The pooled overall in-hospital mortality rate was 54% (CI95%: 47-62%). Studies conducted before 2010 showed a pooled mortality rate of 67% (CI95%: 52-79%), while more recent studies a pooled mortality rate of 51% (CI95%: 44-57%). Main risk factors for CA were neonatal age, univentricular physiology, acute heart failure, arrhythmias, and higher surgical complexity. The presence of an arterial line and an expert attending decreased the risk of CA. Main risk factors for in-hospital mortality were univentricular physiology, renal failure, cerebral damage, higher vasoactive-inotropic-score, longer CPR, CA during the weekend, and limited nurse experience, while admission to a CICU decreased the risk of mortality.

Conclusion: A non-negligible proportion (5%) of critically ill patients with cardiac disease experience CA, with a trend of improvement over time. About one quarter of patients are supported with ECPR. Overall, 35% of patients do not achieve ROSC, and 54% do not survive to hospital discharge. Similarly to the incidence of CA, there is a trend of improved survival over time. Modifiable associated factors as team expertise, type of monitoring and time of CA must be taken into consideration in our everyday practice.

Background and Significance

Children with cardiac disease are at high risk of ineffective circulation, heart failure, arrhythmias, cardiac arrest (CA), and death. The incidence of CA and the mortality rate after this event in this population varies among studies and categories of patients. The CA rate among patients with cardiovascular disease admitted to the cardiac intensive care unit (CICU) or general pediatric intensive care unit (PICU) ranges from 2.6 to 10% (3–14), up to 12.7% in single-ventricle patients during their post-operative Stage 1 palliation period (15). Despite an overall improvement of the survival rate after in-hospital CA over time in the general pediatric population (3-fold improvement over a decade), the mortality rate for cardiac patients remains high, ranging from 30 to 65% (1, 3–6, 11, 12, 16, 28–30).

Multiple reasons may explain the higher likelihood of patients with cardiovascular disease to experience CA. The vast majority of children with cardiac disease have a congenital heart disease (CHDs), in which blood pathway may be abnormal. These patients requires either surgical correction or palliation, and may therefore have residual lesions, different circulation physiology, or develop new lesions, flow problems or complications over time. In fact, this population is at higher risk of myocardial dysfunction, arrhythmias, and – in case of single ventricle patients – unbalanced systemic and pulmonary circulation. Additionally, the cardiorespiratory interactions may be have more impact on the hemodynamic status of patients with cardiac disease, especially when invasively mechanically ventilated. Finally, but not less importantly, the anatomical and physiological substrates of CHD can influence the response and effectiveness of resuscitation, especially in neonates and single ventricle patients (1)

In 2010, the American Heart Association (AHA) officially recognized the pediatric cardiac patient as a peculiar high-risk patient for CA in its official resuscitation guidelines, with particular reference to the single-ventricle patient (31). In the updated 2015 guidelines, the AHA strongly supported the consideration of Extracorporeal Membrane Oxygenation (ECMO) as part of the resuscitation protocol in cardiac patients - named extracorporeal cardiopulmonary resuscitation (ECPR) - when ECMO expertise and equipment are available (32).

We performed a systematic review and meta-analysis with the aim of defining the incidence of CA in pediatric patients admitted to a pediatric general or cardiac intensive care unit (PICU or P-CICU), the proportion of patients supported with ECPR when available, the likelihood of not reaching the return of spontaneous circulation (ROSC) and its mortality rate. We also aimed to review data on risk factors for CA or for mortality following the CA event in this high-risk population.

Methods

The study was conducted in adherence to the guidelines for Systematic Review and Meta-Analysis of Observational Studies (101), as well as the PRISMA International Guidelines suggested by the EQUATOR Network. The Study was registered in the National Institute for Health Research (NIHR) International prospective register of systematic reviews (PROSPERO), with the following ID: CRD42020156247, 2020.

Data Sources and Strategy

An extensive literature search was performed by the investigators with the support of a librarian using PubMed, Cochrane, Web of Science, Embase, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), from inception to September 7th, 2021, and with no language restriction. The search strategy for each data source included both keywords and Mesh-terms regarding the following fields: *cardiac arrest*, *cardiopulmonary resuscitation*, *heart disease*, and *intensive care*. The detail search strategy for Pubmed is

reported as **Supplemental Method**s. The reference list of the most relevant articles identified were searched by hand to identify any article that may have been missed by initial search.

Review process and study selection

The reference list identified by the search strategy was downloaded in EndNote (version 20, Clarivate, Philadelphia, USA) and duplicates were removed. The articles were then imported in Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia), with a second screen for duplicates. The set of records were then screened by two independent investigators (F.S., M.D.). For any article for which a decision could not be reached from title or abstract, the full text was reviewed. Subsequently, all the full text were reviewed, and any study with a sample size ≤ 10 was excluded for eliminate positive outcome bias. Any disagreement was reviewed by a third investigator (A.A.) and resolved by discussion until consensus was reached.

Studies were considered eligible for inclusion if they included data on pediatric (<18 years) cardiac patients admitted to an intensive care unit and included at least one of the following: data on incidence of CA or cardiopulmonary resuscitation (CPR); data on mortality after CA/CPR; data on risk factors for CA/CPR; data on risk factors for mortality after CA/CPR. Studies were excluded if not pertinent, if they did not include any extractable data as review articles, case reports, case series, letters or editorials, studies with no full text or abstract available, and if they included only data on adult patients. We also excluded studies that involved a selected population with CA (e.g. CA during intubation only) and studies regarding cardiac patients who had CA in another setting such as the cardiac catheterization laboratory or the operating room. Finally, studies were excluded if there was no possibility to discern pediatric and adult data, if they included data on both in-hospital and out-of-hospital CA with no possibility of analyzing data separately, if they involved the entire cohort of hospitalized patients with no sub-analysis for PICU or CICU, and studies on cardiac patients outcomes which did not evaluate the frequency of CA. The flow diagram (**Figure 1**) shows the study selection process and exclusion criteria.

Data extraction

Data were extracted from the included studies by two independent investigators (F.S., M.D.) for data extraction. Studies on highly selected population (e.g. low birth-weight neonates, low-risk cardiac surgical procedure only), studies with duplicate data, those that were judged to be of low quality, and conference abstracts were not included in the meta-analysis. In case multiple studies reported data from the same Registry and the same timeframe, the study with larger sample size was chosen for inclusion in the meta-analysis. In case of case-control studies, only data of the cohort of interest were chosen for data extraction. We extracted the following data: study design, study period, setting, name of data-Registry if present, sample size, type of patients included, number of patients who experienced CA or CPR, definition of CA, number of patients undergoing ECPR, number of patients who were not able to reach the ROSC, mortality rate at 24h, at discharge, and at longer follow-up when available. Additionally, we extracted data on crude or adjusted logistic regression (odds ratio [OR]) evaluating the association between clinical characteristics and CA, or clinical/CPR characteristics and mortality after CA. The adjusted estimate was always prioritized if more options were available.

Quality assessment and risk of bias

Included studies were analyzed for quality using the 14-item National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies checklist (**Supplemental Table 1**) (11). Two investigators (M.D., A.A.) independently rated quality of each study as good, fair or poor. Any disagreement between investigators about quality assessment was resolved via consensus after consulting a third investigator (F.S.). Studies that were judged to be of poor quality were excluded. Publication bias was assessed using the funnel plot analysis.

Statistical analysis

Descriptive statistics was reported as frequency and percentiles for categorical variables, median and interquartile range for continuous variables. Overall agreement on quality assessment between the reviewers was reported as percentage and 95% CI using the binomial method. A *weighted* k was also calculated to measure overall agreement between the two independent reviewers' assessments, with level of agreement interpreted as follows: 0.81–1.00 almost perfect, 0.61–0.80 substantial, 0.41–0.60 moderate, 0.21–0.40 fair, and 0–0.20 slight (102). A random effects meta-analysis was performed to calculate the pooled incidence of CA, proportion of ROSC, proportion of ECPR, and mortality rate. Pooled proportion were reported as percentage and 95% confidence intervals. Heterogeneity across studies was assessed using the I2 statistic. I2 levels were defined as follows: potentially unimportant (0–19%), moderate (20–49%), substantial (50–79%), and considerable heterogeneity (> 80%). A meta-regression approach was also used to control the variability of the effects across studies (heterogeneity).

Results

Study selection

The initial database search identified 2,574 records. Following removal of duplicates, 2,078 studies were screened. Additionally, other 130 studies were reviewed by reference screen. After examination for inclusion and exclusion, a final list of 25 articles were included in the final systematic review (**Figure 1**), with a total sample of 126,087 children admitted to the PICU/CICU. Of them, 5,185 experienced at least one CA.

A detailed description of the included studies is reported in **Table 1**. Of the 25 studies included, 23 were observational cohort studies, while 2 were case-controls. Of the cohort studies, 20 were retrospective and 3 were prospective; 8 were multicenter and 15 where single-center. Among the multicenter studies, 7 used data from official data registries, while 1 was designed as a dedicated study including 3 individual tertiary-care centers.

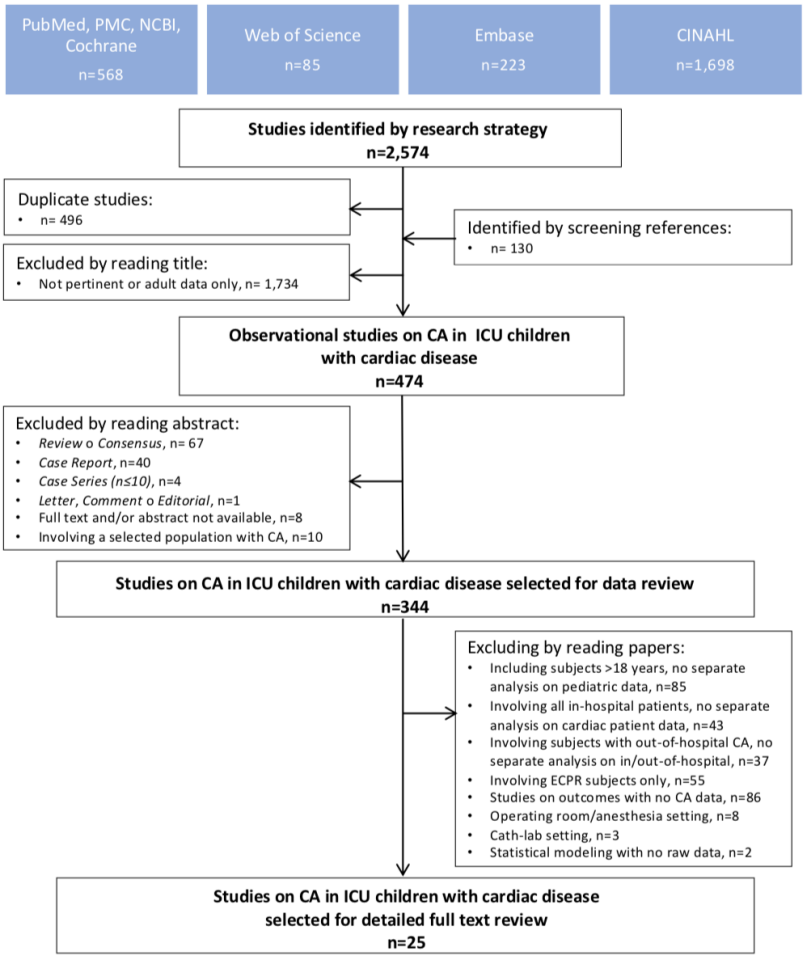
Quality assessment

Among the included studies, 2 were conference abstracts, 1 included duplicate data, 3 included data of selected populations (low birth weight, weight <2.5 kg at the time of surgery, and low-risk procedure only). Thus, 19 studies were evaluated for quality (**Supplemental Table 1**). On the three-level quality scale, the vast majority of the included studies were judged to be fair or good (18/19, 95%). Reviewers' quality classification was concordant in 15 of the 19 studies (percentage of agreement 84%, 95% CI 62–95%) for a substantial overall agreement (*weighted* k statistic 0.76).

Population

Since one study was judged to be of poor quality, a total of 18 studies were included in the meta-analysis, for a total sample size of 123,736 patients. Of them 4,173 experienced at least one CA.

Figure 1. Flow chart of the study selection process



By proportion random effects meta-analysis, a pooled proportion of 5% (CI95%: 4-7%) of patients admitted to the PICU/CICU experienced at least one CA (**Figure 2**). Since the heterogeneity and publication bias of this analysis were high, we performed multiple sensitivity analysis. A sensitivity analysis based on type of study (single center studies *vs* Registry studies) was able to reduce the heterogeneity, while controlling the publication bias (**Figure 3**). A pooled proportion of 6% (CI95%: 5-8%) of patients who experienced CA was calculated for single center studies, while a pooled proportion of 3% (CI95%: 3-3%) was computed for studies based on Registries.

Figure 2. Pooled proportion of patients experiencing CA by random effects meta-analysis

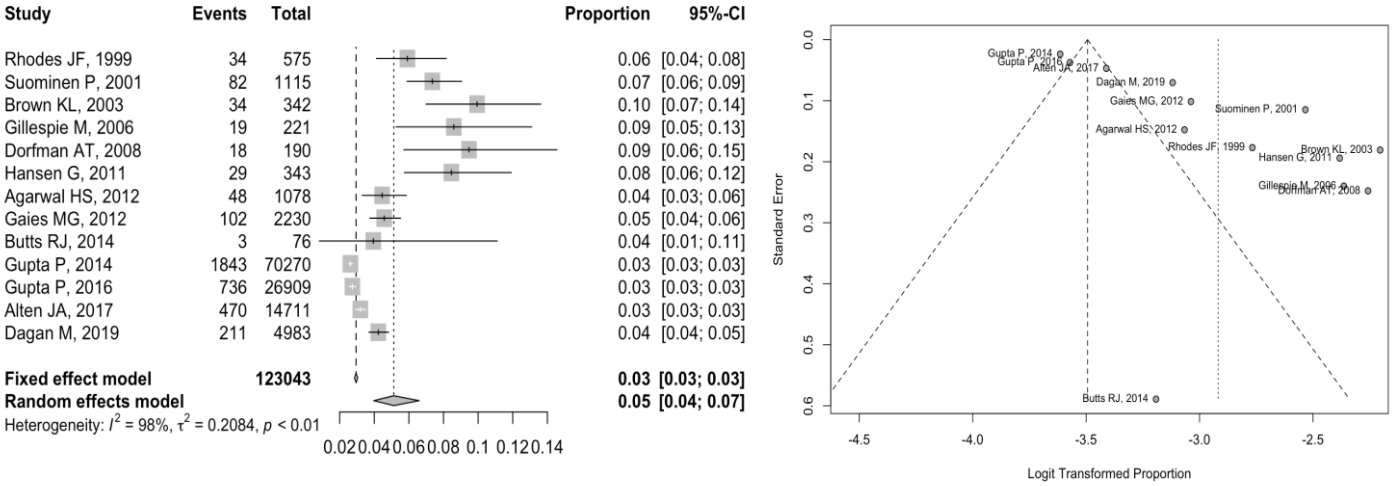
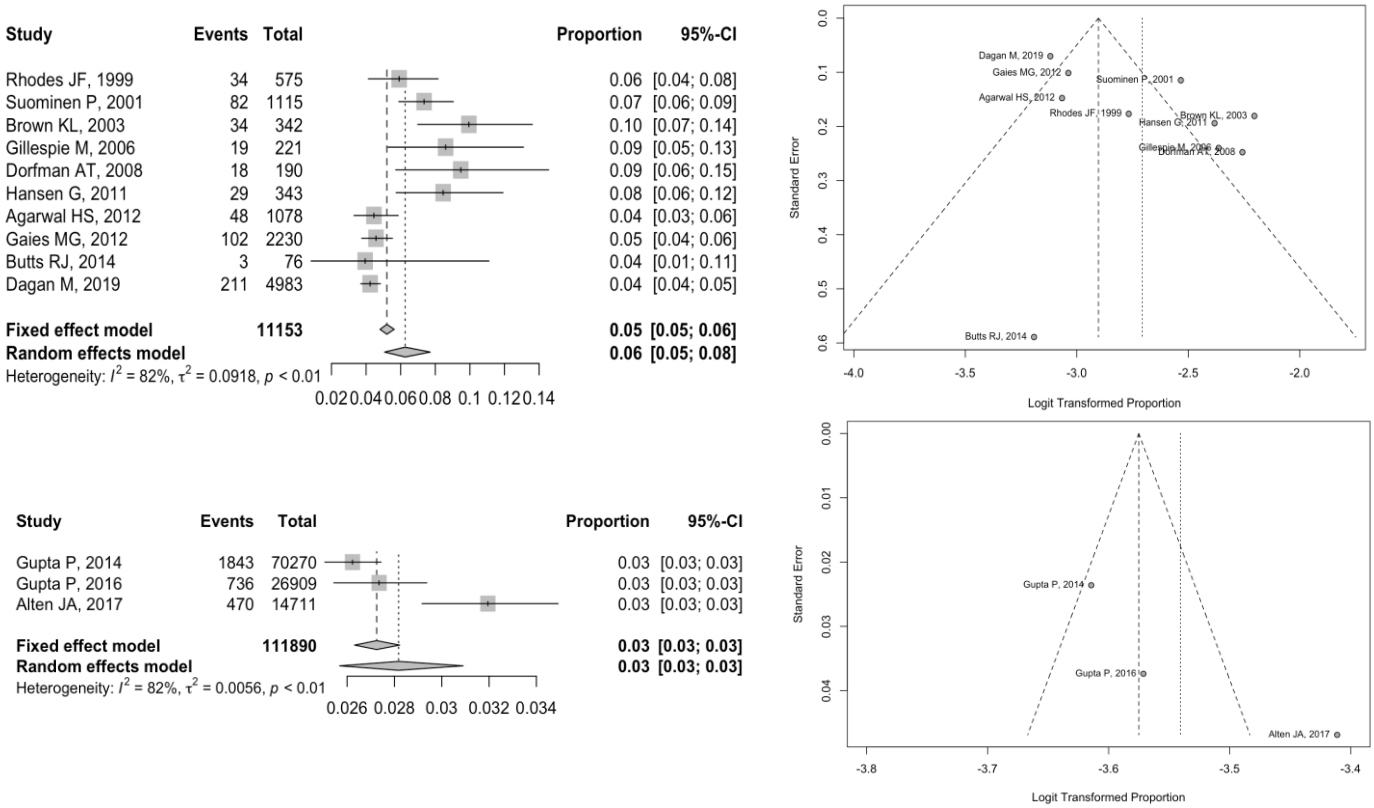
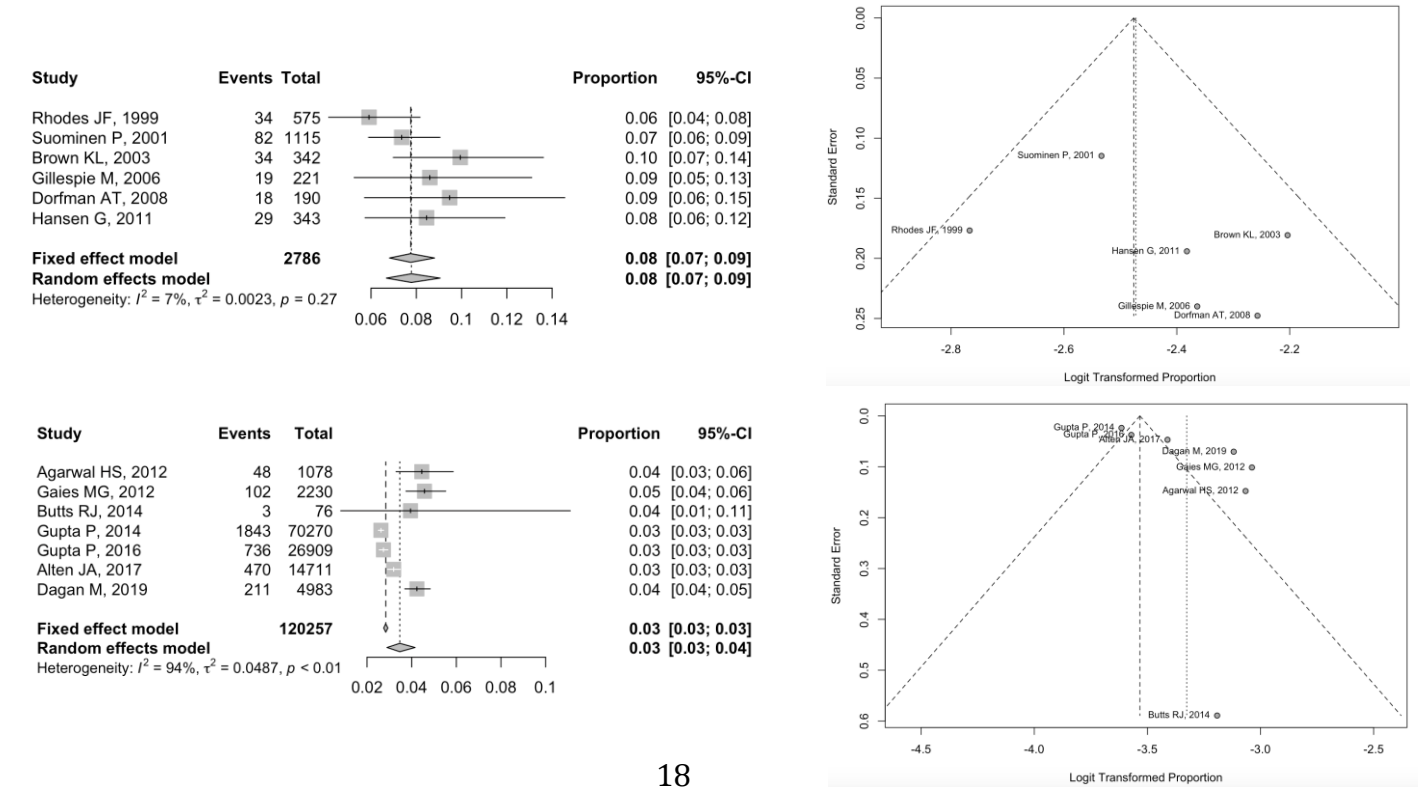


Figure 3. Pooled proportion of patients experiencing CA by random effects meta-analysis in single center studies (upper) and in studies based on registries (lower)



A second sensitivity analysis was performed based on publication year, with a cut-off year equal to 2010. Similarly to the first analysis, this analysis was able to significantly reduce the heterogeneity and the publication bias (**Figure 4**), especially in older studies. The pooled proportion of patients experiencing CA based on older studies was 8% (CI95%: 7-9%), while the one for newer studies was 3% (CI95%: 3-4%) .

Figure 4. Pooled proportion of patients experiencing CA by random effects meta-analysis according to publication period (≤2010, upper, and >2010, lower)



In centers with ECMO expertise, a pooled proportion of 21% of patients (CI95%: 15-28%) underwent ECPR (**Figure 5**). Overall, a pooled proportion equal to 35% of patients (CI95%: 27-44%) did not reach ROSC (**Figure 6**).

Figure 5. Pooled proportion of patients undergoing ECPR by random effects meta-analysis

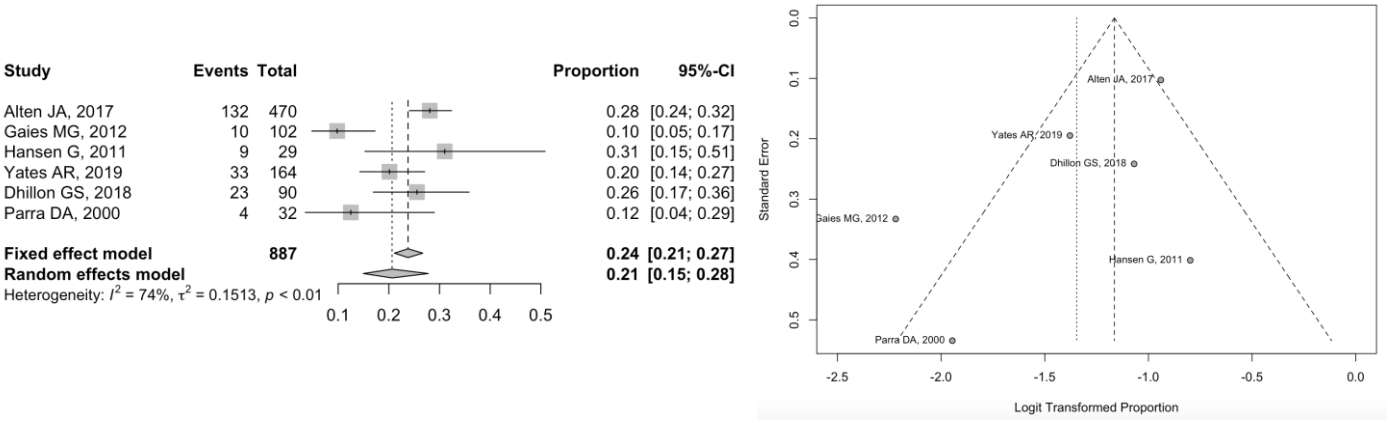


Figure 6. Pooled proportion of patients who did not achieved ROSC by random effects meta-analysis

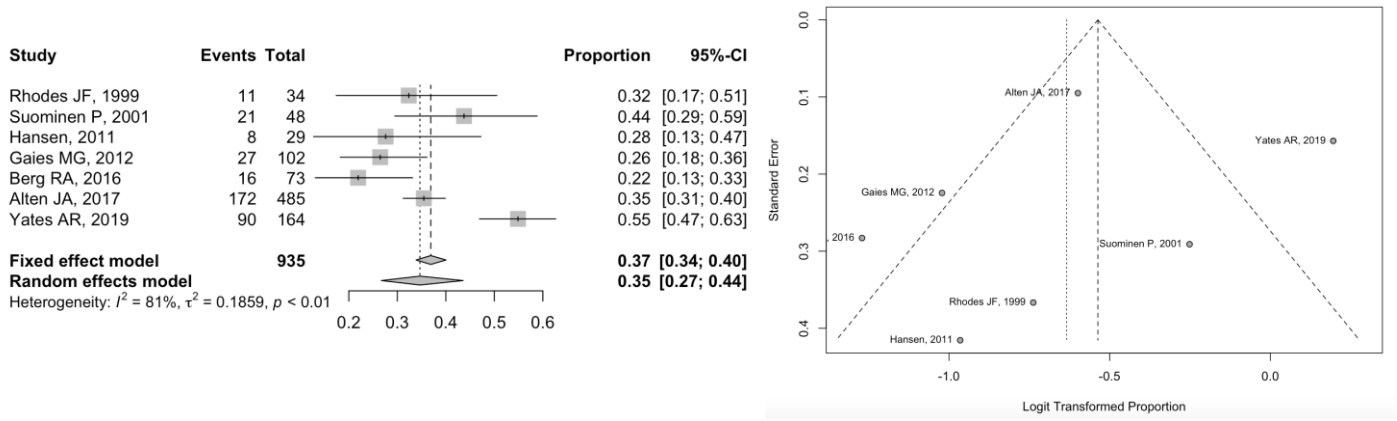
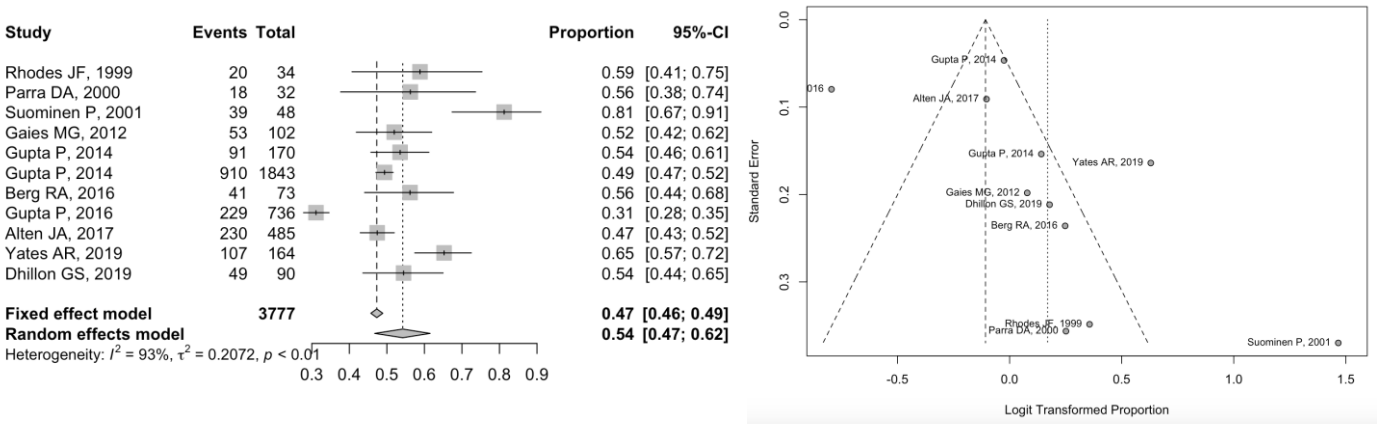


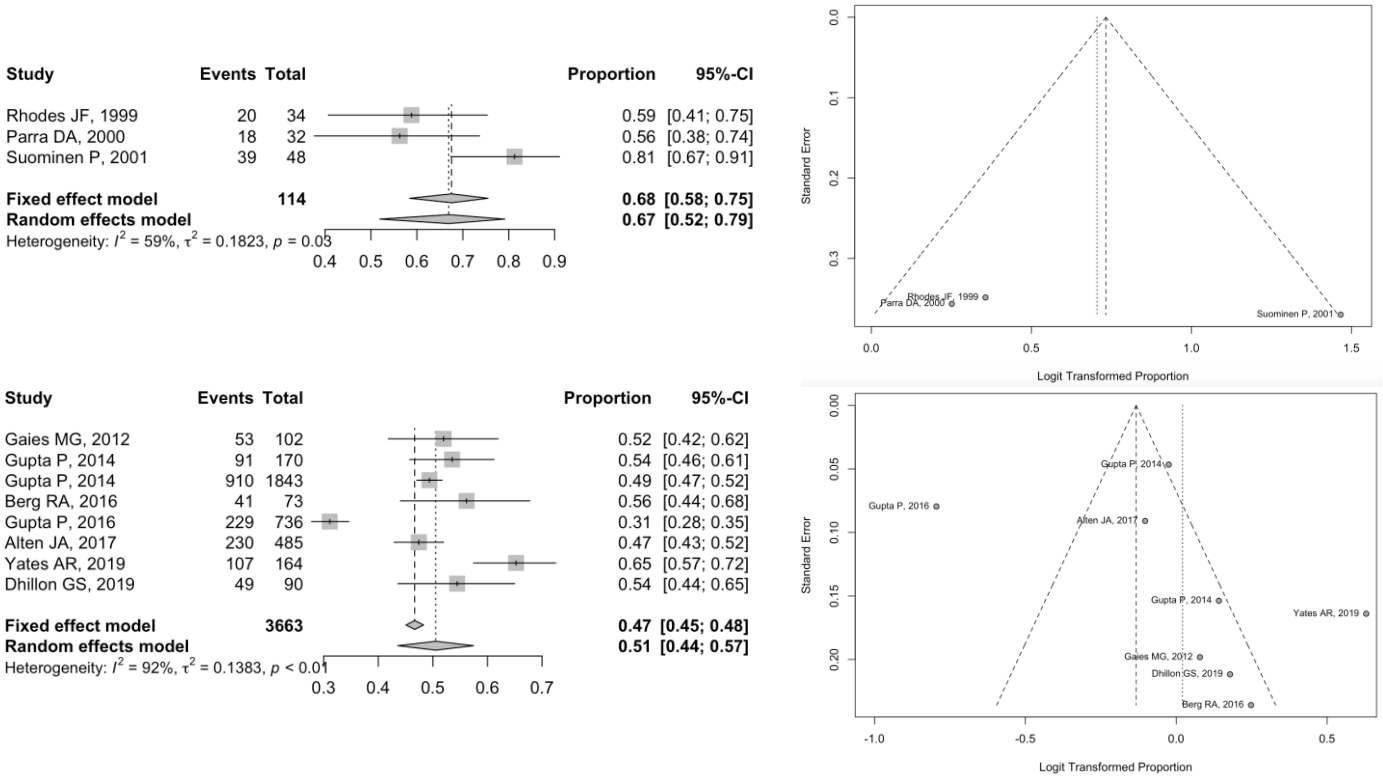
Figure 7. In-hospital pooled mortality rate by random effects meta-analysis



The pooled overall mortality rate was 54% (CI95%: 47-62%) (**Figure 7**). To control the publication bias and to decrease the heterogeneity of this analysis, data were spilt in older and newer studies as before, with the cut-off year equal to 2010. The sensitivity analysis was able to reduce the heterogeneity, controlling at least

partially the publication bias (**Figure 8**). In particular, for the old studies we computed a pooled mortality rate of 67% (CI95%: 52-79%), for the most recent studies a pooled mortality rate of 51% (CI95%: 44-57%).

Figure 8. In-hospital pooled mortality rate by random effects meta-analysis according to publication period (≤2010, upper, and >2010, lower)



Risk factors for CA and for mortality after CA

A detailed summary of the risk factors identified by the included studies by logistic regression - or associations with the outcome by univariate analysis in absence of any logistic regression- is reported in **Table 1**. Main risk factors for CA were neonatal age, univentricular physiology, acute heart failure, arrhythmias, and higher surgical complexity. The presence of an arterial line and an expert attending decreased the risk of CA. Main risk factors for in-hospital mortality were univentricular physiology, renal failure, cerebral damage, higher vasoactive-inotropic-score, longer CPR, CA during the weekend, and limited nurse experience, while admission to a CICU decreased the risk of mortality.

Conclusion

A non-negligible proportion (5%) of critically ill patients with cardiac disease experienced CA, with a trend of improvement over time. About one quarter of patients are supported with ECPR. Overall, 35% of patients do not achieve ROSC, and 54% do not survive to hospital discharge. Similarly to the incidence of CA, there is a trend of improved survival over time. Modifiable associated factors as team expertise, type of monitoring and time of CA must be taken into consideration in our everyday practice.

Table 1: Details of the studies selected for inclusion.

Author, year	Study design, Setting and Study period	Patients	Sample size No.	Age	Exclusion criteria	Definition of CA	Patients with CA No. (%)	E-CPR No. (%)	Outcome measures		Predictors / Risk factors		
									Short term mortality No. (%)	Late mortality No. (%)	CA	CA-related Mortality	Model inclusion criteria
Perry T, 2020 (Conference abstract)* (103)	Retrospective, Multicenter, GWTG-R Registry, 2014-2018	PICU or P-CICU patients (medical and surgical) who underwent CPR	866	<18 years	NA	NA	866 (100)		No ROSC 121 (14) At discharge 364 (42.0)	NA	NA	NA	NA
Yates AR, 2019 (29)	Prospective, Multicenter (PICqCPR study, USA centers, CPCCRN network), 2013-2016	PICU or P-CICU patients (medical and surgical) with invasive arterial blood pressure monitoring line prior and during CPR	164	Range 0-19 yes	Patients for which first compression was not captured on the waveform data, or compression start and stop could not be determined	CPR for at least 1 min	164 (100)	33 (20)	No ROSC 90 (35.0) At discharge 107 (65.0)	NA	NA	Univariate analysis: Diastolic BP ≥25 mmHg for infants or ≥30 mmHg for children (cohort surgical patients only, p=0.018)	NA
Dagan M, 2019 (6)	Retrospective, Single-center (Melbourne, Australia), 2007-2016	P-CICU patients post cardiac surgery	4983 admission (3781 patients)	Median 6 months (IQR 1-50 months)	Children with medical cardiac conditions, children who suffered CA following procedures as cardiac catheterization, CA prior to cardiac surgery, DNR	Cessation of cardiac mechanical activity requiring cardiac massage for ≥1 min	211 (4.3)	NA	At discharge 64 (30.1)	NA	NA	Univariate analysis: Younger age (p<0.001), lower weight (p<0.001), prematurity (p<0.001), chromosomal/genetic syndrome (p<0.001), higher RACHS-1 category (p<0.001)	NA
Dhillon GS, 2018 (30)	Retrospective, Single-center (Texas, USA), 2011-2016	P-CICU patients who experienced at least 1 CA	90	NA	Multiple events in the same patient, events with incomplete documentation, CA outside the CICU	CPR ≥ 2 min	90 (100)	23 (25.5)	At discharge 49 (54.4)	NA	NA	Univariate analysis: No epinephrine infusion pre-CA (p=0.02 for CHD medical patients, p=0.03 for surgical patients), no arterial line pre-CA (p=0.02 for surgical patients), longer CA duration (p=0.02 for surgical patients), higher number of epinephrine doses (p<0.01 for surgical patients)	NA
Alten JA, 2017 (5)	Retrospective analysis of prospective data, PC4 Registry, Multicenter (23 USA Centers), 2014-2016	P-CICU patients (medical and surgical)	15908	Range 0-18 yrs	None	Cardiopulmonary arrest requiring chest compressions and/or defibrillation for pulseless VT or acute respiratory compromise requiring emergency assisted ventilation leading to cardiopulmonary arrest requiring chest compressions and/or defibrillation	485 (3.3)	132/485 (27.2)	No ROSC 172/485 (40 death) (35.5) At 24h 89/215 (41.1) At discharge 230 (46.7)	NA	Multivariable predictive model: For SURGICAL patients: premature neonate OR 5.04 (2.98-8.54), term neonate OR 3.77 (2.54-5.60), infant OR 2.48 (1.69-3.63), underweight OR 1.56 (1.17 - 2.08), any chromosomal abnormality/ syndrome OR 1.36 (1.04-1.78), any STS preop risk factor OR 2.14 (1.68-2.74), STS-EACTSCHS mort cat 4 or5 OR 3.92 (2.94-5.22). For MEDICAL patients: premature neonate OR 3.15 (1.54-5.37), medical condition OR 2.20 (1.56-3.34), acute H OR 2.23 (1.47-3.19), lactate>3 mmol/L within 2 hrs of CICU admission OR 3.00 (1.86-4.86), MV 1hr post CICU admission OR 2.61 (1.70-3.82)	NA	Variables with p<0.1 at univariate model
Berg RA, 2016 (16)	Prospective, CPCCRN Registry, Multicenter (6 USA Centers), 2011-2013	Cardiac patients cohort of PICU patients with at least 1 episode of CA	73	Range 0-18 yrs	Patients with vital signs incompatible with life for at least the first 2 hours after PICU admission (i.e., moribund patients)	CPR event: chest compressions for >1 min and /or defibrillation. The reasons for initiation of chest compressions were categorized as a pulseless CA or poor perfusion with	73 (100)	NA	No-ROSC 16 (21.9) At discharge 41 (56.2)	NA	NA	NA	NA

						bradycardia and/ or hypotension							
Gupta P, 2016 Resuscitation (14)	Retrospective analysis of prospective data, VPS (NACHRI) Registry, Multicenter (62 USA Centers) 2009-2014	P-CICU patients with CHD post cardiac surgery	26909	Mean 37.6 months (SD 55.7)	ICU readmission, surgical lack documentation, surgical closure of isolated PDA or surgery not listed in STS-EACTS	Any event characterized by either pulselessness or critically compromised perfusion treated with external chest compression and/or defibrillation	736 (2.7)	NA	At discharge 229 (31.1)	NA	Multivariable predictive model: RISK: Younger age OR 0.73 (CI 0.56-0.96), Female OR 1.18 (CI 1.01-1.38), Development disorder OR 1.71 (CI 1.16-2.51), High complexity operations OR 1.81 (CI 1.51-2.16), MV before surgery OR 2.79 (CI 2.33-3.35), Higher PIM-2 score OR 1.28 (CI 1.20-1.36), SV anatomy OR 1.3 (CI 1.08-1.57), PH OR 1.8 (CI 1.4-2.3), Acute lung injury OR 1.50 (CI 1.27-1.77), RI OR 2.92 (CI 2.29-3.71), Chylothorax OR 1.65 (CI 1.11-2.47), Arrhythmia OR 2.69 (CI 2.29-3.16), Seizures OR 3.60 (CI 2.82,-4.59), Brain hemorrhage OR 2.13 (CI 1.27-3.57), MV after surg OR 1.52 (CI 1.07-2.16), Hemodialysis cath. OR 1.98 (CI 1.13-3.46). PROTECTIVE: Younger Age (>28d,<1years) OR 0.73 (CI 0.56-0.96), Higher weight OR 0.73 (CI 0.88-0.00), Arterial line OR 0.58 (CI 0.35-0.96), Attending intensivist PR 0.35 (CI 0.26-0.47)	Multivariable predictive model: RISK: ECMO OR 3.04 (CI 2.02, 4.57), SV anatomy OR 1.60 (CI 1.04, 2.46), RI OR 2.78 (CI 1.70, 4.54), Brain hemorrhage OR 3.09 (CI 1.10, 8.62), Hemodialysis catheter OR 3.42 (CI 1.05, 11.15). PROTECTIVE: Younger age (<28days) OR 0.47 (CI 0.28, 0.81), Presence of Cardiac PICU OR 0.48 (CI 0.25, 0.92)	CA model Age, gender, weight, PIM-2, complexity of operation, genetic abnormality, development disorder, SV, MV pre-surgery, PH, sepsis, acute lung injury, RI, seizures, arrhythmia, vocal cord paralysis, diaphragm paralysis, chylothorax, brain hemorrhage, arterial line, MV, central venous catheter use of hemodialysis catheter, presence of residency or fellowship training, 24/7 coverage, dedicated cardiac ICU, aver-age annual cardiac surgery cases for each center Mortality model: All the above plus of ECMO and use of ventricular assist device
McMillan KN, 2016 (Conference abstract)* (104)	Retrospective, Single-Center	P-CICU patients post cardiac surgery	461	<21 years	NA	NA	28 patients (6), 34 events	5/34 (14.7)	No-ROSC 2/34 (6) At discharge 9/27 (33)	NA	NA	NA	NA
Butts RJ, 2014 (13)	Retrospective analysis of prospective randomized trial, Single center (Charleston, USA) 2007-2009	Neonates post cardiac surgery with CPB	76	Range 0-1 month	<36 weeks gestational age at time of surgery, previous treatment or contraindication to steroid therapy, preoperative use of mechanical circulatory support or active resuscitation at time of proposed randomization	CPR as CA requiring chest compression	3 (3.9)	0 (0.0)	No-ROSC 0 (0.0)	NA	NA	NA	NA
Kalfa D, 2014* (105)	Retrospective, Single-center (New York, USA), 2006-2012	P-CICU Neonates with CHD and weight<2.5 kg post cardiac surgery	146	Mean 18.2 (24.2)	Patients who underwent isolated PDA closure alone	Not defined	18 (12.3)	NA	At discharge 14 (77.8)	NA	NA	NA	NA
Gupta P, 2014 Ann Thorac Surg (12)	Retrospective analysis of prospective data, STS-CHSD Registry, Multicenter (97 USA Centers), 2007-2012	P-CICU patients with CHD post cardiac surgery	70270	Median 156 days (IQR 21-1359)	Surgery not classified into one of the STS-EACTS Mortality Categories, missing outcome data	Cessation of effective cardiac mechanical function	1843 (2.6)	NA	At discharge 910 (49.4)	NA	Univariate model: Female sex (p=0.003), lower age (p<0.0001), lower weight(p<0.0001), prematurity (p<0.0001), congenital disorders (p<0.0001), preop. LOS (p<0.0001), preop. MV (p<0.0001), preop. sepsis (p<0.0001), preop. shock (p<0.0001), preop. RI (p<0.0001), preop. CPR (p<0.0001), CPB time(p<0.0001), previous cardiothoracic surgery (p<0.0001), STS-EACTS Mortality high risk(p<0.0001), STS Morbidity high risk (p<0.0001). Multivariable causal model: NS	Multivariable causal model: Low volume centers (<150 case/y) OR 2.0 (1.52-2.63), low-medium volume centers (150-250 case/y) OR 1.39 (1.09-1.77), STS-EACTS Mortality Risk Cat 1-3 in low and in medium volume centers (OR 2.29 (1.19-4.41) and 1.88 (1.12-3.18)); STS-EACTS Mortality Risk Cat 4-5 in low and medium-low volume centers (OR 2.0 (1.37-2.9) and 1.41 (1.03-1.94)).	CA model: Age, weight, any chromosomal, genetic, or non-cardiac abnormality, any preoperative risk factor, any previous cardiothoracic surgeries, year of surgery, case complexity (STS Morbidity Category) Mortality model: All the above but STS morbidity category, plus STS-EACTS Mortality Risk Category

Gupta P, 2014 PCCM (106)	Retrospective, Multicenter (3 USA Centers) 2002-2010	Cardiac patients cohort of PICU patients with at least 1 episode of CA	170	NA	Out-of-hospital, out-of-PICU, CPR ongoing at admission, patients receiving only drugs and/or MV without chest compressions and/or defibrillation	Monitored cardiopulmonary arrest treated with chest compressions for >1 min	170	NA	No-ROSC 35 (20.6) At 24h 48 (28.2) At discharge 91 (53.5)	NA	NA	NA	NA
Ahmadi A, 2013* (107)	Single-center (Tehran, Iran), 2001-2002	P-CICU patients <7 years of age, post cardiac surgery	529	<7 years of age	Not defined	Not defined	59 (11)	NA	At discharge 37 (62.7)	NA	NA	Univariate analysis: Lower mean arterial BP before the CA (p=0.04)	
Watkins SC, 2013* (108)	Retrospective, STS Registry, Single center (Nashville, USA) 2006-2011	P-CICU patients with CHD and RACHS1 undergoing surgical non cardiac procedures	71	Range 0-18 yrs	Not defined	Requirement for chest compressions, electrical defibrillation or cardioversion, or initiation of pharmacotherapy	3 (4.2)	2 (66.7)	No-ROSC 2 (0 death) (66.6) At 24h 0 (0.0)	NA	NA	NA	NA
Argawal HA, 2012 (109)	Prospective, Single center (Nashville, USA), 2007-2010	P-CICU patients post cardiac surgery	1078	Range 0-18 yrs	Patients managed in NICU, adult ICU and pediatric cardiology floor	Not defined	48 (4.4)	NA	NA	NA	NA	NA	NA
Gaies MG, 2012 (11)	Retrospective, Single center (Ann Arbor, USA) 2006-2008	P-CICU patients with at least 1 episode of CA	102 (of 2230 P-CICU admission)	Median 79 days (IQR 12-420)	Not defined	Event requiring active chest compressions for any duration	102 (4.6)	10 (9.8)	No-ROSC 27 (16.5) (17death) At discharge 53 (52.0)	NA	NA	Mutlivariate predictive model: Arrest during weekend OR 4.4 (1.2-15.5), experience of primary nurse <1yr OR 9.4 (1.6-55.0), VIS>=20 OR 6.4 (1.8-22.9)	Risk Adjustment Congenital Heart Surgery 1 categories 1–3, high vasocative support, experience of primary nurse <1yr, arrest during weekend
Hansen G, 2011 (110)	Case-control, Single center (Edmonton, Canada) 1996-2005	NICU patients post cardiac surgery with CPB, ≤6 weeks of age. Cases: with at least 1CPR event, Controls: without CPR events	87 (of 343 patients post cardiac surgery)	NA	Cardiac surgery not requiring CPB, patients having CPR preoperatively or in the operating room	Not defined	CPR 29 (8.4)	9 (31.0)	No-ROSC 8 (27.6)	At 1 month 11 (37.9) At 2 years 17 (58.6)	Univariate analysis: Lower birth weight (−0.57; 95% CI, −0.84, −0.31 kg) and gestational age (−1.5; 95% CI, −2.64, −0.40 weeks), longer preoperative ventilator days (4.1; 95% CI, 1.0, 7.2), and worse postoperative day 1 peak lactate (4.1; 95% CI, 2.3, 5.9 mmol/L), base deficit (−2.9; 95% CI,−5.4,−0.3), pH (−0.04; 95% CI,−0.08,−0.01), and inotrope score (11.6; 95% CI, 3.3, 22.4)	Multivariable predictive model on all cohort, not CA only: Minutes of chest compression OR 1.04 (CI 1.01, 1.06)	Not defined
Ades AM, 2010* (111)	Retrospective, Single center (Philadelphia, USA), 2000-2004	Patients with CHD and low birth weight (<2.5kg) post cardiac surgery	105	Median 5 days, Range 0-125	Patients who underwent isolated PDA closure alone	Not defined	23 (21.9)	Not ECPR Center	No-ROSC 7 (30.4) At discharge 17 (73.9)	NA	NA	NA	NA
Gaies MG, 2010* (10)	Retrospective, Single center (Ann Arbor, USA), 2007-2008 Overlap Data	P-CICU patients post cardiac surgery with CPB	173	Range 0-6 months	Not defined	Not defined	15 (8.7)	NA	NA	NA	NA	NA	NA
Dorfman AT, 2008 (9)	Retrospective, Single center (Philadelphia, USA)	P-CICU and NICU neonates with cardiac disease	190	Median 1 day (range 0-27)	Neonates with recovery from anesthesia or sedation from a non-cardiac procedure; <37 weeks' gestation admitted to NICU with an isolated PDA or PFO, asymptomatic ASD	Not defined	CPR 18 (9.5)	NA	NA	NA	NA	NA	NA

					or VSD transferred to the NICU for a specific non-CV pediatric subspecialty evaluation								
Gillespie M, 2006 (112)	Retrospective, Single center (Philadelphia, USA), 2000	P-CICU patients with CHD and <6months post cardiac surgery	221	Range 0-6 months	Not defined	Not defined	19 (8.6)	NA	NA	NA	NA	NA	NA
Brown KL, 2003 (8)	Retrospective, Single center (London, UK), 1999-2000	P-CICU patients post cardiac surgery with CPB	342	Range 0-18 yrs	Incomplete data, unclassifiable operation, multiple admissions	Not defined	CPR 34 (9.9)	NA	NA	NA	NA	NA	NA
Suominen P, 2001 (7)	Case control Single center (Helsinki, Finland), 1990-1994	P-CICU patients with CHD post cardiac surgery. Cases: with at least 1 episodes of CA, Controls1: with DHCA without CA, Controls2: without DHCA without CA	82 CA (48 CPR) (of 1115 post cardiac surgery patients)	Range 0-18 yrs	Patients who only received resuscitation drugs or MV, or who had received CPR in the operating theater	Absence of consciousness, apnea, and lack of palpable pulses in major arteries	82 (7.3) CPR 48	Not ECPR Center	No-ROSC: 21 (43.7) At discharge: 39 (81.2)	At 1-year 39 (81.2)	Univariate analysis: Younger age (p=0.04), SV (p<0.01) Preop. MV (p=0-03) PGE1 (p<0.001) Preop. inotropic support (p=0.04) Longer mean aortic-cross-clamp time (p<0.0001) Longer CPB time (p=0,0002) Longer DHCA time (P =0,0002) More inotropic support during surgery (p<0.0001) and postop. (p=0.002)	NA	NA
Parra DA, 2000 (4)	Retrospective, Single center (Miami, USA), 1995-1997	P-CICU patients with at least 1 episode of CA	32	Median 1 month (range: 1 day-21 years)	DNR patients	Cessation of circulation and respiration that required CPR for>2 mins	32	4 (12.5)	At discharge: 18 (56.2)	At 6 months: 21 (65.6)	NA	Univariate analysis: NS	NA
Rhodes JF, 1999 (3)	Retrospective, Single center (New York, USA), 1994-1998	P-CICU patients with CHD and age <12months post-cardiac surgery	575	Range 0-12 months	Not defined	Chest compressions or the absence of a palpable spontaneous pulse that was not resolved with only airway intervention	34 (5.9)	Not ECPR Center	No-ROSC 11 (32.2) At discharge: 20 (58.8)	At 6 months 20 (58.8) At follow-up (median 21 months) 21 (61.8)	NA	Univariate analysis: Lower pre-arrest MAP (p=0.0003), Lower arterial pH (p<0.02), Higher epinephrine doses (p<0.001), Higher bicarbonate dose (p=0.005), Longer CPR duration p<0.001)	NA

*Excluded from the meta-analysis.
CA: Cardiac Arrest; CHD: Congenital Heart Disease; CMP: Cardiomyopathy; CPB: Cardiopulmonary Bypass; CPR: Cardiopulmonary Resuscitation; CV: cardiovascular; DHCA: Deep Hypothermic Circulatory Arrest; DNR: Do Not Resuscitate; E-CPR: ECMO- Cardiopulmonary Resuscitation; ED: Emergency Department; H: Hospital; HF: Heart Failure; HFOV: High frequency oscillatory ventilation; MAP: Mean Arterial Pressure; MV: Mechanical Ventilation; NICU: Neonatal Intensive Care Unit; OR: Odd Ratio; PH: Pulmonary Hypertension; PICU: Pediatric Intensive Care Unit; Preop.: Preoperative; Postop.: postoperative; RI: Renal Insufficiency; ROSC: Return of Spontaneous Circulation; Surg: surgery; SV: Single ventricle.

Supplemental Table 1. Quality assessment of studies addressing the incidence of cardiac arrest and its outcomes in cardiac critically ill patients.

Author	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Reviewer 1 (M.D.)	Reviewer 2 (A.A.)	Agreement
Yates A	**2019**	Y	Y	Y	Y	N/A	Y	Y	N/A	Y	N/A	Y	N/A	Y	N	Good	Good	Good
Dagan M	**2019**	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Good	Good	Good
Dhillon GS	**2018**	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Good	Good	Good
Alten JA	**2017**	Y	Y	Y	Y	N/A	Y	Y	N/A	Y	Y	Y	N/A	N	Y	Good	Good	Good
Berg RA	**2016**	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Good	Good	Good
Gupta P	**2016**	Y	Y	Y	Y	N/A	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Good	Good	Good
Butts RJ	**2014**	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Good	Good	Good
Gupta P *(Ann T S)*	**2014**	Y	Y	Y	Y	N/A	Y	Y	Y	Y	N/A	Y	N/A	Y	Y	Good	Good	Good
Gupta P *(PCCM)*	**2014**	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Good	Good	Good
Ahmadi	**2013**	Y	Y	Y	Y	N/A	Y	Y	Y	N	N/A	Y	N/A	Y	N	Poor	Poor	Poor
Argawal HA	**2012**	Y	Y	Y	Y	N/A	Y	Y	N/A	N/A	N/A	Y	N/A	N/A	N	Fair	Fair	Fair
Hansen G	**2011**	Y	Y	Y	Y	N/A	Y	Y	N/A	Y	N/A	Y	N/A	Y	Y	Good	Good	Good
Gaies MG	**2012**	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Good	Good	Good
Dorfman AT	**2008**	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y	N/A	Y	N	Fair	Fair	Fair
Gillespie M	**2006**	Y	Y	Y	Y	N/A	Y	Y	Y	Y	N/A	Y	N/A	N/A	Y	Fair	Good	Fair
Brown KL	**2003**	Y	Y	Y	Y	N/A	Y	Y	Y	Y	N/A	Y	N/A	N/A	Y	Fair	Good	Fair
Suominen P	**2001**	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y	N/A	Y	N	Fair	Fair	Fair
Parra DA	**2000**	Y	Y	Y	Y	N/A	Y	Y	Y	Y	N/A	Y	N/A	Y	N	Good	Fair	Fair
Rhodes J	**1999**	Y	Y	Y	Y	N/A	Y	Y	Y	Y	N/A	Y	N/A	Y	N	Fair	Fair	Fair

Supplemental Methods

Detailed search strategy for Pubmed

(Resuscitation[mesh:noexp] OR "Cardiopulmonary Resuscitation"[mesh:noexp] OR "Heart Massage"[mesh] OR "Electric Countershock"[mesh] OR resuscitate[tw] OR resuscitation[tw] OR resuscitator[tw] OR resuscitators[tw] OR resuscitative[tw] OR "Cardiopulmonary Resuscitation"[tw] OR CPR[tw] OR "heart massage"[tw] OR "heart massages"[tw] OR "cardio pulmonary resuscitation"[tw] OR "cardio-pulmonary resuscitation"[tw] OR "Code blue"[tw] OR resuscitations[tw] OR resuscitated[tw] OR defibrillate[tw] OR defibrillated[tw] OR defibrillation[tw] OR defibrillations[tw] OR defibrillator[tw] OR defibrillators[tw] OR "chest compression"[tw] OR "chest compressions"[tw] OR "heart compression"[tw] OR "heart compressions"[tw] OR "cardiac compression"[tw] OR "cardiac compressions"[tw]) AND ("Heart Arrest"[mesh:noexp] OR "Heart Arrest"[tw] OR "Cardiac Arrest"[tw] OR "Heart arrests"[tw] OR "cardiac arrests"[tw] OR "Cardiopulmonary Arrest"[tw] OR "cardiorespiratory arrest"[tw] OR "cardiac event"[tw] OR "cardiac events"[tw] OR "poor perfusion"[tw] OR "poor perfusions"[tw] OR "cardiopulmonary arrests"[tw] OR "cardiorespiratory arrests"[tw] OR "cardiopulmonary event"[tw] OR "cardiopulmonary events"[tw] OR "cardiorespiratory event"[tw] OR "cardiorespiratory events"[tw] OR "compromised perfusion"[tw] OR "compromised perfusions"[tw] OR pulseless[tw] OR pulselessness[tw] OR CA[tw] OR CAs[tw] OR CPA[tw] OR CPAs[tw]) AND ("Intensive Care Units"[mesh] OR "Critical Care"[mesh:noexp] OR "Intensive Care Units, Pediatric"[mesh] OR "Intensive Care, Neonatal"[mesh] OR "intensive care"[tw] OR "critical care"[tw] OR "intensive therapy"[tw] OR "intensive treatment"[tw] OR ICU[tw] OR NICU[tw] OR PICU[tw] OR CICU[tw] OR ICUs[tw] OR NICUs[tw] OR PICUs[tw] OR CICUs[tw]) AND ("Heart Diseases"[mesh:noexp] OR "Heart Defects, Congenital"[mesh] OR "Cardiovascular Diseases"[mesh] OR "Vascular Diseases"[mesh:noexp] OR "Heart Defect"[tw] OR "Heart Defects"[tw] OR "Heart Abnormalities"[tw] OR "Heart Abnormality"[tw] OR "congenital heart malformation"[tw] OR "congenital heart malformations"[tw] OR "malformation of the heart"[tw] OR "malformations of the heart"[tw] OR "heart disease"[tw] OR "heart diseases"[tw] OR "cardiac disease"[tw] OR "cardiac diseases"[tw] OR "cardiac abnormality"[tw] OR "cardiac abnormalities"[tw] OR "cardiac malformation"[tw] OR "cardiac malformations"[tw] OR "cardiac pathology"[tw] OR "cardiac pathologies"[tw] OR "heart pathology"[tw] OR "heart pathologies"[tw] OR "heart malformation"[tw] OR "heart malformations"[tw] OR "cardiac conditions"[tw] OR "cardiac condition"[tw] OR "heart condition"[tw] OR "heart conditions"[tw] OR "heart anomaly"[tw] OR "heart anomalies"[tw] OR "cardiac anomaly"[tw] OR "cardiac anomalies"[tw] OR cardiopathy[tw] OR cardopathies[tw] OR "heart deficiency"[tw] OR "heart deficiencies"[tw] OR "heart deformity"[tw] OR "heart deformities"[tw] OR "cardiac deformity"[tw] OR "cardiac deformities"[tw] OR "cardiac disorder"[tw] OR "cardiac disorders"[tw] OR "heart disorder"[tw] OR "heart disorders"[tw] OR "heart dysfunction"[tw] OR "heart dysfunctions"[tw] OR "cardiac dysfunction"[tw] OR "cardiac dysfunctions"[tw] OR angiocardiopathy[tw] OR angiocardiopathies[tw] OR "angiocardiovascular disease"[tw] OR "angiocardiovascular diseases"[tw] OR "Cardiovascular complication"[tw] OR "cardiovascular complications"[tw] OR "heart complication"[tw] OR "heart complications"[tw] OR "cardiovascular disorder"[tw] OR "Cardiovascular disorders"[tw] OR "cardiovascular disturbance"[tw] OR "cardiovascular disturbances"[tw] OR "heart disturbance"[tw] OR "heart disturbances"[tw] OR "Cardiovascular anomaly"[tw] OR "cardiovascular anomalies"[tw] OR "cardiovascular deformity"[tw] OR "cardiovascular deformities"[tw] OR "angiocardiovascular deformity"[tw] OR "angiocardiovascular deformities"[tw] OR "angiocardiovascular anomaly"[tw] OR "angiocardiovascular anomalies"[tw] OR "angiocardiovascular abnormality"[tw] OR "angiocardiovascular abnormalities"[tw] OR "Cardiovascular abnormality"[tw] OR "cardiovascular abnormalities"[tw] OR "cardiovascular dysfunction"[tw] OR "cardiovascular dysfunctions"[tw] OR "angiocardiovascular dysfunction"[tw] OR "angiocardiovascular dysfunctions"[tw] OR "cardiac complication"[tw] OR "cardiac complications"[tw] OR "cardiopulmonary compromise"[tw] OR "cardiorespiratory compromise"[tw] OR "cardiovascular compromise"[tw] OR "cardiac compromise"[tw]) AND (Pediatrics[mesh] OR Child[mesh] OR Infant[mesh] OR Adolescent[mesh] OR Pediatric[tw] OR Pediatrics[tw] OR Paediatric[tw] OR Paediatrics[tw] OR child[tw] OR children[tw] OR infant[tw] OR infants[tw] OR infantile[tw] OR neonate[tw] OR neonates[tw] OR neonatal[tw] OR newborn[tw] OR newborns[tw] OR adolescent[tw] OR adolescents[tw] OR adolescence[tw] OR adolescent[tw] OR youth[tw] OR youths[tw] OR teen[tw] OR teens[tw] OR teenager[tw] OR teenagers[tw] OR baby[tw] OR babies[tw])

Project 2

Predict

Shock index, coronary perfusion pressure and rate pressure product as predictors of adverse outcome after pediatric cardiac surgery

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Oral presentation and **Best Scientific Contribution Award**, AMIETIP 2020, Italy

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Abstract

Objective: To determine whether shock index (SI), coronary perfusion pressure (CPP), or rate pressure product (RPP) in the first 24-hours after congenital heart surgery are independent predictors of subsequent clinically significant adverse outcomes.

Design: Retrospective cohort study.

Setting: Tertiary-care center.

Patients: All patients <18 years who underwent cardiac surgery at BCH between Jan 1, 2010 and Dec 31, 2018.

Interventions: None.

Measurements and Main Results: SI (heart rate [HR]/systolic blood pressure [SBP]), CPP (diastolic blood pressure-right atrial pressure), and RPP (HR*SBP) were calculated every 5 seconds and the median value for the first 24 hours of CICU admission for each was used as a predictor. The composite, primary outcome was the occurrence of any of the following adverse events in the first 7 days following CICU admission: cardiopulmonary resuscitation (CPR), extracorporeal CPR, mechanical circulatory support, unplanned surgery, heart transplant, or death. The association of each variable of interest with this outcome was tested in a multivariable logistic regression model. Of the 4,161 patients included, 296 (7%) met the outcome within the specified timeframe. In a multivariable regression model adjusted for age, surgical complexity, inotropic and respiratory support, and organ dysfunction, SI > 1.83 was significantly associated with the primary outcome (OR 6.6 [95% CI 4.4-10.0]), and CPP >35 mmHg was protective against the outcome (OR 0.5 [0.4-0.7]). RPP was not found to be associated with the outcome. However, the predictive ability of the SI and CPP models were not superior to their component hemodynamic variables alone.

Conclusions: Both SI and CPP may offer predictive value for adverse outcomes following cardiac surgery in children, although they are not superior to the primary hemodynamic variables.

Background and Significance

The postoperative period remains a vulnerable phase of care in children following congenital heart surgery, during which hemodynamic instability and unplanned reinterventions may occur (22). The incidence of cardiac arrest (CA) events following cardiac surgery based on large multicenter reviews ranges from 2.6% overall (12) to 12.7% in univentricular patients following stage 1 operation (15). Unplanned cardiac reinterventions occur in approximately 5% of patients after surgery and are independently associated with higher mortality and morbidity (113). The occurrence of CA following congenital heart surgery may result from low cardiac output from coronary insufficiency, myocardial edema, residual lesions, pulmonary overcirculation, restrictive ventricular physiology or others. Identifying patients in whom the physiologic state has a higher likelihood of a CA or need for other management strategy would allow for earlier intervention, including consideration of reoperation or cardiac catheterization. Predicting such events may be useful in provision of critical care.

Mathematically combining isolated hemodynamic variables, such as blood pressure or heart rate, into indices may capture information regarding a patient's status more powerfully than the same variables in isolation. For example, a shock index (SI) >0.9 is associated with mortality and the need for massive transfusion in adult trauma patients (114). During cardiopulmonary resuscitation (CPR), maintaining a coronary perfusion pressure (CPP) of at least 15 mmHg has been associated with a higher likelihood of return of spontaneous circulation (ROSC) (115). Similarly, the change in the rate pressure product (RPP), is associated with mortality in acute exacerbations of heart failure in adult patients (116). However, little data exist regarding the predictive ability of such variables following congenital cardiac surgery. The purpose of this study was to determine whether SI, CPP or RPP can independently predict a clinically significant outcome when measured in the first 24 hours after congenital heart surgery.

Methods

Study design, setting and population

The following study was approved by the Institutional Review Board at Boston Children's Hospital (IRB P-00030743) under exemption from informed consent. We performed a retrospective cohort study of all pediatric patients (<18 years) who underwent their first cardiac surgery at our institution between January 1, 2010 and December 31, 2018 and for whom continuous hemodynamic monitoring data were available for the first 24 hours postoperatively. We excluded patients undergoing non-cardiac thoracic procedures (i.e. airway, pulmonary, or non-cardiac mediastinal procedures), heart transplantation, pacemaker placement, continuous-flow ventricular assist device placement, and those unable to wean off CBP with subsequent ECMO cannulation following their first surgery (**Figure 1**).

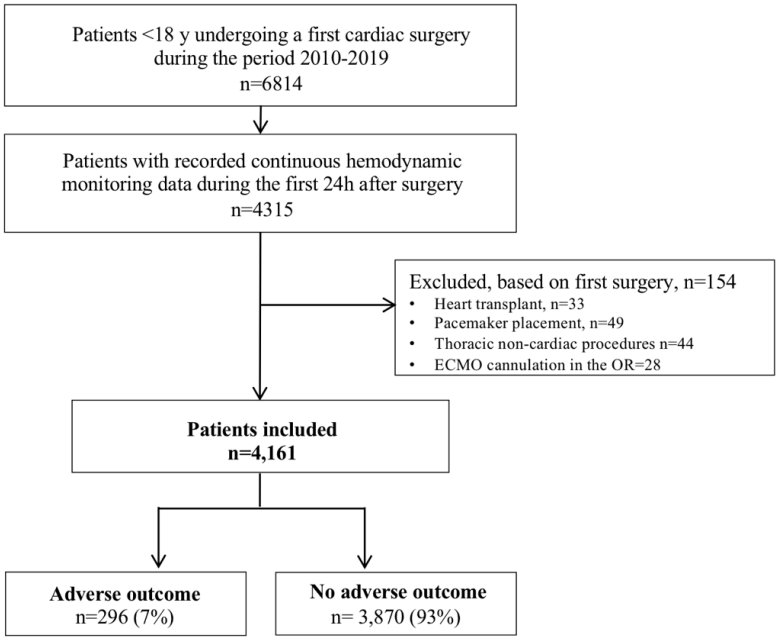
Data collection and categorization

Demographic, clinical, laboratory, and surgical details were automatically extracted from the electronic medical record (Cerner Corporation) and an internal surgical database. CPR events were collected from a separate internal database. Cardiac surgical procedures were categorized based on complexity, using the Risk Adjusted Congenital Heart Surgery-1 (RACHS-1) (117). Type and level of ventilatory support were summarized using a respiratory support score that incorporates all respiratory support types into a single continuous variable (118). Briefly, regions of the score are defined based on the device used to support the patient (i.e. room air = 0, nasal cannula or aerosol mask = 1-5, high flow nasal cannula or continuous positive

airway pressure = 6-15, bilevel positive airway pressure = 16-25, pressure support-only ventilation = 26-35, conventional mechanical ventilation = 36-70, high frequency oscillatory or jet ventilation = 71-80, and ECMO support = 81-100); the fine-tuning of the score within these ranges is based on the individual settings used therein (higher the pressures and FiO2, higher is the score). Renal dysfunction was assessed using the cut-off values included in the Pediatric Logistic Organ Dysfunction Score-2 (PELOD-2) (119).

Hemodynamic data (heart rate [HR], systolic blood pressure [SBP], diastolic blood pressure [DBP], right atrial pressure [RAP], central venous pressure [CVP]) were extracted at 5 second intervals (T3, Etiometry, Boston, Massachusetts). We extracted all available data elements for the first 24 hours following Cardiac Intensive Care Unit (CICU) admission. We calculated the variables of interest (SI, RPP and CPP) every 5 seconds using the following formulas: SI =HR/SBP, RPP= SBP*HR, CPP=DBP-RAP(or CVP). The median value of each over 24 hours was used subsequent statistical analysis.

Figure 1. Study flow-chart



Outcome measure

The primary outcome measure was the presence of a major adverse outcome within the first 7 days after CICU admission. We defined a major adverse outcome as the presence of any of the following events within 7 days of ICU admission: CPR, extracorporeal CPR, need for any mechanical circulatory support (extracorporeal membrane oxygenation [ECMO] or ventricular assist device [VAD]), heart transplant, death, or unplanned surgery (including mediastinal exploration). If more than one major adverse event occurred, the first event encountered was chosen for outcome categorization. Patients experiencing the outcome within 24 hours of CICU admission, hemodynamic data was truncated at the time of the outcome (e.g. vital signs following ECMO cannulation were not used in the predictive model).

Statistical analysis

Descriptive data were reported as frequencies and percentages for categorical variables, and as median and inter-quartile range (IQR) for continuous variables. Demographic, clinical, surgical and post-operative characteristics were compared between patients who experienced the outcome and patients who did not. The Pearson chi square test was used to compare categorical data. Distributions of continuous data were tested for

normality using the Kolmogorov Smirnov test. Since they did not meet the criterion of normality, the Mann-Whitney U test was used to compare continuous data between groups.

The association of each variable of interest (SI, RPP, CPP) with the outcome was first tested using an unadjusted logistic regression. A multivariable logistic regression model was then developed to test the association of each variable of interest (SI, RPP, CPP) with the outcome adjusting for additional factors. Candidate variables for inclusion in the model were selected from the univariate analysis comparing patients who experienced the outcome and patients who did not. All variables with a univariate *P* value <0.1 and the variable of interest for that model were selected for inclusion in the multivariable model. Variables with 10% or more of missing data were excluded. A backward conditional strategy was used for entry and retention of variables in the model. A candidate variable was retained in the model if the *P* value was <0.05. Variables containing continuous data that were retained in the multivariable model were tested for linear association; those not meeting the linearity assumption were categorized for inclusion in the model using quantiles. Age and weight were tested for correlation using the Spearman's Rho test according to their non-parametric distribution. Since a positive correlation was proven, weight was not chosen for inclusion in the model. RACHS-1 categories were combined into a three-category variable (RACHS 1 to 3, RACHS 4 to 6, not assigned). The Hosmer-Lemeshow test was used to test the goodness of fit of each model. A receiver operator characteristic (ROC) curve was finally used to assess the prediction ability of each model.

Additional models were constructed for the neonatal population given their peculiar clinical and physiological characteristics. In order to investigate the association between the predictors of interest (SI, CPP and RPP) and different categories of outcomes, two similar multivariable logistic regression model for each variable of interest were developed using the same methodology to separately test their relationships with either unplanned reoperations or major adverse cardiovascular events (CPR, ECPR, ECMO, VAD, heart transplant or death). To explore the potential superiority of the derived physiological variables (SI, CPP and RPP) over the primary hemodynamic variables (HR, SBP, DPB, RAP) in predicting the adverse outcome, a similar multivariable model was developed for each primary hemodynamic variable. The ROC curves of the models and their confidence intervals (Cis) were then compared. All statistical analyses were performed using the IBM SPSS statistical software (version 25.0, IBM Corp. Armonk, New York, U.S.A.). Statistical significance was set at a two-sided P value <0.05.

Results

Study population

Of the 6,418 patients who underwent a first cardiac surgery at Boston Children's Hospital between January, 2010 and December, 2018, 4,315 (67%) had continuous hemodynamic monitoring data available for analysis. After applying the inclusion and exclusion criteria, 4,161 patients were included in the analysis (**Figure 1**). Demographic information, laboratory values, and clinical characteristics of patients at baseline and during the first 24 hours of CICU admission are described in **Table 1**. The median age at the time of first surgery was 356 days (IQR 62-1958). Cardiac procedures were RACHS-1 categories 1-3 in 3,562 patients (86%), category 4-6 in 495 patients (12%), and unassigned 104 patients (2%). Nighty-one percent of patients (n=3,795) required invasive mechanical ventilation in the first 24 hours after surgery, and 52% (n=2,162) required inotropic support. Laboratory evaluation of end organ dysfunction are reported in **Table 1**. A total of 296 patients (7%) met the outcome within 7 days in a median time of 1.2 days (IQR 0.3-3.6). Patients meeting the outcome included 201 patients (5%) who required an unplanned surgery (**Table 2**), 52 patients (1%)

requiring CPR, 33 patients (1%) undergoing ECPR, 5 patients requiring ECMO for low cardiac output, 2 patients undergoing a VAD placement, 1 patient undergoing a heart transplant and 2 patients who died within 7 days after surgery.

Table 1. Demographic, clinical, surgical details and outcomes.

Variable	Total (n=4161)	Adverse outcome (n=296)	No adverse outcome (n=3870)	P value
Age (days), median (IQR)	356 (62-1958)	69 (5-602)	407 (70-2064)	<0.001
Weight (kg), median (IQR)	8 (4-18)	4.0 (3.0-9.6)	8.5 (4.2-18.5)	<0.001
Gender (male), n (%)	2291 (55)	167 (56)	2124 (55)	0.625
Main cardiac surgery procedure RACHS-1 score, n (%)				
1	483 (12)	7 (2)	476 (13)	
2	1350 (32)	44 (15)	1306 (34)	
3	1729 (42)	138 (47)	1591 (41)	
4	320 (8)	41 (14)	279 (7)	<0.001
5	2 (0)	0 (0)	2 (0)	
6	173 (4)	47 (16)	126 (3)	
Not assigned	104 (2)	19 (6)	85 (2)	
Patients' characteristics during first 24 hours of PICU admission				
Hemodynamic status				
Heart rate (beats/min), median (IQR)	120 (106-137)	139 (120-153)	120 (105-135)	<0.001
Systolic blood pressure (mmHg), median (IQR)	83 (74-94)	73 (63-83)	84 (75-95)	<0.001
Diastolic blood pressure (mmHg), median (IQR)	50 (45-55)	46 (41-53)	50 (46-55)	<0.001
Atrial pressure (mmHg), median (IQR) [a]	8 (6-10)	8 (6-10)	10 (8-12)	<0.001
Inotropic support, n (%)	2162 (52)	202 (68)	1960 (51)	<0.001
Dopamine (mcg/kg/min), median (IQR)**	1.6 (0.1-3.9)	1.6 (0.1-2.9)	1.6 (0.1-4.0)	0.320
Epinephrine (mcg/kg/min), median (IQR)**	0.01 (0.01-0.02)	0.01 (0.01-0.03)	0.01 (0.01-0.02)	0.029
Norepinephrine (mcg/kg/min), median (IQR)**	0.02 (0.01-0.05)	0.01 (0.01-0.04)	0.02 (0.01-0.06)	0.355
Milrinone (mcg/kg/min), median (IQR)**	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.496
Vasopressin (mU/kg/h), median (IQR)**	0.05 (0.03-0.30)	0.03 (0.03-0.03)	0.06 (0.03-0.33)	0.221
Respiratory and ventilation status				
Respiratory support score, maximum, median (IQR)[b] ***	56 (52-60)	59 (54-64)	56 (52-60)	<0.001
Arterial pCO2, highest (mmHg)[c]	52 (45-60)	60 (52-70)	51 (45-59)	<0.001
Blood values, median (IQR)				
Hematocrit (%), median[d]	43 (37-48)	38 (35-40)	37 (34-40)	<0.001
White blood count (x10^9/L), median[d]	10 (8-13)	11 (9-13)	10 (9-13)	0.434
Platelets (x10^9/L), median[d]	214 (161-279)	198 (134-278)	214 (162-279)	0.002
International normalized ratio, highest[e]	1.37 (1.17-1.81)	1.69 (1.31-2.40)	1.35 (1.16-1.75)	<0.001
Partial thromboplastin time (s), highest[e]	53 (36-108)	104 (50-163)	50 (36-98)	<0.001
Creatinine (mg/dl), highest[f]	0.4 (0.3-0.6)	0.6 (0.4-0.9)	0.4 (0.3-0.6)	<0.001
Blood urea nitrogen (mmol/L), highest[f]	18 (13-28)	39 (20-66)	17 (12-26)	<0.001
Alanine aminotransferase (IU/L), highest[g]	25 (15-64)	41 (20-152)	24 (14-56)	<0.001
Aspartate aminotransferase (IU/L), highest[g]	63 (38-138)	121 (64-310)	57 (38-118)	<0.001
Lactatemia, highest (mmol/L)[h]	1.9 (1.3-2.9)	2.9 (1.6-5.1)	1.8 (1.2-2.5)	0.008
Renal dysfunction, n (%)*[f]	1510 (36)	1343 (35)	167 (56)	<0.001
Derived physiological variables, during first 24hs of PICU admission, median (IQR)				
Shock index, median	1.44 (1.14-1.83)	1.94 (1.45-2.44)	1.41 (1.12-1.77)	<0.001
Rate pressure product, median	9,894 (8,924-11,011)	9,685 (8,773-10,994)	9,916 (8,928-11,016)	0.134
Coronary perfusion pressure, median[i]	42 (36-48)	37 (31-43)	42 (37-48)	<0.001
Outcome within 7 days of admission, n (%)	296 (7)	296 (100)		
Cardiopulmonary resuscitation	52 (1)	52 (17)		
Extracorporeal cardiopulmonary resuscitation	33 (1)	33 (11)		
ECMO, low cardiac output	5 (0)	5 (2)		
Unplanned surgery	201 (5)	201 (68)	-	-
Ventricular assistance device	2 (0)	2 (1)		
Heart transplant	1 (0)	1 (0)		
Death	2 (0)	2 (1)		

Missing data, n (outcome, no outcome): [a] 322 (4, 318); [b] 197 (54,143); [c] 1712 (15, 1697); [d] 118(3, 115); [e] 1883 (29, 1854); [f] 116 (4, 112); [g] 2356 (89, 141); [h] 4071 (279, 3792); [i] 19 (2,17). *Renal dysfunction is defined by PELOD-2 creatinine cut-offs for age; **The maximum dosage over 24 hours was used. ***RSS categories are: room air (0), nasal cannula or aerosol mask (1-5), high flow nasal cannula or CPAP (6-15), BiPAP (16-25), pressure support-only ventilation (26-35), conventional mechanical ventilation (36-70), high frequency oscillatory or jet ventilation (71-80), ECMO (81-100) ECMO: Extra-Corporeal Membrane Oxygenation; IQR: Inter-Quartile Range; RACHS-1: Risk Adjusted Congenital Heart Surgery Score 1.

Table 2. Frequency of unplanned reinterventions within 7 days in cardiac post-surgical patients.

Unplanned reintervention	n (%) (Total=201)
Cardiac surgical reintervention	70 (35)
Pacemaker insertion	20 (10)
Mediastinal exploration	60 (30)
Thoracotomy for postoperative bleeding or hemothorax	39 (19)
Pleural procedure/thoracostomy tube	11 (5)
Diaphragm plication	1 (<1)

Comparison of patients meeting and not meeting the outcome

A comparison of the two groups based on the outcome is outlined in **Table 1**. Patients meeting the outcome were younger, with a median age of 69 days compared to 407 (P<0.001). RACHS-1 score was significantly different between groups, with the outcome group undergoing more complex surgical operations compared with the other group (P<0.001). Patients meeting the outcome had a higher incidence of inotropic support than patients not meeting the outcome (68% vs 51%, P<0.001) and higher dosages of epinephrine infusion (P=0.029). They also displayed a higher respiratory support score compared with patients not meeting the outcome (median score 59 vs 56, P<0.001; this indicates higher conventional mechanical ventilation settings), and higher maximum arterial PaCO2 levels (median 60 mmHg vs 51 mmHg, p<0.001). Patients meeting the outcome showed also a significantly lower hematocrit, longer coagulation times, higher creatinine and urea nitrogen, and higher hepatocyte-toxicity markers (all P<0.001) and higher lactatemia (P=0.008).

With the exception of RPP, all vital signs and derived physiological variables significantly differed between the two groups. Patients meeting the outcome presenting with a higher SI (median 1.94 vs 1.41, P<0.001) and lower CPP (median 37 vs 42, $p < 0.001$). There was no statistically significant difference between the median RPP between the two groups.

Analyses of SI, CPP and RPP as predictors of adverse outcome

In the unadjusted analysis, a SI greater than 1.44 was associated with the outcome (>1.44 and ≤1.83, OR 2.17; >1.83 OR 6.65, **Table 3**). When adjusted for age, the complexity of surgery, inotropic support, respiratory support score, hematocrit level, thrombocytopenia and renal dysfunction, SI was retained in the model predictive of the adverse outcome when >1.83 (OR 4.22 [CI 2.73-6.52]). RACHS-1 higher categories, lower platelet count and presence of renal dysfunction were also associated with the adverse outcome. The ROC curve demonstrated good predictive ability of the model (AUC = 0.738, **Table 3** and **Figure 2**). When the same model was computed for the neonatal population, the same predictors were retained in the model, and a shock index >2.48 was identified as independently associated with the outcome (OR 4.07 [CI 2.29-7.22]) (**Supplemental Table 1).**

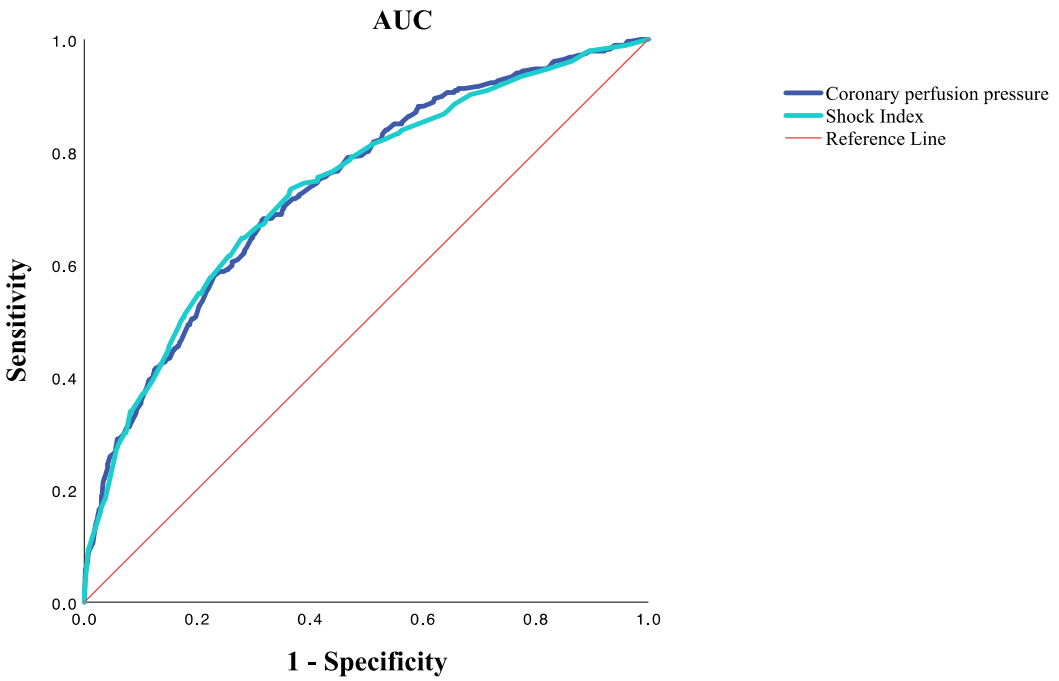
Table 3. Unadjusted and adjusted logistic regression for testing shock index as a predictor of adverse outcome.

Variables	Odds Ratio	95% Confidence Interval	p-value
Unadjusted logistic regression			
Shock index			<0.001
≤ 1.14	1	Reference group	-
> 1.14 and ≤ 1.44	1.572	0.978-2.527	0.062
> 1.44 and ≤ 1.83	2.168	1.378-3.410	0.001
> 1.83	6.653	4.436-9.977	<0.001

Adjusted logistic regression model			
Shock index			<0.001
≤ 1.14	1	Reference group	-
> 1.14 and ≤ 1.44	1.379	0.848-2.243	0.196
> 1.44 and ≤ 1.83	1.575	0.980-2.531	0.061
> 1.83	4.218	2.729-6.519	<0.001
RACHS-1 category			<0.001
RACHS 1 to 3	1	Reference group	-
RACHS 4 to 6	2.177	1.611-2.942	<0.001
RACHS not assigned	2.969	1.674-5.267	<0.001
Platelets (x10^9/L)			<0.001
≤ 161	1	Reference group	-
> 161 and ≤ 214	0.516	0.364-0.732	<0.001
> 214 and ≤ 279	0.466	0.331-0.657	<0.001
> 279	0.560	0.404-0.777	0.001
Renal dysfunction*	1.924	1.487-2.490	<0.001

Unadjusted logistic regression: N= 4161; Hosmer and Lemeshow Test *p* value= 1.000; AUC 0.692. **Adjusted** logistic regression model included the following variables: shock index, age (days), RACHS-1 category, inotropic support, respiratory support score, hematocrit (%), platelet (x10^9/L), renal dysfunction. N= 3747; Hosmer and Lemeshow Test P value = 0.944; AUC 0.738. *Renal dysfunction is defined by PELOD-2 Creatinine cut-offs for age. RACHS-1: Risk Adjusted Congenital Heart Surgery Score 1.

Figure 2. Receiver operating characteristics analysis of the adjusted logistic regression models for SI (AUC=0.738) and CPP (AUC=0.736).



The second model evaluated associations between CPP and the outcome (**Table 4**). When the analysis was not adjusted, CPP >35 mmHg was demonstrated to be a protective factor against the adverse outcome. When adjusted for the candidate variables, CPP>35 mmHg was retained in the model as a protective factor for the adverse outcome. Lower age (≤62 days), higher RACH-1 score, lower platelet count and presence of renal dysfunction all increased the risk of an adverse outcome (AUC of final model = 0.736). When the model was computed for only the neonatal population, a CPP>32 mmHg was identified as an independent protective factor for the adverse outcome **(Supplemental Table 2).**

Table 4. Unadjusted and adjusted logistic regression for testing Coronary Perfusion Pressure as a predictor of adverse outcome.

Variables	Odds Ratio	95% Confidence Interval	p-value
Unadjusted logistic regression			
Coronary perfusion pressure			<0.001
≤ 35	1	Reference group	
> 35 and ≤ 40	0.400	0.289-0.552	<0.001
> 40 and ≤ 44	0.304	0.210-0.440	<0.001
> 44 and ≤ 50	0.210	0.138-0.320	<0.001
> 50	0.280	0.189-0.415	<0.001
Adjusted logistic regression model			
Coronary perfusion pressure			<0.001
≤ 35	1	Reference group	-
> 35 and ≤ 40	0.514	0.368-0.718	<0.001
> 40 and ≤ 44	0.485	0.328-0.717	<0.001
> 44 and ≤ 50	0.398	0.254-0.622	<0.001
> 50	0.576	0.374-0.887	0.012
Age (days)			<0.001
≤ 62	1	Reference group	-
> 62 and ≤ 356	0.466	0.326-0.667	<0.001
> 356 and ≤ 1958	0.501	0.349-0.718	<0.001
> 1958	0.423	0.273-0.654	<0.001
RACHS-1 category			<0.001
RACHS 1 to 3	1	Reference group	-
RACHS 4 to 6	2.127	1.562-2.896	<0.001
RACHS not assigned	2.984	1.645-5.284	<0.001
Platelets ($x10^9$/L)			<0.001
≤ 161	1	Reference group	-
> 161 and ≤ 214	0.510	0.359-0.724	<0.001
> 214 and ≤ 279	0.466	0.328-0.662	<0.001
> 279	0.529	0.377-0.742	<0.001
Renal dysfunction*	2.056	1.560-2.710	<0.001

Unadjusted logistic regression: N= 4128; Hosmer and Lemeshow Test P value = 1.000; AUC 0.653. **Adjusted** logistic regression model: Candidate variables: Coronary perfusion pressure, Age (days), RACHS-1 category, Inotropic support, Respiratory Support Score, Hematocrit (%), Platelet ($x10^9$/L), Renal dysfunction. N= 4008; Hosmer and Lemeshow Test P value= 0.769; AUC= 0.736 *Renal dysfunction is defined by PELOD-2 Creatinine cut-offs for age. RACHS-1: Risk Adjusted Congenital Heart Surgery Score

The third model explored associations between RPP and the outcome (**Table 5)**. At the unadjusted analysis, RPP was not associated with the outcome. When adjusted for the same candidate variables, RPP was not retained in the model, while age ≤62 days, higher surgery complexity, lower platelet count and presence of renal dysfunction were all associated with the onset of the adverse outcome. The same results were observed when the model was computed for the neonatal population (**Supplemental Table 3**).

Table 5. Unadjusted and adjusted logistic regression for testing Rate Pressure Product as a predictor of adverse outcome.

Variables	Odds Ratio	95% Confidence Interval	p-value
Unadjusted logistic regression			
Rate pressure product			0.372
≤ 8924	1	Reference group	-
> 8924 and ≤ 9894	0.907	0.657-1.252	0.553
> 9894 and ≤ 11011	0.746	0.533-1.046	0.089

> 11011	0.602	0.836-0.602	0.284
Adjusted logistic regression model			
Age (days)			<0.001
≤ 62	1	Reference group	-
> 62 and ≤ 356	0.391	0.276-0.552	<0.001
> 356 and ≤ 1958	0.460	0.324-0.655	<0.001
> 1958	0.334	0.221-0.505	<0.001
RACHS-1 category			<0.001
RACHS 1 to 3	1	Reference group	-
RACHS 4 to 6	2.392	1.768-3.235	<0.001
RACHS not assigned	3.068	1.746-5.391	<0.001
Platelets ($x10^9$/L)			<0.001
≤ 161	1	Reference group	-
> 161 and ≤ 214	0.494	0.349-0.699	<0.001
> 214 and ≤ 279	0.446	0.316-0.629	<0.001
> 279	0.512	0.368-0.714	<0.001
Renal dysfunction*	2.266	1.730-2.968	<0.001

Unadjusted logistic regression: N= 4161; Hosmer and Lemeshow Test *p* value= 1.000; AUC 0.530. **Adjusted** logistic regression model: Candidate variables: Rate Pressure Product, Age (days), RACHS-1 category, Inotropic support, Respiratory Support Score, Hematocrit (%), Platelet ($x10^9$/L), Renal dysfunction. N= 4040; Hosmer and Lemeshow Test *p* value= 0.712; AUC 0.726. *Renal dysfunction is defined by PELOD-2 Creatinine cut-offs for age. RACHS-1: Risk Adjusted Congenital Heart Surgery Score 1.

As part of the model, we computed neonate-specific quartile cut-offs for each variable which are described in the results below. SI was found to be a significant predictor of adverse outcomes when equal or greater to 2.48 (vs 1.83 when considering the entire population). Similarly, CPP was found to be protective when higher or equal 32 (vs 35 of the entire population).

When models were developed to examine associations between predictors and separately major adverse cardiovascular events and unplanned reoperations, all independent predictors identified in the main analysis remained associated with both major adverse cardiovascular events and unplanned surgery (**Supplemental Tables 4-9**).

Assessing the potential superiority of derived variables over the primary variables

The ROC curves and their CI of the models including derived and primary physiological variables are shown in **Table 6**. As demonstrated by the overlapping of the ROC CIs, derived physiological variables were neither superior nor inferior to primary hemodynamic variables in predicting the outcome.

Table 6. Area under the receiver operating characteristic (ROC) curves of adjusted primary and derived hemodynamic variables.

Hemodynamic variables*	N	Hosmer Lemeshow test	AUC curve	95% confidence intervals
Primary hemodynamic variables				
Heart rate	4,040	0.435	0.739	0.708-0.769
Systolic blood pressure	4,040	0.416	0.740	0.710-0.770
Diastolic blood pressure	4,021	0.803	0.734	0.704-0.764
Atrial pressure	3,756	0.292	0.728	0.698-0.758
Derived hemodynamic variables				
Shock index	3,747	0.944	0.738	0.707-0.768
Rate pressure product**	-	-	-	-
Coronary perfusion pressure	4,008	0.769	0.736	0.706-0.796

*The models were adjusted for the following variables: age (days), RACHS-1 category, inotropic support, respiratory support score, hematocrit (%), platelet ($x10^9$/L), renal dysfunction. **Not retained in the adjusted model. AUC: area under the ROC curve.

Discussion

We have shown that the median SI and the median CPP over the first 24 hours following congenital heart surgery are independently associated with the occurrence of major adverse events in the first 7 days following surgery. However, we have also shown that the median values of the component vital signs - HR, SBP, DBP, and atrial pressure - over the same time period are independently associated with the adverse outcome and are equally predictive of the outcome as SI and CPP. Among several laboratory and patient-level predictors we explored, increased surgical complexity, renal dysfunction, and thrombocytopenia were associated with the outcome. It is likely that the presence of renal dysfunction is a surrogate for the degree of ischemic injury and that thrombocytopenia is associated with (if not causative of) the need for thoracic exploration, a component of our composite endpoint.

Many factors are known to be associated with poor postoperative outcomes, including higher procedural complexity, arrhythmia, and residual lesions (12, 22, 113). It is also well known that early hemodynamic perturbations are associated with poor outcomes in a variety of clinical circumstances (1, 11). As such, several tools are available for early detection of such perturbations, often laboratory- or spectroscopy-based measures. For example, the rate of rise of serum lactic acid is known to be associated with postoperative mortality (120). Intraoperative near-infrared spectrometry readings are known to correlate with both short-term (25) and long-term outcomes (121) following a variety of cardiac operations. In animal models, the monitoring of myocardial mitochondrial redox state accurately predicts impending cardiovascular collapse (122). Moreover, scores quantifying the level of vasoactive/inotropic support (i.e. the vasoactive inotropic score [VIS] and the ventilation vasoactive renal score [VVR]) are currently used as indirect measures of the magnitude of hemodynamic perturbation, and were found to be independent predictors of adverse outcome in pediatric patients when measured within the 24h after cardiac surgery (123, 124). Perhaps the most well-established prediction algorithms include data from multiple aspects of care, such as the PIM-3 score that models hemodynamic and laboratory data on pediatric ICU admission to predict hospital mortality (125).

Here we show that HR and SBP over the first 24 hours – even in isolation - are quite predictive of a meaningful short-term outcome. Surprisingly, this has not been previously demonstrated. However, many groups have examined computed hemodynamic variables, such as SI, CPP and RPP, and their associations with outcome. For example, a SI > 0.9 in adults has been associated with mortality and the need for massive transfusion following major trauma (114). In children, an age-adjusted SI has been predictive of morbidity and mortality in trauma patients (126–129) and in patients with septic shock (130–132). Similarly, CPP >15 mmHg during CPR is known to be a predictor of both acute resuscitative success (115) and of 24 hour survival (133). Additionally, CPP is a predictor of outcome following percutaneous coronary intervention following acute myocardial infarction (134). We show that both of these predictors are strongly associated with outcome following congenital heart surgery in children, though we found these predictors to be non-inferior to their component vital signs in isolation. Whether derived hemodynamic variables are more predictive of outcome than their component variables remains a subject of debate. For example, although SI was found to be superior to age-related hypotension in predicting the need for operation, intubation or transfusion in pediatric trauma patients (128), a more complete analysis on pediatric patients with septic shock demonstrated that SI was not superior to HR and SBP in predicting mortality (131).

We found that RPP was not associated with the outcome in our population. RPP has been found to be associated with mortality in acute exacerbations of heart failure in adult patients (116), and, when adjusted for

age, to be a predictor of cardiovascular events in patients undergoing a dobutamine stress test (135). In its essence, RPP is a measure of cardiac work that is used primarily in heart failure patients to amplify the signals of compensatory tachycardia and hypertension. However, it may be a poor marker of shock in that the signal produced by low SBP is offset by a high HR, which may explain why it was poorly associated with the outcome in our study.

Our study has several limitations. Our most important limitation was the use of a single median value of each variable to represent hemodynamics during the first 24 hours. We chose this approach in order to decrease the number of predictors, to remove extremes, and to facilitate computation. However, it is likely that additional signal exists within the primary data. For example, the maximum or minimum value, the variability over time, the change in response to an intervention, or the first derivative of any of the included parameters are likely of interest and should be explored in the future. Another important limitation is that although we statistically corrected each model for age, the SI, CPP and RPP data that we included in the model was in raw form; in the future, a similar analysis could be undertaken using age-adjusted Z-scores of each hemodynamic variable rather than the value itself as a more precise way to account for age-related variability. In the future, threshold values of these predictors may become useful tools at the bedside.

Conclusion

Vital signs, including median heart rate and blood pressure in the first 24 hours of admission, as well as derived variables, such as SI and CPP, are associated with a meaningful short-term outcome following cardiac surgery in children.

Supplemental Table 1. Unadjusted and adjusted logistic regression for testing Shock Index as a predictor of adverse outcome in neonates.

Variables	Odds Ratio	95% Confidence Interval	p-value
Unadjusted logistic regression			
Shock Index			<0.001
≤ 1.96	1	Reference group	-
> 1.96 and ≤ 2.22	1.967	1.069-3.619	0.030
> 2.22 and ≤ 2.48	1.216	0.632-2.339	0.558
> 2.48	4.070	2.295-7.219	<0.001
Adjusted logistic regression model			
Shock Index			<0.001
≤ 1.96	1	Reference group	-
> 1.96 and ≤ 2.22	1.528	0.810-2.880	0.190
> 2.22 and ≤ 2.48	0.994	0.506-2.531	0.986
> 2.48	3.060	1.681-5.571	<0.001
Platelets ($x10^9$/L)			0.003
≤ 174	1	Reference group	-
> 174 and ≤ 238	0.483	0.284-0.821	0.007
> 238 and ≤ 299	0.459	0.268-0.786	0.005
> 299	0.423	0.423-0.236	0.006
Renal dysfunction*	2.657	1.769-3.992	<0.001

Unadjusted logistic regression: N= 836; Hosmer and Lemeshow Test *p* value= 1.000; AUC= 0.648**. Adjusted** logistic regression model: Candidate variables: Shock index, RACHS-1 category, inotropic support, respiratory support score, hematocrit (%), platelet ($x10^9$/L), renal dysfunction. N= 834; Hosmer and Lemeshow Test *p* value= 0.973; AUC= 0.723.
*Renal dysfunction is defined by PELOD-2 Creatinine cut-offs for age.

Supplemental Table 2. Unadjusted and adjusted logistic regression for testing Coronary Perfusion Pressure as a predictor of adverse outcome in neonates.

Variables	Odds Ratio	95% Confidence Interval	p-value
Unadjusted logistic regression			
Coronary perfusion pressure			<0.001
≤ 32	1	Reference group	
> 32 and ≤ 37	0.350	0.209-0.584	<0.001
> 37 and ≤ 42	0.314	0.183-0.539	<0.001
> 42	0.382	0.220-0.666	0.001
Adjusted logistic regression model			
Coronary perfusion pressure			<0.001
≤ 32	1	Reference group	-
> 32 and ≤ 37	0.412	0.242-0.701	0.001
> 37 and ≤ 42	0.347	0.196-0.616	<0.001
> 42	0.417	0.417-0.235	0.003
Platelets ($x10^9$/L)			<0.001
≤ 174	1	Reference group	-
> 174 and ≤ 238	0.463	0.271-0.791	0.005
> 238 and ≤ 299	0.401	0.229-0.705	0.001
> 299	0.357	0.200-0.637	<0.001
Renal dysfunction*	2.450	1.617-3.714	<0.001

Unadjusted logistic regression: N= 823; Hosmer and Lemeshow Test *p* value= 1.000; AUC= 0.626. **Adjusted** logistic regression model: Candidate variables: coronary perfusion pressure, RACHS-1 category, inotropic support, respiratory support score, hematocrit (%), platelet ($x10^9$/L), renal dysfunction. N= 821; Hosmer and Lemeshow Test *p* value= 0.783; AUC= 0.718.
*Renal dysfunction is defined by PELOD-2 Creatinine cut-offs for age.

Supplemental Table 3. Unadjusted and adjusted logistic regression for testing Rate Pressure Product as a predictor of adverse outcome in neonates.

Variables	Odds Ratio	95% Confidence Interval	p-value
Unadjusted logistic regression			
Rate Pressure Product			0.096
≤ 8440	1	Reference group	-
> 8440 and ≤ 9242	0.749	0.425-1.318	0.316
> 9242 and ≤ 10036	0.778	0.444-1.362	0.379
> 10036 and ≤ 11016	0.398	0.207-0.765	0.006
> 11016	0.824	0.472-1.438	0.495
Adjusted logistic regression model			

RACHS-1 category			0.005
RACHS 1 to 3	1	Reference group	-
RACHS 4 to 6	1.914	1.280-2.862	<0.002
RACHS not assigned	0.748	0.154-3.641	0.719
Platelets (x10^9/L)			0.002
≤ 174	1	Reference group	-
> 174 and ≤ 238	0.478	0.282-0.808	0.006
> 238 and ≤ 299	0.473	0.278-0.805	0.006
> 299	0.396	0.223-0.705	0.002
Renal dysfunction*	2.734	1.825-4.095	<0.001

Unadjusted logistic regression: N= 836; Hosmer and Lemeshow Test *p* value= 1.000; AUC= 0.571. **Adjusted** logistic regression model: Candidate variables: Rate Pressure Product, RACHS-1 category, Inotropic support, Respiratory Support Score, Hematocrit (%), Platelet (x10^9/L), Renal dysfunction. N= 834; Hosmer and Lemeshow Test *p* value= 0.804; AUC= 0.694.
*Renal dysfunction is defined by PELOD-2 Creatinine cut-offs for age.
RACHS-1: Risk Adjusted Congenital Heart Surgery Score 1

Supplemental Table 4. Unadjusted and adjusted logistic regression for testing Shock Index as predictor of Major Adverse Cardiovascular Events.

Variables	Odds Ratio	95% Confidence Interval	p-value
Unadjusted logistic regression			
Shock index			<0.001
≤ 1.14	1	Reference group	-
> 1.14 and ≤ 1.44	1.500	0.532-4.229	0.443
> 1.44 and ≤ 1.83	3.135	1.239-7.929	0.016
> 1.83	11.199	4.823-26.006	<0.001
Adjusted logistic regression model			
Shock index			<0.001
≤ 1.14	1	Reference group	-
> 1.14 and ≤ 1.44	1.358	0.476-3.877	0.567
> 1.44 and ≤ 1.83	2.308	0.885-6.014	0.087
> 1.83	7.338	3.025-17.798	<0.001
RACHS-1 category			0.006
RACHS 1 to 3	1	Reference group	-
RACHS 4 to 6	1.658	1.008-2.728	0.046
RACHS not assigned	3.357	1.419-7.943	0.006
Platelets (x10^9/L)			<0.001
≤ 161	1	Reference group	-
> 161 and ≤ 214	0.523	0.297-0.918	0.024
> 214 and ≤ 279	0.386	0.216-0.691	0.001
> 279	0.323	0.176-0.594	<0.001
Renal dysfunction*	2.261	1.437-3.555	<0.001

Unadjusted logistic regression: N= 4161; Hosmer and Lemeshow Test *p* value= 1.000; AUC= 0.741**. Adjusted** logistic regression model: Candidate variables: shock index, RACHS-1 category, inotropic support, respiratory support score, hematocrit (%), platelet (x10^9/L), renal dysfunction. N= 4040; Hosmer and Lemeshow Test *p* value= 0.774; AUC= 0.804.*Renal dysfunction is defined by PELOD-2 Creatinine cut-offs for age.
RACHS-1: Risk Adjusted Congenital Heart Surgery Score 1

Supplemental Table 5. Unadjusted and adjusted logistic regression for testing Shock Index as predictor of unplanned cardiac surgeries.

Variables	Odds Ratio	95% Confidence Interval	p-value
Unadjusted logistic regression			
Shock index			<0.001
≤ 1.14	1	Reference group	-
> 1.14 and ≤ 1.44	1.581	0.930-2.686	0.091
> 1.44 and ≤ 1.83	1.875	1.117-3.148	0.017
> 1.83	4.879	3.075-7.739	<0.001
Adjusted logistic regression model			
Shock index			<0.001
≤ 1.14	1	Reference group	-
> 1.14 and ≤ 1.44	1.376	0.799-2.369	0.250
> 1.44 and ≤ 1.83	1.375	0.800-2.364	0.249
> 1.83	3.030	1.842-4.985	<0.001
RACHS-1 category			<0.001
RACHS 1 to 3	1	Reference group	-
RACHS 4 to 6	2.296	1.612-3.270	<0.001
RACHS not assigned	2.341	1.170-4.684	0.016
Platelets (x10^9/L)			0.013
≤ 161	1	Reference group	-

> 161 and ≤ 214	0.562	0.368-0.857	0.007
> 214 and ≤ 279	0.568	0.379-0.853	0.006
> 279	0.769	0.528-1.122	0.173
Renal dysfunction*	1.665	1.231-2.251	<0.001

Unadjusted logistic regression: N= 4161; Hosmer and Lemeshow Test *p* value= 1.000; AUC= 0.659**. Adjusted** logistic regression model: Candidate variables: shock index, RACHS-1 category, inotropic support, respiratory support score, hematocrit (%), platelet (x10^9/L), renal dysfunction. N= 4040; Hosmer and Lemeshow Test *p* value= 0.952; AUC= 0.703.*Renal dysfunction is defined by PELOD-2 Creatinine cut-offs for age.

Supplemental Table 6. Unadjusted and adjusted logistic regression for testing Coronary Perfusion Pressure as a predictor of Major Adverse Cardiovascular Events.

Variables	Odds Ratio	95% Confidence Interval	p-value
Unadjusted logistic regression			
Coronary perfusion pressure			<0.001
≤ 35	1	Reference group	
> 35 and ≤ 40	0.486	0.287-0.822	0.007
> 40 and ≤ 44	0.305	0.159-0.584	<0.001
> 44 and ≤ 50	0.151	0.064-0.358	<0.001
> 50	0.276	0.137-0.555	<0.001
Adjusted logistic regression model			
Coronary perfusion pressure			0.072
≤ 35	1	Reference group	-
> 35 and ≤ 40	0.654	0.380-1.124	0.124
> 40 and ≤ 44	0.489	0.244-0.981	0.044
> 44 and ≤ 50	0.333	0.137-0.811	0.015
> 50	0.720	0.342-1.517	0.387
Age (days)			<0.001
≤ 62	1	Reference group	-
> 62 and ≤ 356	0.377	0.216-0.657	0.001
> 356 and ≤ 1958	0.324	0.171-0.616	0.001
> 1958	0.286	0.079-0.441	<0.001
Platelets (x10^9/L)			<0.001
≤ 161	1	Reference group	-
> 161 and ≤ 214	0.484	0.275-0.852	0.012
> 214 and ≤ 279	0.351	0.193-0.640	0.001
> 279	0.262	0.139-0.493	<0.001
Renal dysfunction*	2.592	1.597-4.205	<0.001

Unadjusted logistic regression: N= 4128; Hosmer and Lemeshow Test *p* value= 1.000; AUC= 0.671 **Adjusted** logistic regression model: Candidate variables: coronary perfusion pressure, Age (days), RACHS-1 category, inotropic support, respiratory support score, hematocrit (%), platelet (x10^9/L), renal dysfunction. N= 4008; Hosmer and Lemeshow Test *p* value= 0.333; AUC= 0.781.
*Renal dysfunction is defined by PELOD-2 Creatinine cut-offs for age.

Supplemental Table 7. Unadjusted and adjusted logistic regression for testing Coronary Perfusion Pressure as a predictor of unplanned cardiac surgeries.

Variables	Odds Ratio	95% Confidence Interval	p-value
Unadjusted logistic regression			
Coronary perfusion pressure			<0.001
≤ 35	1	Reference group	
> 35 and ≤ 40	0.385	0.260-0.571	<0.001
> 40 and ≤ 44	0.327	0.211-0.506	<0.001
> 44 and ≤ 50	0.255	0.158-0.412	<0.001
> 50	0.304	0.191-0.484	<0.001
Adjusted logistic regression model			
Coronary perfusion pressure			<0.001
≤ 35	1	Reference group	-
> 35 and ≤ 40	0.454	0.304-0.678	<0.001
> 40 and ≤ 44	0.438	0.279-0.686	<0.001
> 44 and ≤ 50	0.373	0.227-0.611	<0.001
> 50	0.456	0.280-0.744	0.002
RACHS-1 category			<0.001
RACHS 1 to 3	1	Reference group	-
RACHS 4 to 6	2.701	1.921-3.798	<0.001
RACHS not assigned	2.388	1.196-4.764	0.014
Platelets (x10^9/L)			0.025
≤ 161	1	Reference group	-
> 161 and ≤ 214	0.569	0.373-0.868	0.009
> 214 and ≤ 279	0.611	0.406-0.919	0.018
> 279	0.816	0.559-1.190	0.290
Renal dysfunction*	1.625	1.206-2.190	0.001

Unadjusted logistic regression: N= 4128; Hosmer and Lemeshow Test *p* value= 1.000; AUC= 0.637. **Adjusted** logistic regression model: Candidate variables: coronary perfusion pressure, Age (days), RACHS-1 category, inotropic support, respiratory support score, hematocrit (%), platelet ($x10^9$/L), renal dysfunction. N= 4008; Hosmer and Lemeshow Test *p* value= 0.714; AUC= 0.707.
*Renal dysfunction is defined by PELOD-2 Creatinine cut-offs for age. RACHS-1: Risk Adjusted Congenital Heart Surgery Score 1

Supplemental Table 8. Unadjusted and adjusted logistic regression for testing Rate Pressure Product as a predictor of Major Adverse Cardiovascular Events.

Variables	Odds Ratio	95% Confidence Interval	p-value
Unadjusted logistic regression			
Rate pressure product			0.598
≤ 8924	1	Reference group	-
> 8924 and ≤ 9894	1.304	0.723-2.351	0.553
> 9894 and ≤ 11011	1.051	0.566-1.951	0.089
> 11011	1.414	0.791-2.526	0.284
Adjusted logistic regression model			
Age (days)			<0.001
≤ 62	1	Reference group	-
> 62 and ≤ 356	0.367	0.210-0.645	<0.001
> 356 and ≤ 1958	0.308	0.162-0.586	<0.001
> 1958	0.170	0.073-0.394	<0.001
RACHS-1 category			0.002
RACHS 1 to 3	1	Reference group	-
RACHS 4 to 6	1.871	1.129-3.101	0.015
RACHS not assigned	3.563	1.524-8.330	0.003
Platelets ($x10^9$/L)			<0.001
≤ 161	1	Reference group	-
> 161 and ≤ 214	0.474	0.270-0.831	0.009
> 214 and ≤ 279	0.343	0.191-0.614	<0.001
> 279	0.268	0.145-0.495	<0.001
Renal dysfunction*	2.567	1.604-4.106	<0.001

Unadjusted logistic regression: N= 4161; Hosmer and Lemeshow Test *p* value= 1.000; AUC= 0.539**. Adjusted** logistic regression model: Candidate variables: rate pressure product, age (days), RACHS-1 category, inotropic support, respiratory support score, hematocrit (%), platelet ($x10^9$/L), renal dysfunction. N= 4040; Hosmer and Lemeshow Test *p* value= 0.386; AUC= 0.787.
*Renal dysfunction is defined by PELOD-2 Creatinine cut-offs for age. RACHS-1: Risk Adjusted Congenital Heart Surgery Score 1

Supplemental Table 10. Unadjusted and adjusted logistic regression for testing Rate Pressure Product as a predictor of unplanned cardiac surgeries.

Variables	Odds Ratio	95% Confidence Interval	p-value
Unadjusted logistic regression			
Rate Pressure Product			0.108
≤ 8924	1	Reference group	-
> 8924 and ≤ 9894	0.784	0.537-1.145	0.208
> 9894 and ≤ 11011	0.658	0.442-0.978	0.038
> 11011	0.659	0.443-0.980	0.039
Adjusted logistic regression model			
Age (days)			<0.001
≤ 62	1	Reference group	-
> 62 and ≤ 356	0.446	0.293-0.678	<0.001
> 356 and ≤ 1958	0.598	0.397-0.900	0.014
> 1958	0.480	0.300-0.769	0.002
RACHS-1 category			<0.001
RACHS 1 to 3	1	Reference group	-
RACHS 4 to 6	2.475	1.737-3.528	<0.001
RACHS not assigned	2.434	1.222-4.848	0.011
Platelets ($x10^9$/L)			0.010
≤ 161	1	Reference group	-
> 161 and ≤ 214	0.549	0.360-0.838	0.005
> 214 and ≤ 279	0.562	0.373-0.845	0.006
> 279	0.742	0.505-1.090	0.129
Renal dysfunction*	1.977	1.439-2.716	<0.001

Unadjusted logistic regression: N= 4161; Hosmer and Lemeshow Test *p* value= 1.000; AUC= 0.546. **Adjusted** logistic regression model: Candidate variables: rate pressure product, age (days), RACHS-1 category, inotropic support, respiratory support score, hematocrit (%), platelet ($x10^9$/L), renal dysfunction. N= 4040; Hosmer and Lemeshow Test *p* value= 0.454; AUC= 0.692.
*Renal dysfunction is defined by PELOD-2 Creatinine cut-offs for age. RACHS-1: Risk Adjusted Congenital Heart Surgery Score 1

Project 3

Predict

Extracorporeal membrane oxygenation support for failure to wean from cardiopulmonary bypass after pediatric cardiac surgery: analysis of ELSO Registry data

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Abstract

Objectives: Extracorporeal Membrane Oxygenation (ECMO) has been used to support children who fail to wean from cardiopulmonary bypass (CPB) after pediatric cardiac surgery, but little is known about outcomes. We aimed to describe epidemiology and ECMO factors associated with in-hospital mortality in these patients.

Design: Retrospective multicenter registry-based cohort study. **Setting:** International pediatric ECMO centers.

Patients: Children <18 years supported with ECMO for failure to wean from CPB after cardiac surgery during 2000-2016 and reported to Extracorporeal Life Support Organization's registry.

Intervention: None.

Measurements and Main Results: The primary outcome measure was in-hospital mortality. Cardiac surgical procedural complexity was assigned using Risk-Adjustment-in-Congenital-Heart-Surgery-1 (RACHS-1). Multivariable logistic regression was used to identify factors independently associated with the primary outcome. We included 2,322 patients, with a median age of 26 days [Interquartile range (IQR) 7-159]; 47% underwent complex surgical procedures (RACHS 4-6 categories). In-hospital mortality was 55%. The multivariable model evaluating associations with in-hospital mortality showed non-cardiac congenital anomalies (OR 1.78, CI 1.36-2.32), comorbidities (OR 1.59, CI 1.30-1.94), pre-operative cardiac arrest (OR 1.67, CI 1.20-2.34), pre-operative mechanical ventilation >24h (OR 1.49, CI 1.21-1.84), pre-operative bicarbonate administration (OR 1.42, CI 1.08-1.86), longer CPB time (>251 min, OR 1.50, CI 1.13-1.99), complex surgical procedures (OR 1.43, CI 1.13-1.81), longer ECMO duration (>104 h, OR 1.54, CI 1.17-2.02), and ECMO complications increased the odds of in-hospital mortality. Age >26 days (OR 0.56, CI 0.42-0.75) reduced the odds of mortality.

Conclusions: Children supported with ECMO for failure to wean from CPB after cardiac surgery are at high risk of mortality (55%). Younger patients, those with congenital abnormalities and comorbidities, undergoing complex procedures, requiring longer CPB, those experiencing ECMO complications and longer ECMO duration have higher mortality risk. These data can help assessing prognosis in this high-risk population.

Background and Significance

Children with congenital (CHD) or acquired heart disease undergoing open-heart surgery and failing to wean from cardiopulmonary bypass (CPB) after surgery face imminent mortality (39). Failure to wean from CPB may result from severe post-CPB cardiac and/or pulmonary dysfunction or hemodynamically significant residual lesions. In these patients, transition to Extracorporeal Membrane Oxygenation (ECMO) can provide longer duration of cardiopulmonary support while awaiting cardiac and/or pulmonary recovery, bridge to a surgical or catheter-based intervention aimed at correcting a residual lesion, or bridge to transplantation (39, 40). Previous reports of children supported with ECMO for failing to wean from CPB document variable in-hospital mortality (23 to 60%) (**Supplemental Table 1**) (42–45). These single-institution reports are limited by small sample size and generalizability (3-15) .

We sought to estimate mortality for a large cohort of pediatric patients supported with ECMO after failing to wean from CPB following cardiac surgery, using multicenter data from the Extracorporeal Life Support Organization (ELSO) registry. Additionally, we explored demographics, pre-surgical support and surgical details, ECMO support and complications independently associated with in-hospital mortality.

Methods

Data Source

The ELSO Registry collects data on ECMO use and outcomes for a wide range of ages and indications. Over 300 US and international centers contribute ECMO data to the registry, and data from >100,000 patients are available for research (34). Member centers report data on voluntary basis, after approval by the local Institutional Review Boards (IRB). A data use agreement between ELSO and member centers allows release of limited de-identified datasets to the member centers for research purposes, waiving the need for regulatory approval. The present study qualified for human subjects research exemption by Boston Children's Hospital Review Board.

Study Population

We extracted data from children (age <18 y) who underwent a cardiac surgical procedure and required ECMO for failure to wean from CPB, during 2000-2016. "Failure to wean from CPB" is an extractable ECMO indication reported through the Cardiac Addendum. We excluded patients already on ECMO at the time of surgery, patients with no documented cardiac surgical procedure, those in whom the time of surgical procedure was not reported, and ECMO indication as respiratory failure or support of cardiopulmonary resuscitation. Finally, for patients with more than one ECMO run, only the first run was included in the analyses.

Data Collection

Data extracted included demographics, cardiac surgical procedure details, pre-operative evaluation, pre-ECMO support variable, and ECMO support information and complications. Our primary outcome measure was in-hospital mortality. Secondary outcome measures were successful wean-off ECMO and ECMO duration. We assumed pre-ECMO variables documented patient illness and support prior to cardiac surgery and ECMO. Patient selection, pre-surgical support, surgical decision making including weaning from CPB, and management of ECMO patients were not standardized, and therefore subject to wide practice variability.

Data Categorization

Primary and secondary diagnoses, reported using the International Classification of Disease (ICD-9-CM) for cases recorded up to 2015, and ICD-10CM for cases recorded from 2016, were used to classify non-cardiac anomalies and comorbid conditions. Surgical procedures were reported using the Common Procedural Terminology (CPT) codes (Supplemental Information). Cardiac surgical procedures were categorized based on complexity, using the Risk Adjusted Congenital Heart Surgery-1 (RACHS-1) method (136). ECMO complications were grouped using the ELSO-Registry complication codes using a previously described system (64).

Statistical analysis

Data are reported as frequencies and percentages for categorical, and median and inter-quartile range (IQR; 25^{th}-75^{th} percentile) for continuous variables. Demographic, clinical, pre-operative and ECMO support details, and ECMO complications were compared between survivors and non-survivors. The Pearson chi square test was used to compare categoric data; the Fisher exact test was used when expected count in > 20% of cells was <5. The Mann-Whitney U test was used to compare continuous data.

Three multivariable logistic regression models were developed to independently evaluate the association of pre-surgical factors, ECMO-related factors, and both pre-surgical and ECMO-factors with in-hospital mortality. Candidate variables for inclusion in the first two models were selected from the univariate analysis comparing survivors and non-survivors. All variables with a univariate p value <0.1 were selected for inclusion in the multivariable model. Variables with >10% of missing data were excluded. A backward conditional strategy was used for entry and retention of variables in the model. A candidate variable was retained in the model if the p value was <0.05. All the variables significantly associated with mortality in the first two models were included in the third comprehensive model.

Variables containing continuous data that were retained in the multivariable model were tested for linear association; those not meeting the linearity assumption were categorized for inclusion in the model. Age and weight were tested for correlation using the Spearman's Rho test; only age was used for modelling as age and weight were collinear. Because comorbid conditions were only present in small number of subjects, a comprehensive "comorbid conditions" variable was created for inclusion into the model, combining the following pre-ECMO variables: prematurity, heart failure, cardiogenic shock, respiratory disease, neurologic disease, renal disease, coagulation defects, hemorrhage and hematologic or immunologic defect. Genetic syndrome and non-cardiac congenital anomalies were included as a combined variable called "non-cardiac congenital anomalies". RACHS-1 categories were combined into a three-category variable (RACHS 1 to 3, RACHS 4 to 6, not assigned).

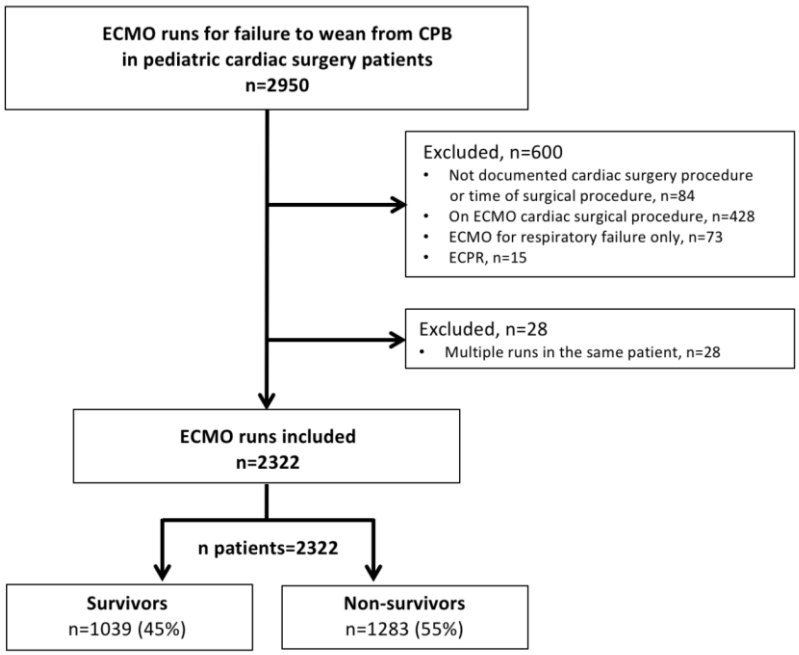
All statistical analyses were performed using the IBM SPSS statistical software (version 25.0, IBM Corp. Armonk, New York, U.S.A.). Statistical significance was set at a two-sided p value <0.05.

Results

Study population

Two thousand nine hundred fifteen patients underwent 2,950 runs for failure to wean from CPB during the study period. After application of the exclusion criteria, 2,322 patients (80%) were selected as our study cohort (**Figure 1**).

Figure 1. Study Flow chart.



Demographic and clinical characteristics of patients are described in **Table 1**. The median age at ECMO initiation was 26 d (IQR: 7-159). A genetic syndrome or congenital anomalies were present in 17%, single ventricle CHD in 34% (n = 793), and 10% had pre-operative cardiac arrest (CA). Cardiac procedures in RACHS-1 1-3 categories included 1,108 patients (48%) and RACHS 4-6 1,103 patients (47%). The median CPB time was 251 min (IQR: 174-351).

Table 1. Demographic and clinical features of patients using extracorporeal membrane oxygenation after failure to wean from cardiopulmonary bypass.

Variable	Total (n=2322)	Survivors (n=1039)	Non-survivors (n=1283)	p value
Age (days), median (IQR)	26 (7-159)	59 (9-234)	15 (9-114)	<0.001
Age category, n (%)				
Neonates	1207 (52)	446 (43)	761 (59)	
Infants	752 (32)	379 (36)	373 (29)	<0.001
Children	363 (16)	214 (21)	149 (12)	
Weight (kg), median (IQR)[a]	3.6 (3.0-5.7)	4.0 (3.2-7.0)	3.4 (2.9-4.7)	<0.001
Gender (male), n (%)[b]	1273 (55)	565 (54)	708 (55)	0.184
Race, white, n (%)[c]	1311 (58)	619 (61)	692 (55)	0.005
Comorbid conditions, n (%)				
Genetic syndrome	215 (9)	77 (7)	138 (11)	0.006
Non-cardiac congenital anomalies	221 (9)	81 (8)	140 (11)	0.011
Prematurity*	208 (9)	48 (4)	166 (13)	<0.001
Cardiac associated disease				
Arrhythmia	348 (15)	148 (14)	200 (16)	0.367
Heart failure	516 (22)	207 (20)	309 (24)	0.016
Shock, cardiogenic	142 (6)	52 (5)	90 (7)	0.044
Pulmonary hypertension	103 (4)	47 (4)	56 (4)	0.853
Cardiomyopathy	69 (3)	32 (3)	37 (3)	0.782
Other	116 (5)	49 (5)	67 (5)	0.578
Respiratory disease	449 (20)	173 (17)	276 (21)	0.003
Neurologic disease	233 (10)	78 (7)	155 (12)	<0.001
Renal disease	284 (12)	59 (6)	225 (17)	<0.001
Gastrointestinal disease	139 (6)	62 (6)	77 (6)	0.972
Infectious disease	175 (8)	67 (6)	108 (8)	0.074
Metabolic, endocrine, electrolyte abnormalities	111 (5)	45 (4)	66 (5)	0.361
Coagulation defects	42 (2)	8 (1)	34 (3)	0.001
Hemorrhage	112 (5)	32 (3)	80 (6)	<0.001

Immunologic or hematologic disease	87 (4)	29 (3)	58 (4)	0.029
Other comorbidities	221 (10)	107 (10)	114 (9)	0.249
Pre-operative cardiac arrest, n (%)**	238 (10)	89 (8)	149 (12)	0.016
Pre-operative echocardiography, n (%)	1253 (54)	592 (57)	661 (51)	0.009
Pre-operative cardiac catheterization, n (%)	381 (17)	174 (17)	207 (16)	0.692
Main cardiac surgery procedure RACHS-1 score, n (%)				
1	16 (1)	7 (1)	9 (1)	
2	255 (11)	141 (14)	114 (9)	
3	837 (36)	433 (44)	404 (33)	
4	508 (22)	193 (20)	315 (25)	<0.001
5	30 (1)	8 (1)	22 (2)	
6	565 (24)	196 (20)	369 (30)	
Not assigned	111 (5)	61 (6)	50 (4)	
ECMO year, n (%)				
2000-2005	559 (24)	241 (23)	318 (25)	
2006-2011	896 (39)	400 (38)	496 (39)	0.583
2012-2016	867 (37)	398 (38)	469 (37)	
Surgery details				
CPB time (min), median (IQR)[d]	251 (174-351)	238 (169-336)	266 (180-365)	<0.001
ACC, n (%)	1979 (85)	911 (88)	1068 (83)	0.003
DHCA, n (%)	974 (42)	412 (40)	562 (44)	0.044

Missing data, n (survivors, non-survivors): [a] 19 (11, 8); [b] 20 (13, 7); [c] 65 (30, 35); [d] 230 (89, 141)
* Prematurity is defined as gestational age ≤ 36 weeks; ** within 24h prior to ECMO

CPB: Cardio-Pulmonary Bypass; DHCA Deep Hypothermic Cardiac Arrest; ECMO: Extra-Corporeal Membrane Oxygenation; IQR: Inter-Quartile Range; RACHS-1: Risk Adjusted Congenital Heart Surgery Score 1

A compilation of survival to hospital discharge estimates based on surgical procedures is shown in **Figure 2** and a detailed list is provided in **Table 2**.

Figure 2. Number of survivors and non-survivors at hospital discharge according to most frequent cardiac procedures.

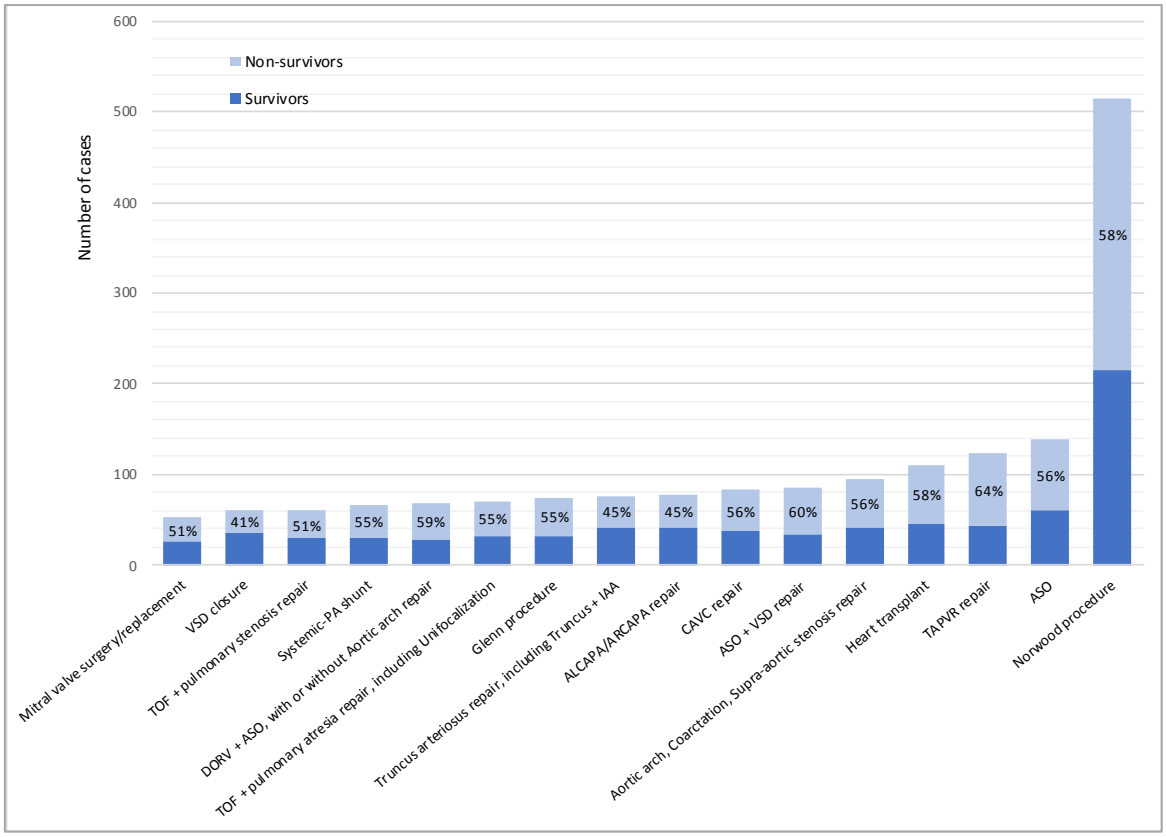


Table 2. Cardiac surgical procedures and associated in-hospital mortality in patients using Extracorporeal Membrane Oxygenation after failure to wean from cardiopulmonary bypass.

Cardiac surgical procedure, n (%)	Total (n=2322)	% Mortality	Survivors (n=1039)	Non-survivors (n=1283)	p-value
ALCAPA/ARCAPA repair	77 (3)	45	42 (4)	35 (3)	0.079
Aortic arch, Coarctation, Supra-aortic stenosis repair	96 (4)	56	42 (4)	54 (4)	0.841
Aortic arch repair in single ventricle physiology	6 (0)	50	3 (0)	3 (0)	1.000[#]
Aortic arch repair + PA band	20 (1)	50	10 (1)	10 (1)	0.635
Ross, Ross-Konno operation	33 (1)	60	13 (1)	20 (2)	0.533
VSD + Aortic arch repair	34 (2)	62	13 (1)	21 (2)	0.442
Aortic valve surgery/replacement	39 (2)	46	21 (2)	18 (2)	0.249
ASD + isolated PAPVR repair	7 (0)	43	4 (0)	3 (0)	0.707[#]
ASO	138 (6)	56	61 (6)	77 (6)	0.895
ASO + VSD repair	85 (4)	60	34 (3)	51 (4)	0.370
ASO + Coarctation/Aortic arch repair	36 (2)	64	13 (1)	23 (2)	0.294
Atrial septectomy, isolated	4 (0)	100	0 (0)	4 (0)	0.133[#]
CAVC repair	84 (4)	56	37 (4)	47 (4)	0.896
Cor triatriatum repair	4 (0)	75	1 (0)	3 (0)	0.633[#]
VAD positioning	4 (0)	50	2 (0)	2 (0)	1.000[#]
Coronary surgery repair, not ALCAPA/ARCAPA	15 (1)	40	9 (1)	6 (1)	0.233
Damus-Kaye-Stansel procedure	44 (2)	54	20 (2)	24 (2)	0.924
IAA repair, including Yasui procedure	49 (2)	61	19 (2)	30 (2)	0.396
DORV repair	19 (1)	47	10 (1)	9 (1)	0.488
DORV + ASO, with or without Aortic arch repair	68 (3)	59	28 (3)	40 (3)	0.548
DORV TOF repair	39 (2)	38	24 (2)	15 (1)	0.033
Double switch operation	8 (0)	50	4 (0)	4 (0)	1.000[#]
Ebstein's anomaly repair, all procedures	30 (1)	60	12 (1)	18 (2)	0.599
Fontan procedure	26 (1)	46	14 (1)	12 (1)	0.348
Glenn procedure	74 (3)	55	33 (3)	41 (3)	0.979
Mustard/Senning procedure for d-TGA	7 (0)	57	3 (0)	4 (0)	1.000[#]
Mitral valve surgery/replacement	53 (2)	51	26 (3)	27 (2)	0.523
Cardiac tumor surgery	9 (0)	56	4 (0)	5 (0)	0.985
Norwood procedure	515 (22)	58	215 (21)	300 (23)	0.121
RVOTO repair, pulmonary valve surgery/replacement, Branch PA surgery	38 (2)	50	19 (2)	19 (2)	0.511
Pulmonary vein surgery, not TAPVR	5 (0)	80	1 (0)	4 (0)	0.388
RV-PA conduit replacement, isolated	34 (2)	50	17 (2)	17 (1)	0.535
LVOTO surgery including Konno procedure, Subaortic stenosis repair	16 (1)	44	9 (1)	7 (1)	0.353
Systemic-PA shunt	67 (3)	55	30 (3)	37 (3)	0.996
TAPVR repair	123 (5)	64	44 (4)	79 (6)	0.040
TOF + pulmonary atresia repair, including unifocalization	71 (3)	55	32 (3)	39 (3)	0.955
TOF + pulmonary stenosis repair	61 (3)	51	30 (3)	31 (2)	0.480
TOF + CAVC repair	15 (1)	73	4 (1)	11 (1)	0.158
Heart transplant	110 (5)	58	46 (4)	64 (5)	0.527
Truncus arteriosus repair, including Truncus + IAA	76 (3)	45	42 (4)	34 (3)	0.061
Tricuspid valve surgery/replacement	11 (0)	36	7 (1)	4 (0)	0.236[#]
VSD closure	61 (3)	41	36 (4)	25 (2)	0.023
CAVC + Coarctation/Aortic arch repair	9 (0)	44	5 (1)	4 (0)	0.525
Other procedures*	2 (0)	100	0 (0)	2 (0)	0.505[#]

ALCAPA: Anomalous Left Coronary Artery from Pulmonary Artery; ARCAPA: Anomalous Right Coronary Artery from Pulmonary Artery; ASD: Atrial Septal Defect; ASO: Aortic Switch Operation; CAVC: Complete Atrioventricular Canal; Cardio-Pulmonary Bypass; DORV: Double Outlet Right Ventricle; d-TGA: d-Transposition of the Great Arteries; ECMO: Extra-Corporeal Membrane Oxygenation; PA: Pulmonary Artery; IAA: Interrupted Aortic Arch; LVOTO: Left Ventricular Outflow Tract Obstruction; PAPVR: Partial Anomalous Pulmonary Venous Return; RV: Right Ventricle; RVOTO: Right Ventricular Outflow Tract Obstruction; TAPVR: Total Anomalous Pulmonary Venous Return; TOF: Tetralogy of Fallot; VAD: Ventricular Assist Device; VSD: Ventricular Septal Defect
*Other procedures are palliative ASO in Single Ventricle with Tricuspid Atresia (n=1) and Pericardial Window (n=1); [#]Fisher's Exact Test

Pre-ECMO support and ECMO details are shown in **Table 3**. Pre-operative MV was used in 1,198 patients (51%). The most common vascular access sites for ECMO cannulation included the aorta (n=2044, 88%) and the right atrium (n=1982, 85%); 13% (n = 312) had left atrial cannulation. The median duration of ECMO support was 104 h (IQR: 65-169). ECMO complications in our study cohort are shown in **Table 4**.

Table 3. Pre-extracorporeal membrane oxygenation support and extracorporeal membrane oxygenation details of patients who failed to wean from cardiopulmonary bypass.

Variable	Total (n=2322)	Survivors (n=1039)	Non-survivors (n=1283)	p value
Pre-ECMO support, n (%)				
Inotropic/vasopressor drugs	1435 (62)	645 (62)	790 (62)	0.804
Vasodilator drugs	440 (19)	195 (19)	245 (19)	0.841
Cardiac pacemaker	196 (8)	91 (9)	105 (8)	0.621
Inhaled nitric oxide	374 (16)	170 (16)	204 (16)	0.763
Steroids	81 (3)	34 (3)	47 (4)	0.610
Pre-ECMO analgesia and sedation, n (%)				
Inhaled anesthetic	160 (7)	68 (6)	92 (7)	0.554
Opioids	1226 (53)	551 (53)	675 (53)	0.840
Pre-ECMO neuromuscular blockers, n (%)	1142 (49)	508 (49)	634 (49)	0.802
Mechanical ventilation, n (%)				
Pre-ECMO				
Conventional	1174 (50)	522 (49)	652 (50)	0.442
HFOV	24 (1)	9 (1)	17 (1)	0.540
At 24h after ECMO initiation[a]				
Conventional	2038 (99)	926 (100)	1112 (99)	
HFOV	14 (1)	1 (0)	13 (1)	0.010[#]
FiO2 (%),median (IQR)[b]				
Pre-ECMO	100 (55-100)	99 (56-100)	100 (52-100)	0.456
At 24h after ECMO initiation	37 (25-40)	40 (30-40)	30 (21-40)	<0.001
Surfactant, pre-ECMO, n (%)	21 (1)	6 (1)	15 (1)	0.134
Duration of MV prior to ECMO (h), median (IQR)[c]	14 (8-87)	12 (7-43)	18 (9-125)	<0.001
MV>24h prior to ECMO, n (%)[c]	900 (40)	326 (32)	574 (46)	<0.001
Arterial blood gas, pre-ECMO[d]				
pH, median (IQR)	7.31 (7.23-7.40)	7.31 (7.24-7.40)	7.31 (7.21-7.39)	0.074
PaCO2 (mmHg), median (IQR)	44 (37-54)	44 (37-54)	44 (36-55)	0.705
PaO2 (mmHg), median (IQR)	77 (39-242)	104 (41-269)	64 (37-225)	<0.001
HCO3 (mEq), median (IQR)	23 (20-26)	23 (20-26)	23 (19-25)	0.018
Pre-operative bicarbonate infusion, n (%)	382 (16)	133 (13)	249 (19)	<0.001
ECMO indications subcategories, n (%)				
Low cardiac output syndrome	1123 (48)	520 (50)	603 (47)	0.144
Pulmonary hypertension	178 (8)	90 (9)	88 (7)	0.104
Cardiac and pulmonary failure	190 (8)	59 (6)	131 (10)	<0.001
ECMO Cannulation sites, n (%)[e]				
Arterial cannulation				
Aorta	2044 (88)	921 (89)	1123 (87)	
Common carotid artery	158 (7)	56 (5)	102 (8)	0.150[#]
Femoral artery	13 (1)	9 (1)	4 (1)	
Other	25 (1)	8 (1)	17 (1)	
Venous cannulation				
Right atrium	1982 (85)	879 (85)	1103 (86)	
Internal jugular vein	154 (7)	62 (6)	92 (7)	0.438
Femoral vein	31 (1)	20 (2)	11 (1)	
Other	72 (3)	35 (3)	37 (3)	
Left atrium	312 (13)	154 (15)	158 (12)	0.078
ECMO pump flow rates (ml/kg/min), median (IQR) [f]				
At 4h after ECMO initiation	115 (95-141)	109 (92-135)	119 (99-145)	<0.001
At 24h after ECMO initiation	119 (98-146)	111 (91-140)	124 (100-150)	<0.001
ECMO support duration (h), median (IQR)[g]	104 (65-169)	86 (51-122)	136 (71-219)	<0.001
Cardiac surgery on-ECMO, n (%)	253 (11)	107 (10)	146 (11)	0.406
Cardiac surgery post-ECMO, n (%)	25 (1)	15 (1)	10 (1)	0.123
Multiple cardiac surgery, n (%)	276 (12)	121 (12)	155 (12)	0.747
Invasive procedure on ECMO, others, n (%)	440 (19)	170 (16)	270 (21)	0.004
Cardiac catheterization within 24h from ECMO, n(%)	320 (14)	132 (12)	188 (15)	0.286
Multiple ECMO runs, n(%)	60 (3)	27 (3)	33 (3)	0.968

Missing data, n (survivors, non-survivor): [a] 270 (112, 158); [b] pre-ECMO 1099 (493, 606), on-ECMO: 214 (82, 132); [c] 71 (25, 46); [d] pH and pCO2: 638 (290, 348), pO2: 646 (292, 354), HCO3: 804 (371, 433); [e] arterial cannulation: 124 (58, 66), venous cannulation: 147 (70, 77); [f] at 4h: 121 (52, 69), at 24h: 233 (99, 134); [g] 18 (8, 10); [#]Fisher's Exact Test

CPB: Cardio-Pulmonary Bypass; ECMO: Extra-Corporeal Membrane Oxygenation; FiO2: Fraction of inspired Oxygen; HFOV: High Frequency Oscillatory Ventilation; IQR: Inter-Quartile Range; MV: Mechanical Ventilation; PCO2: partial Pressure of Carbon dioxide; PaO2: partial Pressure of Oxygen

Table 4. Extracorporeal membrane oxygenation-related complications in patients who failed to wean from cardiopulmonary bypass.

Variable	Total (n=2322)	Survivors (n=1039)	Non-survivors (n=1283)	p value
ECMO circuit complications, n (%)	906 (39)	319 (31)	587 (46)	<0.001
Mechanical problems	245 (11)	71 (7)	174 (14)	<0.001
Clots in ECMO circuit	696 (30)	237 (23)	459 (36)	<0.001
Air embolus	90 (4)	30 (3)	60 (5)	0.026
Cannula problems	119 (5)	40 (4)	79 (6)	0.012
CNS complications, n (%)	409 (18)	107 (10)	302 (23)	<0.001
Seizures	148 (6)	43 (4)	105 (8)	<0.001
Cerebral infarction or intracranial hemorrhage	298 (13)	81 (8)	217 (17)	<0.001
Brain death	30 (1)	0 (0)	30 (2)	<0.001
Cardiac complications, n (%)	1739 (75)	722 (69)	1017 (79)	<0.001
Cardiac arrhythmia requiring treatment	403 (17)	125 (12)	278 (22)	<0.001
CPR on ECMO	74 (3)	10 (1)	64 (5)	<0.001
Cardiac tamponade	243 (10)	97 (9)	146 (11)	0.110
Myocardial stun at echocardiography evaluation	203 (9)	63 (6)	140 (11)	<0.001
Need for inotropic drugs	1503 (65)	609 (59)	894 (70)	<0.001
Hypertension requiring vasodilators	369 (16)	168 (16)	201 (16)	0.742
Peripheral vascular complications	10 (0)	0 (0)	10 (1)	0.003[#]
Pulmonary complications, n (%)				
Pneumothorax requiring treatment	50 (2)	17 (2)	33 (3)	0.122
Pulmonary hemorrhage	187 (8)	39 (4)	148 (11)	<0.001
Hemorrhagic complications (other than pulmonary), n (%)				
Cannulation site bleeding	431 (19)	166 (16)	265 (21)	0.004
Surgical site bleeding	1099 (47)	441 (42)	658 (51)	<0.001
Gastrointestinal bleeding	29 (1)	7 (1)	22 (2)	0.025
Hemolysis*	288 (12)	103 (10)	185 (14)	0.001
Disseminate intravascular coagulation	115 (5)	26 (2)	89 (7)	<0.001
Infectious complications, n (%)				
Culture proven infection	215 (9)	71 (7)	144 (11)	<0.001
White blood cell count < 1500/ml	24 (1)	5 (0)	19 (1)	0.018
Renal complications, n (%)				
Renal failure	299 (13)	78 (7)	221 (17)	<0.001
Serum creatinine 1.5-3.0 mg/dl	169 (7)	41 (4)	128 (10)	<0.001
Serum creatinine > 3.0 mg/dl	54 (2)	20 (2)	34 (3)	0.249
Dialysis required	282 (12)	61 (6)	221 (17)	<0.001
Hemofiltration required	650 (28)	198 (19)	452 (35)	<0.001
Metabolic complications, n (%)				
Arterial pH < 7.20	146 (6)	39 (4)	107 (8)	<0.001
Arterial pH > 7.60	111 (5)	54 (5)	57 (4)	0.397
Blood glucose < 40 mg/dl	41 (2)	14 (1)	27 (2)	0.168
Blood glucose > 240 mg/dl	368 (16)	144 (14)	224 (17)	0.018
Hyperbilirubinemia**	132 (6)	48 (5)	84 (6)	0.046

* Hemolysis is defined as plasma-free hemoglobin >50 mg/dl; ** Hyperbilirubinemia is defined as direct bilirubin >2.0 mg/dl or total bilirubin >15.0 mg/dl; [#]Fisher's Exact Test. CNS: Central Nervous System; CPB: Cardio-Pulmonary Bypass; CPR: Cardio-Pulmonary Resuscitation; ECMO: Extra-Corporeal Membrane Oxygenation

ECMO was successfully weaned in (n =1568) 67% of patients. Three percent of patients (n=70) were converted to a ventricular assist device (VAD) and 2% (n= 41, including 15 previously converted) underwent transplant on-ECMO. In-hospital mortality was 55%, and survival did not change significantly over the study period (Linear-by-Linear association *p* value = 0.13; **Figure 3**).

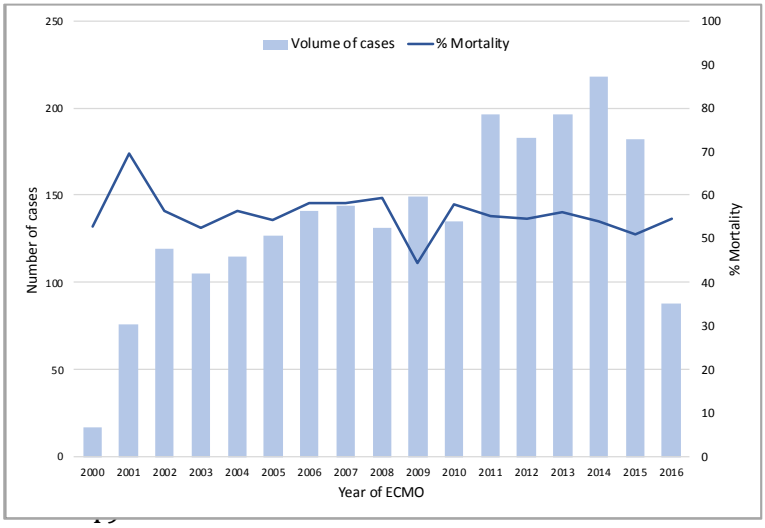


Figure 3. Volume of ECMO cases of failure to wean from CBP per year and associated in-hospital mortality.

Features of survivors and non survivors

Demographic, clinical, and surgical characteristics of survivors and non-survivors are shown in **Table 1**. Age and body weight was significantly lower among non-survivors compared with survivors. The frequency of genetic syndromes, non-cardiac abnormalities, comorbid conditions, and CA prior to surgery were all higher in non-survivors than survivors. Non-survivors had more complex surgery (higher RACHS-1 category) and longer duration of CPB.

Pre-ECMO support and ECMO details in survivors and non-survivors are shown in **Table 3**. Non-survivors had longer duration of pre-ECMO ventilator support, lower partial pressure of oxygen (paO_2) and lower standardized bicarbonate levels on blood gas measurements, and received bicarbonate more frequently. ECMO pump flows were significantly higher in non-survivors both at 4h and 24h after ECMO initiation. At 24 h following ECMO deployment, use of high flow oscillatory ventilation (HFOV) was more frequent, and FiO_2 was lower among non-survivors compared with survivors. Additionally, non-survivors underwent an invasive procedure on ECMO more frequently and had longer duration of ECMO than survivors. ECMO complications were more common in non-survivors (**Table 4**). Patients transplanted during ECMO support had significantly lower mortality compared with patients not transplanted (22% vs 56%, $p<0.001$). Mortality among patients converted to VAD after failure to wean from CBP did not significantly differ compared with mortality of those not-converted (61% vs 55%, $p=0.29$).

Multivariable models of factors associated with mortality

Three multivariable models evaluating factors associated with mortality are presented in **Table 5** and **Table 6**. The first model included demographic and pre-ECMO factors. Older age than neonatal one and white race were both associated with lower mortality. Presence of genetic syndrome and non-cardiac anomalies, comorbidities, pre-ECMO cardiac arrest, pre-ECMO mechanical ventilation, bicarbonate replacement all increased mortality odds. Finally, more complex operations and longer duration of CPB increased mortality.

The second model explored associations of ECMO support variables and complications with mortality (**Table 5**). Use of left atrial cannulation and lower fraction of inspired oxygen concentration (FiO_2) at 24 h post-ECMO reduced and need for higher pump flow at 4 h post-ECMO, longer ECMO duration, and ECMO complications all increased mortality.

In the comprehensive multivariable model including both pre-ECMO and ECMO factors (**Table 6**), only older age (>26 days) lowered mortality. Genetic syndrome or congenital anomalies, comorbidities, pre-ECMO CA, pre-ECMO mechanical ventilation for >24 h, pre-ECMO bicarbonate infusion, longer duration of CPB, procedures of higher surgical complexity, longer ECMO duration and ECMO complications were all associated with increased mortality.

Table 5. Multivariable models of factors associated with mortality in patients using extracorporeal membrane oxygenation after failure to wean from cardiopulmonary bypass.

Variables	Odds Ratio	95% Confidence Interval	p-value
Model I: Pre-ECMO factors			
Demographic and baseline clinical characteristics			
Age (days)			<0.001
≤ 7	1.0	Reference group	-
> 7 and ≤ 26	0.793	0.603-1.042	0.096
> 26 and ≤ 159	0.541	0.409-0.715	<0.001
> 159	0.468	0.345-0.635	<0.001
Race (white)	0.783	0.646-0.948	0.012
Genetic syndrome or congenital anomalies	1.668	1.290-2.157	<0.001
Comorbidities	1.727	1.428-2.087	<0.001
Pre-ECMO cardiac arrest	1.596	1.161-2.194	0.004
Surgery details			
CPB time (min)			<0.001
≤ 174	1	Reference group	-
> 174 and ≤ 251	0.982	0.754-1.279	0.893
> 251 and ≤ 351	1.525	1.166-1.994	0.002
> 351	1.851	1.409-2.431	<0.001
RACHS-1 category			0.003
RACHS-1 1 to 3	1	Reference group	-
RACHS-1 4 to 6	1.449	1.159-1.810	0.001
RACHS not assigned	0.887	0.557-1.415	0.615
Pre-ECMO details			
Pre-ECMO MV duration>24h	1.611	1.319-1.968	<0.001
Pre-ECMO bicarbonate infusion	1.408	1.091-1.818	0.009
Model II: ECMO factors and complications			
ECMO factors			
Left atrium cannulation	0.659	0.494-0.879	0.005
ECMO pump flow at 4h after ECMO initiation (ml/kg/min)			<0.001
≤ 95	1	Reference group	-
> 95 and ≤ 115	1.296	0.985-1.704	0.064
> 115 and ≤ 141	1.529	1.161-2.014	0.003
> 141	1.827	1.379-2.421	<0.001
ECMO support duration (h)			<0.001
≤ 65	1	Reference group	-
> 65 and ≤ 104	0.937	0.711-1.234	0.641
> 104 and ≤ 169	1.732	1.319-2.273	<0.001
> 169	3.873	2.860-5.245	<0.001
On-ECMO details			
FiO2 at 24h after ECMO initiation (%)			0.001
≤ 25	1	Reference group	-
> 25 and ≤ 37	0.639	0.484-0.843	0.002
> 37 and ≤ 40	0.582	0.444-0.764	<0.001
> 40	0.711	0.533-0.948	0.020
Complications			
ECMO circuit complications	1.302	1.060-1.600	0.012
CNS complications	2.189	1.672-2.866	<0.001
Pulmonary hemorrhage	2.811	1.859-4.252	<0.001
Renal failure	1.962	1.428-2.696	<0.001
Hemofiltration required	1.823	1.457-2.280	<0.001

Model I: Candidate variables: age, race (white), genetic syndrome or congenital anomalies, comorbidities, pre-ECMO cardiac arrest, CPB time, DHCA, RACHS-1 category, pre-ECMO echocardiography, pre-ECMO MV duration>24h, pre-ECMO bicarbonate infusion
N= 1987; Hosmer and Lemeshow Test *p* value= 0.547; area under the curve= 0.691

Model II: Candidate variables: left atrium cannulation, cardiac and pulmonary failure indication group, ECMO pump flow at 4h, ECMO pump flow at 24h, ECMO support duration, on-ECMO invasive procedures, FiO2 at 24h after ECMO initiation, ECMO circuit complications, CNS complications, cardiac complications, pulmonary hemorrhage, cannulation/surgical site bleeding, hemolysis, disseminate intravascular coagulation, culture proven infection, renal failure, hemofiltration required, arterial pH <7.20, blood glucose >240 mg/dl, hyperbilirubinemia
N= 2011; Hosmer and Lemeshow Test *p* value= 0.331; area under the curve= 0.749

CNS: Central Nervous System; CPB: Cardio-Pulmonary Bypass; ECMO: Extra-Corporeal Membrane Oxygenation; FiO2: Fraction of inspired Oxygen; RACHS-1: Risk Adjusted Congenital Heart Surgery Score 1; MV: Mechanical Ventilation

Table 6. Comprehensive multivariable model of factors associated with mortality in patients using extracorporeal membrane oxygenation after failure to wean from cardiopulmonary bypass.

Variables	Odds Ratio	95% Confidence Interval	p-value
Demographic and baseline clinical characteristics			
Age (days)			<0.001
≤ 7	1.0	Reference group	-
> 7 and ≤ 26	0.802	0.601-1.069	0.132
> 26 and ≤ 159	0.558	0.416-0.750	<0.001
> 159	0.478	0.346-0.661	<0.001
Genetic syndrome or congenital anomalies	1.776	1.358-2.324	<0.001
Comorbidities	1.586	1.297-1.941	<0.001
Pre-ECMO cardiac arrest	1.675	1.200-2.338	0.002
Surgery details			
CPB time (min)			<0.001
≤ 174	1	Reference group	-
> 174 and ≤ 251	0.967	0.730-1.281	0.816
> 251 and ≤ 351	1.501	1.132-1.990	0.005
> 351	1.609	1.209-2.142	0.001
RACHS-1 category			0.004
RACHS 1 to 3	1	Reference group	-
RACHS 4 to 6	1.435	1.133-1.816	0.003
RACHS not assigned	0.745	0.451-1.231	0.251
Pre-ECMO details			
Pre-ECMO MV duration>24h	1.494	1.211-1.843	<0.001
Pre-ECMO bicarbonate infusion	1.419	1.084-1.857	0.011
ECMO factors			
ECMO support duration (h)			<0.001
≤ 65	1	Reference group	-
> 65 and ≤ 104	0.765	0.581-1.009	0.057
> 104 and ≤ 169	1.539	1.173-2.018	0.002
> 169	3.472	2.557-4.715	<0.001
Complications			
ECMO circuit complications	1.259	1.018-1.558	0.034
CNS complications	1.793	1.358-2.366	<0.001
Pulmonary hemorrhage	2.527	1.672-3.819	<0.001
Renal failure	1.698	1.232-2.341	0.001
Hemofiltration required	1.540	1.224-1.939	<0.001

Model: Candidate variables: age, race (white), genetic syndrome or congenital anomalies, comorbidities, pre-ECMO cardiac arrest, CPB time, RACHS-1 category, pre-ECMO MV duration>24h, pre-ECMO bicarbonate infusion, left atrium cannulation, ECMO pump flow at 4h, ECMO support duration, FiO2 at 24h after ECMO initiation, ECMO circuit complications, CNS complications, pulmonary hemorrhage, renal failure, hemofiltration required
N= 2024; Hosmer and Lemeshow Test *p* value= 0.538; area under the curve= 0.769

CNS: Central Nervous System; CPB: Cardio-Pulmonary Bypass; ECMO: Extra-Corporeal Membrane Oxygenation; RACHS-1: Risk Adjusted Congenital Heart Surgery Score 1; MV: Mechanical Ventilation

Discussion

Extracorporeal Membrane Oxygenation is used in many centers performing pediatric cardiac surgery to rescue children with refractory cardiopulmonary failure or CA after cardiac surgery (34, 40). ECMO has also been used to successfully bridge children failing to wean from CPB following cardiac surgery to survival. We demonstrate that, although mortality when ECMO is used to support children failing to wean from CPB is high (55%), it is similar to mortality reported for cardiac ECMO support of all indications (ELSO 2019 International Summary survival to discharge neonatal cardiac ECMO: 43%; pediatric cardiac ECMO: 52%) (34). Among our high-risk ECMO cohort, neonates, those with comorbid conditions, those undergoing complex congenital cardiac surgery, those requiring long duration of CPB, and those with ECMO complications, not surprisingly, had reduced survival. The use of ECMO to support children who fail to wean off CPB has increased significantly; however, survival has remained unchanged.

In a two-center report of post-operative ECMO use in children with biventricular CHD undergoing cardiac surgery, Chaturvedi et al reported improved survival in patients in whom ECMO was initiated in the operating room, some of whom failed to wean CPB, compared to ECMO initiated in the intensive care unit (64% vs. 29%) (41). They suggested that avoiding prolonged exposure to inadequate cardiac output and CA in post-

operative period improved outcomes for these children. Our analysis showed that ECMO used in the context of failure to wean from CPB in children undergoing cardiac surgery is associated with high mortality (55%). Poor outcomes in our study may be related to the inclusion of a broader variety of CHD diagnosis, including many with complex single ventricle CHD. The prior study included children who weaned CPB, but required ECMO for unstable status in the operating room. Reasons for failure to wean CPB, or if a period of separation from CPB occurred in our study cohort was not available to inform our analyses. Although our findings suggest that ECMO for failure to wean from CPB after pediatric cardiac surgery is associated poor survival, these patients face imminent mortality without ECMO support. Decisions regarding use of ECMO in children failing to wean from bypass have to be made rapidly, and often without optimal clinical and/or imaging information. ECMO deployment in these circumstances may provide an opportunity for a careful evaluation of reversible conditions that may be amenable for correction.

We found many pre-ECMO and pre-surgical factors associated with mortality. The increased odds of death associated with neonatal age, race, and genetic and non-cardiac comorbid conditions have been shown to be associated with poor outcomes when ECMO is used for other cardiac and non-cardiac indications (35, 43, 47, 52). These factors offer little opportunity for improvement. Similarly, the association of pre-surgical factors such as pre-ECMO cardiac arrest, mechanical ventilation, and need for correction of acidosis with increased mortality in our cohort, has been previously described both in cardiac ECMO and for children undergoing CHD surgery by the Society of Thoracic Surgeons, as factors associated with mortality (40).

Complex cardiac surgical procedures and longer CPB duration were both independently associated with mortality in our cohort. Prior reports of ECMO support following cardiac surgery for CHD have reported a high frequency of residual lesions in children requiring post-operative ECMO (48). These reports have also shown that prompt diagnosis and correction of residual lesions is essential to improve ECMO survival. (48). One could argue, that repair of these residual lesions at the time of the index operation may provide optimal hemodynamics for successful ECMO support. However, this would require long CPB duration or repeated exposures to CPB and may worsen outcomes for those who require post-operative ECMO support. (137) Decisions regarding duration of CPB should be made by the primary surgeon and surgical team after weighing the consequences of continuing CPB to correct a residual lesion or deploying ECMO to provide a period of stability and attempting correction at a later time. We did not find an independent association between an additional cardiac surgery on-ECMO and mortality. We expected to find this, as correction of residual lesions after CHD surgery during ECMO has been shown to be associated with improved outcomes (48). However, data on residual lesions after CHD surgery are not mandatory enterable information in ELSO Registry and thus subject to reporting bias.

Left atrial decompression with left atrial cannulation was identified as protective factor for mortality in the model that only including ECMO factors. Because ECMO does not decompress the left ventricle, draining the left atrium can reduce left ventricular distension allowing myocardial rest and recovery. Furthermore, it can also protect from lung injury due to cardiogenic pulmonary edema or hemorrhage from severe left atrial hypertension (69, 74). Even though statistical independence was not confirmed in the final model, we believe that in patients with left atrial hypertension could benefit from left-heart decompression. However, the association of left atrial decompression and improved survival should be interpreted cautiously as there is wide variability in the use of left atrial decompression among ECMO centers and some high-risk procedures (e.g. Norwood operation) may not need left atrial decompression. Another interesting finding of our study is the improved survival for patients receiving heart transplantation on-ECMO. Our findings are similar to the

improved survival described by Alsoufi et al (44). Thus, when there are no signs of recovery on ECMO support, early evaluation and listing for cardiac transplantation can be considered as an exit strategy.

ECMO complications in our study cohort were associated with increased mortality as shown in many previous reports of ECMO (44, 45, 47, 51, 53). Surgical site bleeding is an anticipated complication in patients supported with ECMO after a surgical procedure. Surgical site bleeding was frequent in our cohort and was seen in 47% of patients and was associated with increased mortality (51%). The incidence of surgical site bleeding in our cohort was higher than that reported by the ELSO registry for cardiac ECMO in neonates (26%) and children (25%) (33). The higher rate of surgical site bleeding in our study population may be related to increased risk of bleeding from fresh surgical incisions and residual anticoagulation from CPB. Reduction of surgical bleeding complications with aggressive modification of anticoagulation protocols, use of hemostatic agents, and surgical intervention for hemostasis are essential to improve outcomes for these patients.

We found that although the use of ECMO in patients failing to wean CPB increased over time, survival did not improve. Although speculative, increasing use of ECMO in patients undergoing complex cardiac surgical procedures and in patients with non-cardiac co-morbid conditions may have resulted in no improvement in survival over time.

Several important limitations should be considered when interpreting our analyses. Data reported to the ELSO registry are not specific to studying outcomes for patients supported for failure to wean from CPB, thus important confounders associated with survival may not have been collected. Both ICD and CPT codes do not adequately describe CHD and cardiac surgical procedures and thus may have led to misclassification of complexity. Data reported to ELSO do not contain specific information on the exact reason for failure to wean from bypass, presence and severity of residual surgical lesions after CHD surgery. Finally, the lack of short-term and long-term neurologic outcome data limits meaningful evaluation of survival. Despite these limitations, our study offers important information for assessing patients' prognosis and for future investigation in this high-risk ECMO population.

Conclusion

In conclusion, we found that in hospital mortality was high for children undergoing ECMO for failure to wean from CPB. Younger children, those with genetic abnormalities and comorbid conditions, those with more severe pre-operative illness, those undergoing complex cardiac surgical procedures had higher mortality. ECMO-factors including a longer support duration and on-ECMO complications are also independently associated with mortality. These data can guide prognostication in the high risk population and offer object data for counseling families. Left atrial decompression may improve survival in some patients, and early consideration of heart transplantation represents an important ECMO exit strategy in patients showing no signs of cardiac recovery.

Supplemental Table 1. Characteristics of previous studies addressing the topic of ECMO support for failure to wean from cardio-pulmonary bypass in children.

Author, year	Study design, setting and study period	Patients	Sample size No.	Patients FTW from CPB No. (%)	Age	Exclusion criteria	Outcome: Mortality No. (%)	Predictors / Risk factors for Mortality*
El Mahrouk AF 2019	Retrospective Single center (Jeddah, Saudi Arabia) 2001-2016	CHD patients underwent ECMO after cardiac surgery	113	NA	Median 3 months (range 4days-15 yrs)	Not defined	At discharge: 71 (63)	Univariate analysis ECMO duration (p=0.012) Renal failure (p=0.04) Stroke (p=0.003)
McKenzie JM 2017	Retrospective Single center (Melbourne, Australia) 2005-2014	Neonates underwent ECMO after cardiac surgery (within 30 days prior to ECMO)	110	40 (36)	Median 5 days (IQR 2-9)	Not defined	At discharge: 50 (45)	Multivariable model Protective factor: Gestational age of 39-40 weeks OR 0.27 (0.08-0.84)
Pourmoghadam KK 2015	Retrospective Single center (Orlando, USA) 2005-2013	CHD patients underwent ECMO Group 1: ECPR Group 2: FTW from CPB	39	20 (51)	Median 41 days (range 2-155) **FTW patients**: Median 32 days (range 2-155)	ECMO for acute myocarditis, ECMO not for ECPR or FTW purposes	At 30-days: 9 (23) At discharge: 12 (31) **FTW patients:** At 30-days: 4 (20) At discharge: 6 (30)	Multivariable predictive model SV physiology OR 21 (0.985-445), Initial AST on ECMO OR 1.008 (1.001-1.015), Bicarbonate 24 hours on ECMO OR 0.654 (0.450-0.951)
Peer SM 2014	Retrospective Single center (Washington DC, USA) 2003-2008	CHD patients underwent ECMO after cardiac surgery and survived at hospital discharge	25	5 (20)	Median 124 days (IQR 5-437	Not defined	[At three years: 5%. Assessed only in ECMO survivors at hospital discharge]	-
Agarwal HS 2014	Retrospective Single center (Vanderbilt, USA) 2005-2011	Cardiac patients underwent ECMO after cardiac surgery (within 7 days)	119	40 (52)	Median 12 days (IQR 6-79)	Not defined	At discharge: 49 (41)	Univariate analysis: Late detection of residual lesions (p=0.035) (vs early detection within 3 days)
Bath P 2013	Retrospective Single center (Ann Arbor, USA) 1999-2010	Neonates <3 kg Requiring ECMO after cardiac surgery	64	39 (61)	Median 7 days (IQR 4-9)	Age>30 days at ECMO initiation, ECMO at>7 days after cardiac surgery	At 30-days: 43 (67)	Multivariable predictive model Renal replacement therapy OR 4.3 (1.3-14.9)
Chrysostomou C 2013	Retrospective Single center (Pittsburgh, USA) 2006-2010	Cardiac patients underwent ECMO	95	31 (33)	Pediatric age	Not defined	At discharge: 26 (27) **FTW patients:** 7 (23) At follow-up (median 1.9 yrs): 33 (34)	Multivariable predictive model Chromosomal anomalies OR 8 (2-35) SV physiology OR 6 (3-33) Multiple ECMO runs OR 15 (4-42) Higher 24-hour ECMO flows OR 8 (4-22) Decreased lung compliance OR 5 (2-16) Need for plasma exchange OR 5 (3-18)

Sasaki T 2013	Retrospective Single center (Kanawaga, Japan) 2003-2011	Cardiac patients underwent ECMO after cardiac surgery	36	14 (39)	Median 64 days (range 0-1496)	Not defined	At discharge: 19 (53)	Univariate analysis SV physiology (p=0.019) Younger age (p=0.016) Arterial lactate at initiation of ECMO (p=0.007) Duration of ECMO (p=0.003) Pulmonary hemorrhage (p=0.002)
Kumar TKS 2010	Retrospective Single center (Washington DC, USA) 2003-2008	Cardiac patients underwent ECMO after cardiac surgery	58	19 (33)	Median 12 days (IQR 4-201)	Not defined	At discharge: 34 (59)	Multivariable predictive model SV physiology OR 4.09 (1.6-14.8) Duration of ECMO>10 days OR 18.2 (2.3-150.0) Lactate >4mmol/L OR 14.2 (2.0-118.0) Renal failure OR 9.8 (2.0-48.3)
Li-Fen Ye 2010	Case series Single center (Hangzou, China) 2007-2008	Cardiac patients underwent ECMO after cardiac surgery	4	1 (25)	Median 28 days (range 2-1460)	Not defined	At discharge: 2 **FTW patients:** 1	-
Lo Forte A 2010	Retrospective Single center (Berlin, Germany) 1991-2006	CHD patients underwent ECMO for intraoperative cardiac support	66	46 (70)	Mean 5.2 years (SD 4)	Not defined	At discharge: 30 (45)	Univariate analysis: Arterial lactate at initiation of ECMO (p=0.004) Duration of ECMO (p=0.003)
Alsoufi B 2009	Retrospective Single center (Toronto, Canada) 1990-2007	Cardiac patients underwent ECMO after cardiac surgery	180	83 (46)	Median 109 days (range 1-6168)	ECMO prior to cardiac surgery	At discharge: 112 (62) **FTW patients:** 50 (60)	Multivariable predictive model Renal failure OR 5.07 (1.03-24.95) Neurologic complications OR 14.4 (3.05-68.0) Duration of ECMO OR 1.19 (1.06-1.33) repeat ECMO run OR 13.6 (1.6-133.6) Protective factor: performing HT OR 0.28 (0.09-0.93)
Balasubramanian SK 2007	Retrospective Single-center (Leicester, UK) 1990-2003	CHD patients underwent ECMO after cardiac surgery	53	13 (25)	Median 105 days (range 1-3960)	Not defined	At discharge: 24 (45) **FTW patients:** 6 (46) At follow-up (mean 75 months): 33 (62)	Univariate analysis: Arrhythmia pre-ECMO (p<0.001) Arrhythmia after ECMO (p=0.001) Bleeding complications (p<0.001) Renal replacement therapy (p<0.001) Duration of ECMO (p=0.024) Cardiac Arrest after ECMO (p<0.001)
Morris MC 2004	Retrospective Single center (Philadelphia, USA) 1995-2001	Cardiac patients underwent ECMO in PICU	137	13 (9)	Median 4.7 days (range 1 day-42 yrs)	Not defined	At discharge: 84 (61) Post-operative patients: 53 (60)	Multivariable model: Age < 1 month OR 4.82 (1.38-16.8) Duration of MV prior to ECMO OR 1.44 (1.00-2.06) Renal of hepatic failure on-ECMO OR 6.06 (1.82-20.1)

CHD: Congenital Heart Disease; CPB: Cardio-Pulmonary By-pass; ECMO: Extra-Corporeal Life Support; ECPR: ECMO Cardio-Pulmonary Resuscitation; FTW: Failure To Wean; HT: Heart Transplant; IQR: Inter-Quartile Range; NA: Not Available; OR: Odds Ratio; PICU: Pediatric Intensive Care Unit; SV: Single Ventricle
*Statistical significance is expressed in terms of *p* value for univariate analysis and in terms of OR (CI 95%) for multivariable models

Project 4

Predict

Modeling severe functional impairment or death following ECPR in pediatric cardiac patients: planning for an interventional trial

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Abstract

Aim: We aimed to characterize extracorporeal CPR (ECPR) outcomes in our center and to model prediction of severe functional impairment or death at discharge.

Methods: All ECPR events between 2011-2019 were reviewed. The primary outcome measure was severe functional impairment or death at discharge (Functional Status Score [FSS] ≥16). Organ dysfunction was graded using the Pediatric Logistic Organ Dysfunction Score-2, neuroimaging using the modified Alberta Stroke Program Early Computed Tomography Score. Multivariable logistic regression was used to model FSS≥16 at discharge.

Results: Of the 214 patients who underwent ECPR, 182 (median age 148 days, IQR 14–827) had an in-hospital cardiac arrest and congenital heart disease and were included in the analysis. Of the 110 patients who underwent neuroimaging, 52 (47%) had hypoxic-ischemic injury and 45 (41%) had hemorrhage. In-hospital mortality was 52% at discharge. Of these, 87% died from the withdrawal of life-sustaining therapies; severe neurologic injury was a contributing factor in the decision to withdraw life-sustaining therapies in 50%. The median FSS among survivors was 8 (IQR 6-8), and only one survivor had severe functional impairment. At 6 months, mortality was 57%, and the median FSS among survivors was 6 (IQR 6-8, n=79). Predictive models identified FSS at admission, single ventricle physiology, extracorporeal membrane oxygenation (ECMO) duration, mean PELOD-2, and worst mASPECTS (or DWI-ASPECTS) as independent predictors of FSS≥16 (AUC=0.93) and at 6 months (AUC=0.924).

Conclusion: Mortality and functional impairment following ECPR in children remain high. It is possible to model severe functional impairment or death at discharge with high accuracy using daily post-ECPR data up to 28 days. This represents a prognostically valuable tool and may identify endpoints for future interventional trials.

Background and Significance

Extracorporeal cardiopulmonary resuscitation (ECPR) has been shown to improve survival in pediatric patients with in-hospital cardiac arrest. (62, 138, 139) The most recent guidelines for cardiopulmonary resuscitation include ECPR as a resuscitation strategy where staff and technical expertise are available, including in pediatric cardiac patients with in-hospital cardiac arrest. (1, 32) ECMO utilization as a resuscitative tool is steadily increasing over time.

In the current era, mortality and end-organ injury following ECPR remain high.(4, 35, 64–66) Among children with congenital heart disease, in-hospital mortality rate after ECPR ranges from 44 to 65%.[6,8–13] Additionally, survivors often experience organ failure and adverse neurologic outcome with variable degrees of neurologic dysfunction.(1, 4, 64–66) Among survivors of ECPR events in the THAPCA trial, ~29% of children <6 years of age experienced persistent severe cognitive deficits and 40% experienced at least moderate neurologic injury at 12 month follow-up.(83) It is well established that shorter low-flow duration, shockable cardiac rhythm, higher arterial pH and lower serum lactate are associated with improved survival.(140) However, predictors of severe neurologic impairment are poorly described in the pediatric population and model often do not include neuroimaging details.

The purpose of this work is to lay the groundwork for a future trial of therapeutic inhaled hydrogen gas (H2) following ECPR events. Our group has recently shown that administration of H2 during reperfusion following an experimental global ischemic injury significantly decreases the degree of neurologic and renal injury(100), in part through chemical reduction of the hydroxyl radical.(141) Currently, a phase I safety trial in adult patients is ongoing.(142) The purpose of this work was to characterize ECPR outcomes at our center, identify predictive factors for functional outcomes, and create a prediction model for meaningful outcomes that might serve as a future clinical trial outcomes.

Methods

Study design and population

The study was approved by the institutional review board of Boston Children's Hospital (BCH) (IRB P00034661) under exemption from informed consent. Consecutive cardiac patients undergoing ECPR between January 2011 and December 2019 were identified by retrospective review of an institutional ECMO database. Patients who underwent ECPR for out-of-hospital cardiac arrest or who did not have congenital heart disease were excluded. Patients undergoing multiple ECPR runs during the same admission were included, with data from only the first ECPR run included in the prediction model and the number of ECPR runs analyzed as an additional variable. Patient demographics, baseline clinical characteristics, and ECPR details were manually extracted by review of the electronic health record (EHR). The presence and details of surgical and catheter-based interventions, a subsequent cardiac arrest or ECMO use, heart transplantation or ventricular assist device (VAD) support was also adjudicated by manual chart review, supplemented by automated data extraction from a cardiology-specific database. Laboratory, hemodynamic, and ventilator variables through post-ECPR day 28 were automatically extracted from the EHR (SQL Developer, Oracle Corporation, Austin, Texas).

Categorization of organ dysfunction

A Pediatric Logistic Organ Dysfunction Score-2 (PELOD-2) (143) was computed daily during post-ECPR day 0-28 for each patient, or up to the day before death when death occurred before 28 days. This score ranges from 0 to 33 based on the level of organ dysfunction and includes the following variables: Glasgow Coma Scale (GCS), pupil reaction (both reactive/both fixed), lactate, mean arterial pressure, creatinine, PaO2/FiO2 ratio, PaCO2, invasive ventilation, white blood count (WBC), and platelets count. Following the PELOD-2 rules, the GCS included in the score for sedated and chemically-paralyzed patients was imputed as the patient's most recent unsedated GCS. Since the PaO2/FiO2 ratio in patients supported with ECMO is not reflective of lung function, we assigned a score of 1 to all patients while on ECMO.

Neuroimaging review and scoring

All brain CTs and MRIs performed between days 0-28 post-ECPR were independently evaluated by a neuroradiologist on the study team (A.D.). Hypoxic-ischemic injury was graded according to the modified Alberta Stroke Program Early Computed Tomography Score (mASPECTS(88)) for CT and its corresponding version for MRI (diffusion-weighted magnetic resonance imaging, DWI-ASPECTS(144)). The mASPECTS and the DWI-ASPECTS include the evaluation of intracerebral ischemia based on extension and territory, with the score ranging from 31 (no ischemic damage) to 0 (diffuse hypoxic-ischemic injury). Details regarding type, extension and location of cranial hemorrhages were separately collected. Hemorrhages were classified as follows: epidural hemorrhage (EDH), subdural hemorrhage (SDH), intraparenchymal hemorrhage (IPH), subarachnoid hemorrhage (SAH), and intraventricular hemorrhage (IVH). The most severe neuroimaging score for each patient and presence of hemorrhages were used for creation of a predictive score.

Functional status scoring

Functional status score (FSS) was computed at baseline (admission to the hospital and at 24h before cardiac arrest), discharge, and 6 month follow-up based on a detailed review of neurology notes, primary team notes, nursing notes and physical exam documentation by two independent investigators.[22,23] FSS is a clinical score that has been validated in children and evaluates 6 functional fields: mental status, sensory, communication, motor function, feeding, and respiratory function. Each field is scored 1-5 with a total score ranging from 6 to 30 points. Based on a previous correlation analysis, FSS was demonstrated to positively correlate with Pediatric Cerebral Performance Category (PCPC), with severe disability (PCPC=4) corresponding to a mean FSS=16.(146) For the purpose of our study, death was graded as FSS=31.

Outcome measures

The primary outcome was death or severe functional impairment at discharge, defined as FSS≥16. Secondary outcome measures were mortality at 28 days, in-hospital mortality, and mortality and FSS at 6 months.

Statistical analysis

Descriptive data are reported as absolute frequencies (percentages) for categorical variables, and as mean (standard deviation) or median (inter-quartile range) for continuous variables, as appropriate. Distributions were tested for normality using plotting and the Kolmogorov-Smirnov test. Demographic, clinical, and ECPR details were

compared among patients with unfavorable functional outcome at discharge (FSS≥16) and patients with more favorable neurological outcome (FSS<16). The Pearson-Chi-squared test was used to test categorical data, the Fisher's-exact test was used when expected counts were <5. The t-test and U-Mann Whitney test were used to test continuous variables based on distribution. Laboratory values were tested using the worst values at post-ECPR-day 0-1, as well as the worst value of each test within post-ECPR days 0 to 28, or up to death if this happened before day 28. Different multivariable binary logistic regression models were tested to identify the most accurate combination of independent predictors of FSS≥16 at discharge. All variables with a univariate p-value <0.1 at univariate analysis and those who were judged to be clinically related with the outcome were selected for inclusion in the multivariable model. Continuous variables were tested for collinearity and, if proven, only the clinically more meaningful variable or, if equally meaningful, the variable with lowest P-value was included in the model. Variables with >10% of missing data were excluded, except for the mASPECTS (or DWI-ASPECTS) which was considered a primary predictor. The log-log linearity assumption was tested for continuous variables, and those that did not meet the linearity assumption were categorized for inclusion in the model. A backward conditional strategy was used for entry and retention of variables in the model. A candidate variable was retained in the model if the p-value was <0.05. The Hosmer-Lemeshow test was used to test the goodness of fit of each model. All statistical analyses were performed using R Statistics (version 3.6.2., R Foundation, Vienna, Austria). Statistical significance was set at a two-sided p-value <0.05.

Results

Study population

Of the 214 patients who underwent ECPR at BCH between January 2011 to December 2019, 20 patients underwent ECPR for non-cardiac reasons, and 2 patients experienced an out-of-hospital cardiac arrest, leaving 182 patients included in the study. Demographic, clinical, and ECPR details are reported in **Table 1**.

Table 1. Demographic and clinical characteristics of patients according to FSS score at discharge

Variable	Total (N=182)	Up to moderate functional dysfunction FSS score < 16 (N =87)	Death or severe functional impairment FSS score ≥ 16 (N =95)	p-value
Age, days (median, IQR)	148 (14, 827)	164 (22, 1181)	110 (10, 420)	0.157
Gender, male, n (%)	104 (57)	52 (60)	52 (55)	0.493
Weight, kg (median, IQR)	4.9 (3.1, 11.3)	5.7 (3.4, 14.8)	3.8 (3.0, 9.3)	**0.033**
Primary cardiac diagnosis, n (%)				
Functionally single ventricle (non-HLHS)	37 (20)	15 (17)	22 (23)	
HLHS	34 (19)	14 (16)	20 (21)	
Tetralogy of Fallot	13 (8)	7 (8)	6 (6)	
DORV	12 (7)	5(6)	7 (7)	
Cardiomyopathy	11 (6)	8 (9)	3 (3)	
TGA	11 (6)	7 (8)	4 (4)	
Corrected TGA	8 (4)	3 (3)	5 (5)	
Aortic arch abnormality	7 (4)	3 (3)	4 (4)	
Myocarditis	7 (4)	6 (7)	1 (1)	0.362[#]
Ventricular septal defect	5 (3)	4 (5)	1 (1)	
Anomalous pulmonary veins	5 (3)	1 (1)	4 (4)	
Aortic stenosis	4 (2)	1 (1)	3 (3)	
Ebstein anomaly	2 (1)	1 (1)	1 (1)	
PA/IVS	2 (1)	1 (1)	1 (1)	
Truncus arteriosus	2 (1)	0 (0)	2 (2)	
Others	22 (11)	11 (14)	11 (12)	
SV physiology, n (%)	71 (39)	29 (33)	42 (44)	0.133
Genetic syndrome, n (%)	23 (13)	6 (7)	17 (18)	**0.026**

Within 48 hours post cardiac surgery, n (%)	67 (37)	34 (39)	33 (35)	0.544
FSS score at admission (median, IQR)	7 (6, 10)	6 (6, 8)	8 (7, 11)	**<0.001**
FSS score 24h prior to ECMO (median, IQR)	11 (7, 11)	9 (6, 11)	11 (8, 11)	**0.003**

No missing data. # Fischer's Exact test. HLHS: hypoplastic left heart syndrome; IQR: inter-quartile range; PA/IVS: pulmonary atresia with intact ventricular septum; SV: single ventricle; TGA: transposition of the great arteries

The median age at ECPR was 148 days (IQR 14–827); the median weight was 4.9 kg (IQR 3.1–11.3 kg). The most common specific anatomic diagnosis was hypoplastic left heart syndrome (HLHS). Seventy-one patients (39%) had single ventricle physiology and 23 (13%) had an underlying genetic syndrome. Thirty-seven percent (n=67) had cardiac surgery within 48 hrs of the event. The baseline median FSS score at hospital admission was 7 (IQR 6-10).

ECPR details, ECMO course, and outcomes

Details of cardiopulmonary resuscitation, ECMO, and CICU course are described in **Table 2**.

Table 2. ECPR, ECMO and CICU-stay characteristics of patients according to FSS score at discharge

Variable	Total (N=182)	Moderate or less functional dysfunction FSS score < 16 (N =87)	Death or severe functional impairment FSS score ≥ 16 (N =95)	p-value
Initial rhythm, n (%)				
Bradycardia	70 (38)	30 (34)	40 (42)	
Asystole	42 (23)	24 (28)	18 (19)	
Pulseless electrical activity	27 (15)	12 (14)	15 (16)	0.297#
Ventricular tachycardia	13 (7)	8 (9)	5 (5)	
Ventricular fibrillation	10 (5)	7 (8)	3 (3)	
Unknown	20 (11)	6 (7)	14 (15)	
Duration of CPR before ECMO cannulation (i.e. time to ECMO flow initiation), minutes (median, IQR)	25 (16, 40)	23 (11, 35)	29 (17, 40)	**0.035**
Worst laboratory values at ECMO day 0-1 (median, IQR)				
pH	7.13 (7.02, 7.24)	7.16 (7.04, 7.28)	7.08 (6.99, 7.21)	**0.021**
pCO2, mmHg	64 (54, 82)	60 (53, 72)	69 (57, 91)	**0.006**
pO2, mmHg	46 (34, 77)	50 (35, 77)	44 (34, 75)	0.546
Bicarbonate, mmol/L	15 (12, 19)	16 (12, 20)	14 (11, 19)	0.085
Lactate, mmol/L	14 (10, 18)	13 (9, 15)	16 (11, 20)	**0.001**
Creatinine, mg/dL	0.6 (0.4, 0.8)	0.6 (0.4, 0.8)	0.7 (0.5, 0.9)	**0.007**
Blood urea nitrogen, mg/dL	21 (15, 32)	20 (15, 28)	23 (16, 39)	**0.033**
Potassium, mEq/L	5.1 (4.5, 6.1)	4.8 (4.2, 5.8)	5.1 (4.7, 6.4)	**0.004**
Hemoglobin, g/dL	9.2 (7.8, 10.6)	9.2 (7.7, 10.6)	9.2 (7.8, 10.7)	0.990
White blood, count 10^9/L	4.4 (2.7, 7.4)	4.2 (2.9, 7.0)	4.7 (2.5, 8.1)	0.958
Platelets, count 10^9/L	58 (25, 84)	69 (29, 98)	48 (24, 79)	0.059
AST, U/L	189 (81, 542)	161 (80, 465)	221 (81, 555)	0.293
Total bilirubin, mg/dL	2.2 (1.4, 4.8)	2.1 (1.4, 4.3)	2.6 (1.4, 5.5)	0.378
aPTT, sec	104 (68, 150)	105 (70, 149)	103 (63, 151)	0.520
International normalized ratio	1.8 (1.5, 2.5)	1.7 (1.5, 2.4)	1.9 (1.6, 2.6)	0.055
VIS score at ECMO day 1 (median, IQR)	5 (0, 17)	5 (0, 14)	10 (0, 20)	**0.049**
PELOD-2 (median, IQR)				
on ECMO day 1	11 (10, 14)	11 (8, 12)	13 (11, 15)	**<0.001**
worst (maximum) days 0-28	12 (10, 14)	11 (9, 13)	13 (11, 15)	**<0.001**
median days 0-28	10 (7, 13)	8 (7, 11)	11 (9, 14)	**<0.001**
mean days 0-28	10 (8, 13)	8 (7, 11)	11 (9, 14)	**<0.001**
Subsequent cardiac arrest during CICU stay, n (%)	15 (8)	5 (6)	10 (10)	0.242
Subsequent ECMO during CICU stay, n (%)	18 (10)	2 (2)	16 (17)	**0.001#**
Intervention on ECMO, n (%)				
Heart transplant	6 (3)	3 (3)	3 (3)	1.000#
VAD implantation	6 (3)	4 (5)	2 (2)	0.428#
Other cardiac surgery	42 (23)	10 (11)	32 (34)	**<0.001**
Invasive procedure on ECMO	7 (4)	2 (2)	5 (5)	0.447#
ECMO duration, days (median, IQR)	4 (2, 8)	3 (2, 5)	7 (2, 12)	**0.001**
CICU length of stay, days (median, IQR)	30 (9, 55)	44 (28, 79)	10 (4-35)	**<0.001**

Missing data: pH n=1, pCO2 n=2, bicarbonate n=2, lactate n=3, creatinine n=1, potassium n=2, hemoglobin n=1, white blood n=1, platelets: n=1; AST, bilirubin n=6; aPTT n=15; INR n=1. # Fischer's Exact test. aPTT: activated partial thromboplastin; AST: aspartate transaminase; CPR: cardiopulmonary resuscitation; DORV: double outlet right ventricle; ECMO: Extracorporeal membrane oxygenation; FSS: functional system score; PCO2: partial pressure of carbon dioxide; PELOD: Pediatric Logistic Organ Dysfunction; VIS: Vasoactive-Inotropic Score; WBC: white blood cell count.

The first cardiac arrest monitored rhythm was predominantly bradycardia (38%), asystole (23%), and pulseless electrical activity (15%). The median CPR duration before ECMO cannulation (i.e. time to ECMO flow) was 25 min (IQR 16-40), and the median Vasoactive Infusion Score (VIS) on the first day of ECMO was 5 (IQR 0-17). The median PELOD-2 score on the first day of ECMO was 11 (10-14), the worst PELOD-2 score during days 0-28 was 12 (IQR 10-14). During the CICU stay, 15 patients (8%) experienced recurrent cardiac arrest, 18 (10%) underwent a second ECMO run, and 54 (30%) underwent a subsequent cardiac surgery while on ECMO, including 6 (3%) heart transplantations and 6 (3%) VAD placements. The median ECMO duration was 4 days (IQR 2-8); the median CICU stay was 30 days (IQR 9, 55).

Among the 182 included patients, 95 (52%) either died (n=94) or exhibited severe functional impairment at discharge (n=1). The mortality rate at 28 days was 35% (n=64/182), at discharge 52% (n=94/182) and at 6 months 57% (n=103/182). Among the 94 patients who died prior to hospital discharge, 82 (87%) died from the withdrawal of life-sustaining therapies. Among these 82 patients, severe neurologic injury was a contributing factor in the decision to withdraw life-sustaining therapies in 41 (50%). Among survivors at discharge (n=88), the median FSS was 8 (IQR 6-8), with a delta FSS since admission of 0 (IQR -1, 2) and only one surviving patient with severe functional disability (1%, FFS≥16). Among survivors at 6 months (n=79), the median FSS at 6 months was 6 (IQR 6-8), with a delta FSS since admission of 0 (IQR -1, 1), a delta FSS between discharge and 6 months of 0 (IQR -1, 0); only one patient had FSS≥16 (1%).

Neuroimaging findings and mASPECTS (or DWI-ASPECTS) score

Sixty percent of patients (n=110) underwent at least one brain CT or MRI after ECMO cannulation (total neuroimaging = 367). CTs accounted for 96% of the neuroimaging (n=315), and 4% were MRIs (n=52). Seventy-four percent of patients (n=81) demonstrated at least one pathologic finding including hypoxic-ischemic injury in 52 patients (47%) and a detectable brain hemorrhage in 45 (41%). Neuroimaging details are reported in **Table 3**.

Table 3. Characteristics of brain CT and MRI imaging after ECPR (n=110)

Variable*	**Total (N=110)**	**Up to moderate functional dysfunction FSS score <16 (N =47)**	**Death or severe functional impairment FSS score ≥ 16 (N =63)**	**p-value**
Presence of hypoxic-ischemic injury, n (%)	52 (47)	17 (37)	35 (56)	0.055
Hypoxic-ischemic injury territories (as per mASPECTS)				
Anterior cerebral artery	11 (10)	6 (9)	5 (6)	0.529#
Middle cerebral artery	32 (29)	13 (28)	19 (30)	0.830
Caudate	12 (11)	4 (5)	8 (8)	0.134
Insula	4 (0)	3 (6)	1 (2)	0.310#
Lentiform nucleus	12 (11)	6 (13)	6 (9)	0.562
Internal capsule	2 (0)	1 (2)	1 (2)	1.000#
Thalamus	7 (6)	4 (9)	3 (5)	0.452#
M1-M6	20 (18)	8 (17)	12 (19)	0.825
Posterior cerebral artery	7 (6)	3 (6)	4 (6)	1.000#
Diffuse hypoxic-ischemic injury	21 (19)	3 (6)	18 (29)	**0.004**
Worst (minimum) mASPECTS (or DWI-ASPECTS) during the CICU stay (median, IQR)	31 (23, 31)	31 (28, 31)	30 (0, 31)	**0.011**
Presence of hemorrhage, n (%)	45 (41)	15 (33)	30 (46)	0.152
Hemorrhage type, n(%)				
SDH	21 (19)	6 (13)	15 (24)	

EDH	1 (0)	0 (0)	1 (2)	
IPH	3 (0)	2 (4)	1 (2)	
SAH	5 (1)	1 (2)	4 (6)	
IVH	2 (0)	0 (0)	2 (4)	0.386#
IPH+SDH	6 (1)	3 (6)	3 (6)	
IPH+IVH	1 (0)	1 (2)	0 (0)	
IPH+SAH+IVH	2 (0)	0(0)	2 (4)	
IVH+SDH	3 (0)	1 (2)	2 (4)	
Number of hemorrhage locations (median, IQR)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.118
Combined lesion (ischemia and hemorrhage), n (%)	17 (15)	5 (11)	12 (19)	0.245

*The most severe neuroimaging for each patient was used for analysis. # Fischer's Exact test. mASPECTS: modified Alberta Stroke Program Early Computed Tomography Score; EDH: epidural hemorrhage; IPH: intraparenchymal hemorrhage; IVH: intra ventricular hemorrhage; M1-M6: MCA regions (M1 anterior MCA cortex, M2: MCA cortex lateral to the insular ribbon; M3: posterior MCA cortex; M4, M5, M6: anterior, lateral and posterior MCA territories, respectively); SAH: subarachnoid hemorrhage; SDH: subdural hemorrhage.

Comparison of patients based on functional outcomes at discharge

A comparison of the two groups based on FSS at discharge (FSS<16 vs FSS≥16) is outlined in **Tables 1-3**. Patients with FSS≥16 at discharge had significantly lower weight at time of ECPR (P=0.033) and a higher prevalence of a genetic syndrome (P=0.026) (**Table 1**). Patients with FSS≥16 at discharge also had a significantly higher FSS at admission as well as prior to ECMO (P=<0.001 and P=0.003, respectively). Age, gender, primary diagnosis, single ventricle physiology, and post-cardiac surgery status did not differ significantly between groups.

Patients who had unfavorable outcome experienced a longer CPR duration prior to ECMO cannulation (P=0.035) without significant differences in the initial documented rhythm (**Table 2**). On post-ECPR day 0-1, patients with unfavorable outcomes had a significantly lower arterial pH (P=0.021), as well as higher pCO2 (P=0.006), lactate (P=0.001), creatinine (P=0.007), blood urea nitrogen (P=0.033), potassium (P=0.004), VIS (P=0.049) and PELOD-2 scores (P<0.001). The worst laboratory values during the CICU stay were not significantly different between the two cohorts (**Supplemental Table 1**). Patients with poor outcome more frequently underwent an additional ECMO run or a cardiac surgery while on ECMO (P=0.002 and P<0.001, respectively). The worst, median, and mean PELOD-2 score during the CICU stay were significantly higher in patients with FSS≥16 at discharge (all P<0.001). ECMO duration and CICU length of stay were also significantly longer in patients with unfavorable neurologic outcomes.

While the presence and location of hypoxic-ischemic injury on neuroimaging did not significantly differ between the groups, the presence of a diffuse hypoxic-ischemic injury was significantly more frequent in patients with death or FSS≥16 at discharge (**Table 3**). The worst mASPECTS (or DWI-ASPECTS) score during the CICU stay was significantly lower (more severe injury) in patients with worse outcomes.

Predictive models for severe functional impairment at discharge

Models predicting severe functional impairment or death (FSS≥16) that included only the PELOD-2 score exhibited AUC of ~0.70 (**Table 4, Figure 1**). Those including PELOD-2 with additional candidate clinical variables had an AUC of ~0.88. Models that included PELOD-2, clinical variables, and mASPECTS (or DWI ASPECTS) along with the presence of brain hemorrhage reached an AUC of 0.90-0.93 (**Table 4**, **Figure 1**). The most accurate prediction model of outcome at discharge (AUC=0.932) is reported in **Table 5**, and identifies the FSS at admission, single ventricle physiology, ECMO duration, mean PELOD-2 (D0-28 of ECMO), and mASPECTS (or DWI-ASPECTS) score as independent predictors of unfavorable neurologic outcome. The same model predicted poor outcome at 6 months with an AUC 0.924 (**Table 5, Supplemental Table 2**).

Table 4. Multivariable logistic regression modeling for predition of severe functional impairment at discharge (FSS ≥16)

Model	N	HL test	Sensitivity	Specificity	AUC	95% CI
PELOD-2						
at ECMO day1	182	0.807	0.66	0.63	0.705	0.631-0.779
worst (maximum) days 0-28		0.504	0.56	0.70	0.695	0.619-0.770
median days 0-28		0.064	0.63	0.59	0.715	0.642-0.789
mean days 0-28		0.178	0.56	0.70	0.715	0.642-0.789
PELOD-2 + other clinical variables*	148					
at ECMO day1		0.606	0.80	0.79	0.889	0.838-0.941
worst (maximum) days 0-28		0.783	0.80	0.75	0.885	0.832-0.938
median days 0-28		0.647	0.82	0.81	0.882	0.826-0.937
mean days 0-28		0.844	0.81	0.82	0.879	0.823-0.935
PELOD-2 without GCS + neuroimaging (mASPECTS or DWI ASPECTS and hemorrhage) + other clinical variables*						
at ECMO day1		0.971	0.76	0.87	0.919	0.869-0.969
worst (maximum) days 0-28	110	0.885	0.78	0.87	0.902	0.846-0.958
median days 0-28		0.969	0.81	0.87	0.930	0.884-0.977
mean days 0-28		0.962	0.83	0.88	0.931	0.884-0.977

*Other clinical variables are: weight, genetic syndrome, single ventricle physiology, FSS at admission, duration of CPR prior to cannulation (i.e. time to ECMO flow initiation), pH at day 0-1, bicarbonate at day 0-1, potassium at day 0-1, INR at day 0-1, VIS at day 0-1, further ECMO run, recurrent cardiac arrest, cardiac surgery on-ECMO, ECMO duration.
AUC: area under the curve; DWI: diffusion-weighted magnetic resonance imaging; ECMO: extracorporeal membrane oxygenation; GCS: Glasgow coma score; HL: Hosmer Lemeshow; mASPECTS: Alberta Stroke Program Early Computed Tomography Score: PELOD-2: Pediatric logistic organ dysfunction score-2.

Figure 1. Receiver operating characteristics curves of models predicting death or poor functional outcome at discharge and at 6-months.

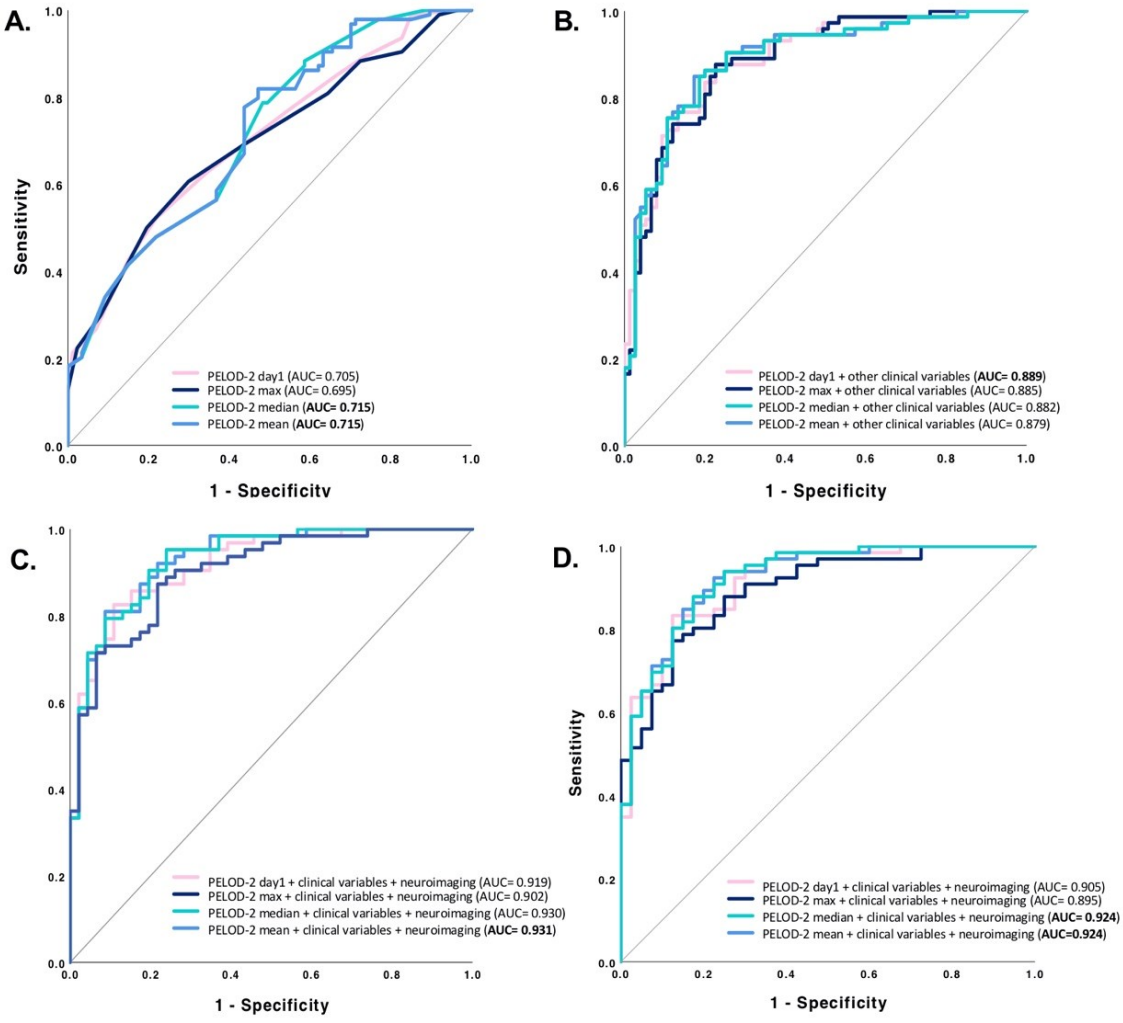

Table 5. Most accurate multivariable logistic regression model for the prediction of severe functional impairment at discharge (FSS ≥16) and at 6 months

Variables	Odds Ratio	95% Confidence Interval	p-value
Death or severe functional impairment at discharge			
FSS at admission	2.134	1.426 – 3.195	<0.001
Single ventricle physiology	3.930	1.119 - 13.805	0.033
ECMO duration	1.238	1.092 -1.404	0.001
PELOD-2 without GCS, mean day 0-28	1.540	1.208 – 1.964	<0.001
mASPECTS or DWI-ASPECTS, worst	0.875	0.817 – 0.937	<0.001
Death or severe functional impairment at 6 months			
FSS at admission	1.997	1.360 – 2.932	<0.001
Single ventricle physiology	3.417	1.000 – 11.713	0.050
ECMO duration	1.214	1.075 -1.371	0.002
PELOD-2 without GCS, mean day 0-28	1.466	1.162 – 1.849	0.001
mASPECTS or DWI-ASPECTS, worst	0.875	0.790 – 0.930	<0.001

Model predicting severe neurologic status at discharge: N=110, Hosmer Lemeshow test =0.969, **AUC=0.931**.
Model predicting severe neurologic status at 6 months: N=110, Hosmer Lemeshow test =0.590, **AUC=0.924**.

Candidate variables were: weight, genetic syndrome, single ventricle physiology, FSS at admission, duration of CPR prior to cannulation (i.e. time to ECMO flow initiation), pH at day 0-1, bicarbonate at day 0-1, potassium at day 0-1, INR at day 0-1, VIS at day 0-1, mean PELOD-2 without GCS days 0-28, worst mASPECT or DWI-ASPECTS, further ECMO run, recurrent cardiac arrest, cardiac surgery on-ECMO, ECMO duration.
DWI: diffusion-weighted magnetic resonance imaging; ECMO: extracorporeal membrane oxygenation; FSS: functional status scale; GCS: Glasgow coma score; mASPECTS: Alberta Stroke Program Early Computed Tomography Score: PELOD-2: Pediatric logistic organ dysfunction score-2.

Discussion

We have shown in a single center cohort that 52% of cardiac patients undergoing ECPR died or experienced severe functional impairment at the time of hospital discharge. Among the patients who died prior to hospital discharge, the majority died from the withdrawal of life-sustaining therapies, among whom severe neurologic injury was a contributing factor in 50%. We modeled mortality (as FSS≥16) prior to discharge and unfavorable neurologic outcome at 6 months with remarkable accuracy using FSS on admission, detailed scoring of both organ dysfunction and neurologic injury and other clinical characteristics using data available up to 28 days post-arrest. Remarkably, survivors at 6 months had a FSS median score of 6 (IQR 6-8), which corresponds to a good cerebral performance by PCPC categories.(146)

Previous studies have attempted to predict poor neurologic outcome including death in adult populations after cardiac arrest or ECPR, while limited modeling attempts exist in the pediatric population. Adult models have been shown to successfully predict a CPC ≥3 at discharge with a prediction accuracy based on AUC ranging from 0.700 to 0.877.(86–89) Notably, Youn included both neuroimaging and EEG details in their predictive model, reaching a prediction accuracy of 0.855.(90) A similar approach was used by Yang following pediatric cardiac arrest, including blood gas analysis and specific CT findings (gray to white matter ratio and ambient cistern effacement) in a model predicting PCPC >3 at discharge, reaching an AUC of 0.897. Brain MRI has been shown to be predictive of unfavorable neurologic outcome in pediatric patients after in-hospital or out-of-hospital cardiac arrest.(92–94) However, data modeling of death or severe neurologic impairment using models that include neuroimaging in the pediatric ECPR population are currently missing.

The survival rate that we describe here is on par with results from the THAPCA trial and other studies of ECMO rescue of in-hospital pediatric cardiac arrest.(62, 83, 147, 148) The variables that we identified as associated with poor outcome included single ventricle physiology and baseline FSS. The previously described association of poor outcomes with single ventricle physiology may be related to inefficient circulation during CPR, compounded

ischemia following cardiopulmonary bypass, small patient size, and other colinear risk factors. We also demonstrate that a higher PELOD-2 score, a validated measure of end organ dysfunction, is correlative with poor outcomes, especially when combined with neuroimaging details. Whether or not this association is modifiable through the amelioration of single score components (e.g. renal and cerebral injury by hydrogen breathing) can only be determined in a prospective trial. However, given that acute renal failure is known to be an independent risk factor for mortality in this clinical situation,(149) it is conceivable that removing this risk factor may improve survival.

The model that we developed was remarkable for its accuracy in predicting mortality at discharge (i.e. FSS≥16). There were several methodologic choices that account for this. First, we used FSS to evaluate patients at baseline and at follow-up, which is a granular and objective score that may be more discriminatory than the often used POPC/PCPC scoring system.(146) Additionally, the inclusion of FSS at admission in the model (and with that a pre-existing functional impairment) improved model efficiency in identifying and weighting real associations with post-ECPR outcome. Second, as described in other populations following cardiac arrest(90), we found that the inclusion of neuroimaging within the predictive model significantly improved its performance. Unlike prior efforts that have dichotomized neuroimaging findings (e.g. severe injury vs not), we used a validated score for grading the level of hypoxic-ischemic injury, the mASPECTS (or ASPECTS-DWI) score, as well as a quantification of brain hemorrhage. Incorporating this granularity into the model allowed us to further account for more subtle differences in neuroimaging, improving the prognostic value of the model.

Our study has several limitations. First, the study was retrospective, such that FSS was scored by a third party based on interpretation of clinical notes rather than by the examiner in real-time. Data missingness was low but not absent. Second, we chose to dichotomize the FSS in order to improve model accuracy, such that more granular differences in outcome were lost. Third, EEG data was not incorporated into the model and may be additive to these data (although perhaps colinear with neuroimaging findings). Finally, the present study was performed at a single, high volume center and did not include an external validation cohort, limiting its implications at other centers. Center-specific nuances are likely particularly important in this study. For example, low-flow time – known to be a significant predictor of outcomes in this setting (150) - was more brief and homogenous in our cohort, notably falling out of our predictive model. This may affect the generalizability of our model to other centers with fewer resources (e.g. a 24/7 in-house cardiovascular surgical trainees) or ECMO expertise. Finally, the majority of patients in our dichotomized outcome died, such that our model was pragmatically one of mortality. In the future, it will be important to validate our model prospectively at multiple centers. With improved power, it may eventually be possible to create a model for the FSS score, or even specified components of the score, permitting a more granular prediction of neurologic outcome.

Conclusion

In conclusion, mortality following cardiac ECPR in children remains high, and neurologic injury is an important component of this mortality. It is possible to model severe functional impairment or death at discharge and 6 months with high accuracy using data in the month following the event, representing a prognostically valuable tool and identifying variables to be examined in a future interventional trial.

Supplemental Table 1. Worst laboratory values during CICU-stay of patients according to FSS score at discharge

Variable	Total (N=182)	Up to moderate functional dysfunction FSS score < 16 (N =87)	Death or Severe functional impairment FSS score ≥ 16 (N =95)	P-value
Worst laboratory values days 0-28 (median, IQR)				
pH	7.12 (7.02, 7.24)	7.11 (7.03, 7.23)	7.14 (7.00, 7.25)	0.946
pO2, mmHg	46 (34, 77)	41 (33, 73)	53 (35, 80)	0.150
pCO2, mmHg	64 (54, 82)	68 (56, 88)	61 (53, 77)	0.071
Bicarbonate, mmol/L	15 (12, 19)	15 (12, 20)	15 (12, 19)	0.835
Lactate, mmol/L	14 (10, 18)	14 (11, 20)	13 (9, 17)	0.134
Creatinine, mg/dL	0.6 (0.4, 0.8)	0.6 (0.4, 0.9)	0.6 (0.4, 0.8)	0.211
Blood urea nitrogen, mg/dL	21 (15, 32)	24 (16, 33)	21 (14, 30)	0.128
Potassium, mEq/L	5.1 (4.5, 6.1)	5.1 (4.6, 6.2)	5.0 (4.5, 5.9)	0.110
Hemoglobin, g/dL	9.2 (7.8, 10.6)	9.2 (7.5, 10.8)	9.2 (8.0, 10.4)	0.625
White blood, count 10^9/L	4.4 (2.7, 7.4)	4.5 (2.9, 7.0)	4.2 (2.7, 8.3)	0.972
Platelets, count 10^9/L	58 (25, 85)	54 (24, 82)	62 (27, 87)	0.546
AST, U/L	189 (81, 542)	222 (87, 567)	147 (75, 394)	0.057
Total bilirubin, mg/dL	2.2 (1.4, 4.8)	2.4 (1.6, 4.8)	2.1 (1.2, 4.9)	0.301
aPTT, sec	104 (68, 150)	105 (70, 149)	102 (64, 150)	0.099
International normalized ratio	1.8 (1.5, 2.5)	1.8 (1.5, 2.4)	1.9 (1.5, 2.7)	0.167

No Missing data. aPTT: activated partial thromboplastin; AST: aspartate transaminase; PCO2: partial pressure of carbon dioxide; WBC: white blood cell count.

Supplemental Table 2. Multivariable logistic regression modeling for predition of severe functional impairment at 6 months (FSS ≥16)

Model	N	HL test	Se	Sp	AUC	95% CI
PELOD-2 without GCS + neuroimaging (mASPECTS or DWI ASPECTS and hemorrhage) + other clinical variables*	110					
at ECMO day1		0.905	0.73	0.85	0.915	0.862-0.969
worst (maximum) days 0-28		0.554	0.75	0.85	0.895	0.837-0.954
median days 0-28		0.905	0.76	0.91	0.924	0.873-0.974
mean days 0-28		0.590	0.76	0.91	0.924	0.873-0.974

*Other clinical variables are: weight, genetic syndrome, single ventricle physiology, FSS at admission, duration of CPR prior to cannulation (i.e. time to ECMO flow initiation), pH at day 0-1, bicarbonate at day 0-1, potassium at day 0-1, INR at day 0-1, VIS at day 0-1, further ECMO run, recurrent cardiac arrest, cardiac surgery on-ECMO, ECMO duration.

AUC: area under the curve; DWI: diffusion-weighted magnetic resonance imaging; ECMO: extracorporeal membrane oxygenation; GCS: Glasgow coma score; HL: Hosmer Lemeshow; mASPECTS: Alberta Stroke Program Early Computed Tomography Score: PELOD-2: Pediatric logistic organ dysfunction score-

Project 5

Treat

Left atrial decompression in pediatric patients supported with ECMO for failure to wean from cardiopulmonary bypass: a propensity-weighted analysis

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Abstract

Background: Left atrial (LA) decompression on Extracorporeal membrane oxygenation (ECMO) can reduce left ventricular distension allowing myocardial rest and recovery, and protect from lung injury secondary to cardiogenic pulmonary edema. However, clinical benefits remain unknown. We sought to evaluate the association between LA decompression and in-hospital adverse outcome (mortality, transplant on-ECMO, or conversion to ventricular-assist-device) in patients who failed to wean (FTW) from cardiopulmonary bypass (CPB) using a propensity-score to adjust for baseline differences.

Methods and Results: Children (<18y) with biventricular physiology supported with ECMO for FTW from CPB after cardiac surgery during 2000 through 2016 reported to the Extracorporeal Life Support Organization's Registry were included. Inverse-probability-of-treatment-weighted logistic regression was used to test the association between LA decompression and in-hospital adverse outcome. Of the 2,915 patients supported with VA-ECMO for FTW from CPB, 1,508 had biventricular physiology and 279 (18%) underwent LA decompression (LA+). Genetic and congenital abnormalities (p=0.001), pulmonary hypertension (p=0.010) were less and baseline arrhythmias (p = 0.022) were more frequent in LA+ patients. LA+ patients had longer pre-ECMO mechanical ventilation and CBP-time (p<0.001), and used aortic-cross-clamp (p=0.001) more frequently. Covariates were well-balanced between the propensity-weighted cohorts. In-hospital adverse outcome rate was 47% in LA+ patients and 51% in the others. Weighted multivariable logistic regression showed LA decompression to be protective for in-hospital adverse outcome (adjusted OR 0.775 [CI 0.644-0.932]).

Conclusions: LA decompression independently decreased the risk of in-hospital adverse outcome in pediatric VA-ECMO patients who FTW from CPB, suggesting that these patients may benefit for LA decompression.

Background and Significance

Extracorporeal membrane oxygenation (ECMO) provides mechanical circulatory support for resuscitation in children who experienced severe acute cardiac failure (33). In the setting of a failing heart and increased left ventricular (LV) afterload secondary to ECMO, the LV end-diastolic volume and pressure can increase, reducing transmural myocardial perfusion and impairing myocardial function and recovery. Left atrial (LA) decompression, either transcatheter or surgical, has been described as a successful strategy for decreasing the left heart pressure in adults and pediatric patients by reducing the LV distension, decreasing the LV wall stress facilitating myocardial rest and recovery (69–75). Furthermore, LA decompression may protect from lung injury secondary to cardiogenic pulmonary edema or pulmonary hemorrhage when severe LA hypertension is present (69, 70, 72, 74).

Different techniques have been described to decompress the left heart in patients supported with ECMO. In patients with central cannulation, addition of a LA cannula through one of the pulmonary veins (or less frequently addition of a pulmonary artery cannula) is the most diffused approach(76–78). In patients with peripheral ECMO or when left atrial cannulation is not anatomically possible, transcatheter or surgical atrial septostomy are the preferred options(73, 74, 76, 77). Finally, in appropriately sized patients, a synergic combination of ECMO with a temporary, minimally invasive, percutaneously implanted intracorporeal left ventricular assist device (i.e. Impella) has been recently described as a valuable alternative(76, 77). Since the LA decompression is not universally done in children on ECMO, and procedure can be associated with adverse events, the benefits of LA decompression need to be defined (73, 76, 77). With the present study, we sought to define the benefit of LA decompression in terms of in-hospital outcome in a cohort of pediatric patients who were supported on VA-ECMO for failure to wean (FTW) from cardiopulmonary bypass (CPB) after cardiac surgery.

In a previous Extracorporeal-Life-Support-Organization (ELSO) Registry analysis, we evaluated a large cohort of children with congenital or acquired heart disease who underwent open-heart surgery and failed to wean from CPB, describing their in-hospital mortality likelihood and associated risk factors (151). In this study, we found that, among ECMO-related factors, LA-cannulation was protective against in-hospital mortality. Although LA-cannulation was not retained in the final model when all the other investigated factors were added, we believe this may have been influenced by the significant number of patients with univentricular physiology included in the study, who did not need a LA decompression because of the underlying surgical anatomy. Therefore, we performed a sub-group analysis of the previously described cohort, including only patients with biventricular physiology and investigating the specific association between LA decompression and in-hospital outcome. A propensity score weighting approach was used to address the existence of selection biases before the intervention.

Methods

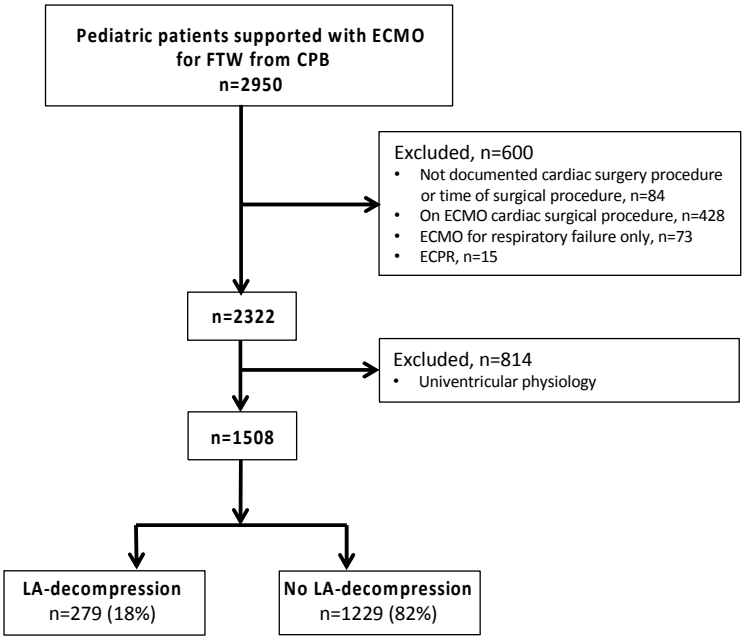
Study Population

We included children (age <18 years) with biventricular physiology who underwent an open-heart surgical procedure and required ECMO for FTW from CPB and were reported to the ELSO-Registry during the period 2000-2016. Patients were excluded if were already on ECMO at the time of surgery, had no documented cardiac surgical procedure or time of surgical procedure, required ECMO for isolated respiratory failure or to support cardiopulmonary resuscitation (ECPR), or had univentricular physiology (**Figure 1**).

Data Source, Collection and Categorization

Data were extracted from the ELSO Registry. Member centers report data on voluntary basis, after approval by their local Institutional Review Board Data user agreement between ELSO and member centers allows release of limited de-identified datasets for research purposes, waiving the need for regulatory approval. The present study qualified for human subjects research exemption by Boston Children's Hospital IRB (IRB-P00035751). Data extracted included baseline demographics and clinical characteristics, cardiac surgical procedure details, pre-ECMO support variables, ECMO support details and ECMO-complications. Cardiac surgical procedures were categorized based on complexity, using the Risk-Adjusted-Congenital-Heart-Surgery-1 (RACHS-1) method (136).

Figure 1. Flow chart of patients' selection.



Predictors and outcome measures

Our primary predictor was the LA decompression (i.e. LA-cannulation, transcatheter atrial septostomy, or surgical atrial septostomy on ECMO). Of note, timing of LA decompression is not included in the ELSO Registry. Our primary outcome measure was any in-hospital adverse outcome, defined as any one of: in-hospital mortality, transplant or conversion to VAD while on ECMO. Secondary outcome measures were ECMO duration and successful weaning off ECMO.

Statistical analysis

Descriptive data are reported as frequencies and percentages for categorical variables, median and inter-quartile range (IQR; 25^{th}-75^{th} percentile) for continuous variables due to distribution characteristics. Given the observational non-randomized nature of this study, significant baseline differences may exist between patients who underwent LA decompression (LA+) and patients who did not (LA-), which may influence the risk analysis. To assess the existence of these selection biases, demographic and clinical pre-ECMO details were compared between LA+ and LA- patients. The Pearson chi square test was used to compare categoric data before weighting; the Fisher

exact test was used when expected count in > 20% of cells was <5. The Mann-Whitney U test was used to compare continuous data. Since significant differences between LA+ and LA- patients were identified, a propensity-weighted approach was chosen to perform a balance adjustment of these biases. In particular, an inverse probability of treatment weighting based on a propensity score was used to weight demographic and clinical baseline differences between LA+ and LA- patients (152, 153). To compute the inverse probability of treatment weights, we estimated each patient's propensity to undergo LA decompression using a logistic regression model with the LA decompression as dependent variable, that included predictor variables selected based on their univariate associations with the treatment ($p<0.1$) and their *a priori* probability of confounding the relationship between LA decompression and mortality. The following baseline variables were defined as candidate to be included in this model: age, race (white), genetic syndrome, other congenital anomalies, prematurity, baseline cardiac conditions as arrhythmias, pulmonary hypertension, and cardiomyopathy, baseline respiratory, neurologic, renal, gastroenterological, infectious endocrine-metabolic diseases, coagulation defects or hemorrhages, pre-operative cardiac arrest, RACHS-1 score, CBP-time, use of aortic cross clamp, use of deep hypothermic circulatory arrest, pre-ECMO vasoactive support. Candidate variables for this model were tested for collinearity; age and weight were found to be collinear thus only age was used for modeling. The predicted probability of the model was saved as "propensity score"; the "inverse probability of treatment propensity score" was then computed assigning LA+ patients a weight of *1/propensity score* and LA- a weight of *1/(1−propensity score)* (153). The performance of the score in balancing the baseline differences between the two groups was confirmed by weighted logistic regression (with LA decompression as dependent variable, Table 1).

Once a balance was confirmed, LA decompression was tested as a predictor of mortality in two weighted logistic regression models. The first model tested the unadjusted relationship with the outcome; the second model was then adjusted for other potential predictors of mortality. Candidate variables for inclusion in the adjusted model were selected from the univariate weighted analysis comparing survivors and non-survivors. All variables with a univariate p value<0.1 were selected for inclusion in the multivariable model. No candidate variables had >10% of missing data, so all of them were included. A backward conditional strategy was used to reach the final model. All statistical analyses were performed using R statistics (version 3.6.2., R Core Team, R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at a two-sided p value <0.05.

Results

Study population

Of the 2,915 patients who were supported with ECMO for FTW from CPB during the study period, 1508 met the inclusion criteria (**Figure 1**). Of these, 279 (18%) patients underwent LA decompression (LA cannulation n=269, transcatheter=4 or surgical atrial septostomy n=9). One-thousand two-hundred and sixty-four patients (245 LA+, 1019 LA-) had available data to compute the propensity score and were therefore included in the weighted logistic regression analysis (Table 1).

Table 1 summarizes the demographic and clinical characteristics of the population, as well as differences between LA+ and LA- patients before and after the propensity-weighting. LA+ patients were less likely to have a diagnosis of genetic syndrome or congenital anomalies (p=0.001) or a diagnosis of pulmonary hypertension

(p=0.010), and more likely to have baseline arrhythmias (p=0.022). There were no other significant differences in terms of comorbidities at baseline. In terms of pre-ECMO support, LA+ patients had longer mechanical ventilation pre-ECMO (0.018). As for surgical characteristics, LA+ patients required longer CBP time (p<0.001) and more commonly underwent aortic-cross-clamp (p=0.001). Once the newly computed propensity score was used to weight the comparison analysis (**Table 1**, on the right), no significant differences persisted between the groups.

Table 1. Demographic, baseline clinical and pre-ECMO characteristics according to left atrial decompression, before and after Inverse Probability of Treatment Weighting

Variable	Cohort before Inverse Probability of Treatment Weighting			Cohort after Inverse Probability of Treatment Weighting		
	Left atrial decompression (n=279)	No left atrial decompression (n=1229)	p value †	Left atrial decompression (n=245)	No left atrial decompression (n=1019)	p value ‡
Age (days), median (IQR)	64 (10-214)	46 (8-193)	0.179	64 (9-220)	46 (8-189)	0.648
Weight (kg), median (IQR)[a]	4.0 (3.3-6.6)	3.8 (3.1-6.3)	0.076	4.0 (3.3-6.7)	3.8 (3.1-6.2)	0.919
Race, white, n (%)[b]	158 (58)	688 (58)	0.888	142 (58)	594 (58)	0.541
Comorbid conditions, n (%)						
Genetic syndrome or other congenital anomalies	32 (11)	244 (20)	**0.001**	29 (12)	202 (20)	0.304
Prematurity*	26 (9)	100 (8)	0.519	22 (9)	86 (8)	0.850
Cardiac associated disease						
Arrhythmia	55 (20)	175 (14)	**0.022**	47 (19)	151 (15)	0.774
Pulmonary hypertension	6 (2)	73 (6)	**0.010**	5 (1)	63 (6)	0.080
Cardiomyopathy	8 (3)	35 (3)	0.986	5 (2)	28 (3)	0.416
Respiratory disease	52 (19)	227 (19)	0.948	47 (19)	194 (19)	0.671
Neurologic disease	34 (12)	113 (9)	0.128	28 (11)	100 (9)	0.468
Renal disease	33 (12)	128 (10)	0.490	30 (12)	113 (11)	0.868
Gastrointestinal disease	15 (5)	76 (6)	0.609	13 (5)	67 (7)	0.315
Infectious disease	25 (9)	83 (7)	0.197	20 (8)	78 (8)	0.915
Metabolic, endocrine, electrolyte abnormalities	11 (4)	59 (5)	0.539	8 (3)	48 (5)	0.710
Coagulation defects	7 (2)	21 (2)	0.371	6 (2)	20 (2)	0.670
Hemorrhage	12 (4)	67 (5)	0.436	10 (4)	61 (6)	0.060
Other comorbidities	25 (9)	113 (9)	0.903	22 (9)	103 (10)	0.229
Pre-operative cardiac arrest, n (%)**	36 (13)	123 (10)	0.155	32 (13)	98 (10)	0.508
Main cardiac surgery RACHS-1 score, n (%)						
1- 3	188 (67)	748 (61)		166 (68)	614 (60)	
4 - 6	79 (28)	435 (35)	0.079	69 (28)	368 (36)	0.738
Not assigned	12 (4)	46 (4)		10 (4)	37 (4)	
Surgery details						
CPB time (min), median (IQR)[c]	288 (207-386)	250 (172-357)	**<0.001**	295 (209-384)	251 (173-359)	0.782
ACC, n (%)	261 (93)	1038 (84)	**0.001**	243 (99)	965 (95)	0.561
DHCA, n (%)	89 (32)	429 (35)	0.340	84 (34)	401 (39)	0.385
Pre-ECMO support, n (%)						
Inotropic/vasopressor drugs	171 (61)	751 (61)	0.955	158 (64)	645 (63)	0.495
Vasodilator drugs	52 (19)	230 (19)	0.976	47 (19)	201(20)	0.681
Inhaled nitric oxide	35 (12)	204 (17)	0.094	31 (13)	170 (17)	0.283
Pre-ECMO neuromuscular blockers, n (%)	149 (53)	583 (47)	0.072	134 (55)	512 (50)	0.196
Pre-ECMO Mechanical ventilation >24h , n (%)	117 (43)	419 (35)	**0.018**	103 (42)	351 (35)	0.649
Pre-operative bicarbonate infusion, n (%)	49 (18)	196 (16)	0.509	47 (19)	170 (17)	0.645

* Prematurity is defined as gestational age ≤ 36 weeks; ** within 24h prior to ECMO
† P values are calculated by Chi squared test and U-Mann-Whitney test ‡ P values are calculated by weighted logistic regression #Fisher exact test
Missing data before weighting, n (LA+, LA-): [a] 10 (2, 8); [b] 42 (7, 35); [c] 159 (18, 141). No missing data after weighting.

ACC: Aortic Cross Clamp; CPB: Cardio-Pulmonary Bypass; DHCA Deep Hypothermic Cardiac Arrest; ECMO: Extra-Corporeal Membrane Oxygenation; Fraction of inspired Oxygen; HCO3: bicarbonate; HFOV: High Frequency Oscillatory Ventilation; IQR: Inter-Quartile Range; LA: left atrium; MV: Mechanical Ventilation; PaCO2: partial Pressure of Carbon dioxide; PaO2: partial Pressure of Oxygen; RACHS-1: Risk Adjusted Congenital Heart Surgery Score 1

ECMO details, hospital-stay characteristics and outcomes of LA+ patients compared to LA-

Patients who underwent LA decompression included a higher proportion of patients with cardiac arrhythmias (p=0.046), myocardial stun (p<0.001), those supported with systemic vasodilators (p<0.001), and hemofiltration (p<0.001). LA+ patients underwent more frequently a further cardiac surgery on ECMO (p<0.001) or

post-ECMO (p=0.012). They had less FiO2 requirements at 24h of ECMO (p <0.001), less frequently hypoglycemia (p=0.003), and needed less frequently inotropic support on-ECMO (p=0.032). ECMO circuit complications and cannulation bleeding were similar between the two groups (**Supplemental Table 1**).

Of the 1264 patients included, 638 (50%) had at least one in-hospital adverse outcome (transplant on-ECMO n=5 [0.4%], conversion to VAD=10 [1%], mortality=633 [50%]). The frequency of adverse outcomes did not significantly differ among the two cohorts by unadjusted weighted analysis (47% in LA+ patients versus 51% in LA- patients, p=0.078 OR 0.868 [CI 0.741-1.016], Table 2). However, when the weighted logistic regression was adjusted for other variables (**Table 2**), LA decompression was found to be an independent protective factor against in-hospital adverse outcome (adjusted OR 0.775 [CI 0.644-0.932], p=0.007, **Table 2**).

Table 2. Unadjusted and adjusted weighted logistic regression testing left atrial decompression as an independent predictor of in-hospital adverse outcome

Variables	Odds Ratio	95% Confidence Interval	p-value‡
Unadjusted logistic regression			
Left atrial decompression	0.868	0.741-1.016	0.078
Adjusted logistic regression model			
Left atrial decompression	0.775	0.644-0.932	**0.007**
ECMO pump flow at 4h of ECMO (ml/kg/min)	1	Reference	-
≤ 97	1.285	1.000-1.650	**0.050**
> 97 and ≤ 115	1.284	1.000-1.650	**0.004**
> 115 and ≤ 140	1.441	1.118-1.857	**<0.001**
> 141	1.862	1.408-2.463	**<0.001**
ECMO support duration (h)	1.004	1.003-1.005	**<0.001**
Cardiac surgery on ECMO	1.743	1.327-2.290	**<0.001**
ECMO circuit complications	1.451	1.192-1.767	**<0.001**
CNS hemorrhage or infarction on ECMO	1.741	1.333-2.274	**<0.001**
Cardiac arrhythmia requiring treatment on ECMO	2.399	1.887-3.049	**<0.001**
CPR on ECMO	2.421	1.139-5.144	**0.021**
Need for systemic vasodilators on ECMO	0.625	0.489-0.797	**<0.001**
Pulmonary hemorrhage on ECMO	2.915	2.111-4.024	**<0.001**
Renal failure on ECMO	1.989	1.465-2.700	**<0.001**
Hemofiltration required on ECMO	1.260	1.029-1.542	**0.025**
Arterial pH < 7.20 on ECMO	3.047	1.862-4.986	**<0.001**
Blood glucose < 40 mg/dl on ECMO	2.678	1.217-5.898	**0.014**

Unadjusted Model: N= 1264; Hosmer and Lemeshow Test *p* value= 1.000; area under the curve= 0.522
Adjusted Model: N= 1205; Hosmer and Lemeshow Test *p* value= 0.863; area under the curve= 0.743

Candidate variables were: Left atrial decompression, ECMO pump flow at 4h of ECMO, ECMO support duration, Cardiac surgery on ECMO, Multiple cardiac surgery on ECMO, Invasive procedure on ECMO, other than cardiac surgeries, ECMO circuit complications, Seizures, CNS hemorrhages or infarction, Cardiac arrhythmia requiring treatment, CPR on ECMO, Need for inotropic drugs on ECMO, need for systemic vasodilators, Pneumothorax requiring treatment, Pulmonary hemorrhage, Cannulation or surgical site bleeding, Hemolysis (plasma-free hemoglobin >50 mg/dl), Disseminate intravascular coagulation, Infectious complications, Renal failure, Hemofiltration required, Arterial pH > 7.60, Arterial pH < 7.20, Blood glucose < 40 mg/dl, Hyperbilirubinemia (direct bilirubin >2.0 mg/dl or total bilirubin >15.0 mg/dl) ‡ P values are calculated by weighted logistic regression. CNS: Central Nervous System; CPR: cardiopulmonary resuscitation; ECMO: Extra-Corporeal Membrane Oxygenation; FiO2: Fraction of inspired Oxygen.

Other predictors for in-hospital mortality

Weighted univariate analysis of variables potentially associated with in-hospital mortality is shown in **Supplemental Table 2**. Patients who had adverse outcome had higher ECMO flow at 4h (60% of them >100 ml/kg/min) and at 24h (both p<0.001), more frequently required an additional cardiac surgery on-ECMO (p<0.001), had longer ECMO duration (p<0.001) and more frequent ECMO complications (**Supplemental Table 2**). At the

weighted multivariable analysis (**Table 2**), Longer ECMO duration, higher ECMO pump-flow, other cardiac surgeries on-ECMO, and ECMO-complications (CNS hemorrhage or infarction, cardiac arrythmia requiring treatment, CPR on ECMO, pulmonary hemorrhages, as well as renal failure, need for hemofiltration, hypoglycemia and acidosis) independently increased the risk of adverse outcome, while need for systemic vasodilators on-ECMO reduced the risk for adverse outcome.

LA decompression and secondary outcomes

ECMO duration did not significantly differ between LA+ and LA- patients (107 hours [IQR 66-181] vs 107 hours [IQR 64-168], weighted p=0.602). Rate of ECMO weaning was similar in the two groups (69% in LA+ patients vs 70% in LA- patients, weighted p=0.437).

Discussion

In this large multicenter cohort of pediatric patients with biventricular physiology supported with VA-ECMO for FTW from CBP, 18% of patients underwent LA decompression on-ECMO. Using a propensity-score-weighted analysis - able to adjust for baseline differences existing between patients who did or did not undergo LA decompression - we have shown that LA decompression was independently associated with decreased in-hospital adverse outcome (mortality, transplantation, or conversion to VAD).

While VA-ECMO effectively support organ perfusion in the setting of a failing heart, it also increases the LV afterload which rises LV end-diastolic pressure and causes LV dilation. Several studies have shown that LV distention prevents an appropriate decrease in the myocardial oxygen demand, reduces the trans-coronary perfusion gradient with impaired myocardial perfusion, and may promote myocardial damage (78, 154, 155). The severity of LV distension was also demonstrated to be inversely related to the likelihood of myocardial recovery and event-free survival (death or transition to VAD) (156). The absence of obvious ejection in the setting of a closed aortic valve may also cause ventricular stasis with higher risk of thrombus formation (157). Finally, LA-hypertension may cause significant pulmonary edema which can negatively affect the right ventricular function and the respiratory gas exchange. In this setting, LA decompression, either surgical or transcatheter, has been proposed as a mean to mitigate these adverse events both in adults and pediatric patients (70–73, 75, 76, 155).

Although LA decompression has become common practice, data have conflicted on the best modality of decompression, best timing, as well as on the overall utility of this intervention. While some studies support its benefits (69, 73), others showed no differences in outcomes between patients who did or did not undergo LA decompression (158). In particular, Baruteau et al. retrospectively reviewed data of 64 patients (32 adults and 32 children) among 4 institutions who underwent a transcatheter balloon atrioseptostomy for LA decompression on VA-ECMO, reporting an improvement of day-1 chest X-ray in 77% of patients, improvement of clinical status in all but one patient, and improvement of pulmonary hemorrhages in all patients who experienced this complication (n=14) (73). Kotani et al. reported a series of 23 pediatric patients who underwent LA decompression within 12 hours of ECMO cannulation and described a 70% of weaning rate(69). In a recent multicenter study of 16 U.S. pediatric centers including a total of 137 patients, early LA decompression (within 18 hours since cannulation) was found to be associated with reduced ECMO-duration, but did not modify the in-hospital and overall survival (75).

Conflicted evidence exists also for the adult population (76, 159); however, a recent meta-analysis of 17 observational studies on adult patients supported on VA-ECMO for cardiogenic shock found that LA+ patients had lower mortality rate compared to others(74, 75, 160).

Several factors may have led to inconsistent conclusions on the benefit of LA decompression. First, populations may have been too heterogeneous, and data on adults may not be comparable to those on–pediatric populations. In fact, while in adults some degree of LV distension is usually well tolerated, threshold for LV-decompression in children might be lower as the infantile myocardium is extremely vulnerable to distension (76, 161); as well, hemodynamics may be more labile in the setting of complex congenital heart diseases. Moreover, in the adult population, alternative strategies to decompress the LV are more available, as the combination of a temporary LVAD (i.e. Impella) and ECMO (76) . Second, time to LA decompression may be critical in defining patients' outcome, given the decreased ability of the myocardium to recover once ischemia has occurred (75). Finally, but not less importantly, selection biases may play a crucial role in influencing and confounding outcome-related analysis.

Our propensity-based approach allowed us to detect and to adjust for the most important treatment-related selection biases. In fact, the initial comparison analysis between LA+ and LA- patients demonstrated that significant differences exist between the two groups: LA+ patients had less frequently a genetic syndrome or congenital anomalies, had more frequently baseline arrhythmias, had longer CBP time, more frequently required an aortic-cross-clamp, and had longer pre-operative mechanical ventilation. The propensity score was able to adjust for these biases, allowing us to investigate the effect of LA decompression on in-hospital adverse outcome on weighted cohorts. At the multivariable weighted analysis, LA decompression was found to be a protective factor against in-hospital adverse outcome (mortality, transplant on ECMO or conversion to VAD), suggesting that clinical benefits may exist in pediatric patients with biventricular physiology who failed to wean off CPB.

Certainly, this is a selected population of patient who required ECMO support due to severe LV impairment. Indeed, 60% of the patients were supported with more than 100 ml/kg/min of ECMO flow at 4 hours. Likely, these high ECMO flows may have also contributed to increased LV afterload.(162) Consistently, ECMO flows at 4h was retained in the final logistic regression model as an independent risk factor for adverse outcome - with higher ORs at increased flows - while LA- decompression and use of systemic vasodilators were identified as protective. Other risk factors for adverse outcome identified by our model may all be related to either insufficient decompression of the LV or insufficient ECMO flow: pulmonary hemorrhage (likely related to LA hypertension), cardiac arrhythmias (possibly related to high filling pressures), renal failure (likely secondary to either right ventricular failure of insufficient ECMO flow), hypoglycemia (likely related to liver failure secondary to right ventricular failure), and acidosis (likely secondary to insufficient ECMO flows). These risk factors were previously reported for other ECMO cohorts (44, 47, 64, 151).

Multiple limitations of this study need to be acknowledged. First, there are no data about the timing of LA decompression and the specific decompression technique used, which would have been an important factor that may have influenced our primary outcome. Data on LV function, ejection across the aortic valve, presence of aortic regurgitation, pre-ECMO existence of atrial communication such atrial septal defects were not available for further analysis. As well, given the retrospective nature of this multi-center registry study, missing data may have influenced our analyses. Lastly, given the high numbers of centers included in this study, it was not possible to take

into consideration a center effect as these data were not available for analysis. Despite these limitations, this represents, at the best of our knowledge, the largest reported cohort of pediatric patients on VA-ECMO who underwent LA decompression, and the first propensity-score adjusted analysis to access its association with in-hospital adverse outcome.

Conclusion

In conclusion, in this multicenter cohort of pediatric patients supported with VA-ECMO for FTW from CPB, we have shown that LA decompression independently decreased the risk of in-hospital adverse outcome, suggesting these patients may benefit from LA decompression. Although only a randomized controlled trial would effectively confirm this evidence, we believe our results add more evidence in supporting LA decompression in this population and may help design future higher-evidence trials.

Supplemental Table 1. Univariate weighted logistic regression analysis of ECMO-related factors and ECMO complications according to left atrial decompression (n total=1264)

Variable	Left atrial decompression (n=245)	No left atrial decompression (n=1019)	OR (95% CI)	p value
ECMO pump flow rates (ml/kg/min), median (IQR)				
At 4h after ECMO initiation [a]	109 (95-133)	111 (93-135)	1.001 (0.999-1.004)	0.286
At 24h after ECMO initiation [b]	115 (98-139)	112 (94-138)	1.002 (0.999-1.004)	0.117
FiO2 at 24h after ECMO initiation (%), h[c]	35 (30-40)	40 (30-42)	0.980 (0.974-0.986)	**<0.001**
ECMO support duration (h), median (IQR)	107 (66-181)	107 (64-168)	1.000 (0.999-1.001)	0.602
Cardiac surgery on-ECMO, n (%)	42 (17)	108 (11)	1.566 (1.240 -1.977)	**<0.001**
Cardiac surgery post-ECMO, n (%)	3 (1)	8 (1)	2.599 (1.234-5.472)	**0.012**
Multiple cardiac surgery, n (%)	44 (18)	115 (11)	1.613 (1.286-2.023)	**<0.001**
Invasive procedure on ECMO, others, n (%)	57 (23)	201 (20)	1.311 (0.083-1.588)	0.006
ECMO circuit complications, n (%)	89 (36)	381 (37)	0.972 (0.826-1.144)	0.730
CNS complications, n (%)	43 (18)	178 (17)	1.112 (0.909-1.360)	0.303
Cardiac complications, n (%)				
Cardiac arrhythmia requiring treatment	55 (22)	185 (18)	1.222 (1.003-1.489)	**0.046**
CPR on ECMO	7 (3)	31 (3)	1.053 (0.669-1.659)	0.823
Cardiac tamponade	23 (9)	116 (11)	0.874 (0.679-1.125)	0.297
Myocardial stun at echocardiography evaluation	33 (13)	91 (9)	1.724 (1.347-2.208)	**<0.001**
Need for inotropic drugs	155 (63)	657 (64)	0.837 (0.710-0.985)	**0.032**
Need for systemic vasodilators	56 (23)	153 (15)	1.618 (1.316-1.989)	**<0.001**
Pulmonary complications, n (%)	33 (13)	125 (12)	1.048 (0.825-1.330)	0.702
Cannulation or surgical site bleeding	139 (57)	548 (54)	1.127 (0.962-1.320)	0.139
Hemolysis*	26 (11)	131(13)	0.800 (0.627-1.020)	0.072
Disseminate intravascular coagulation	9 (4)	58 (6)	0.723 (1.501-1.043)	0.083
Infectious complications, n (%)				
Culture proven infection	23 (9)	110 (11)	0.754 (0.576-0.988)	0.041
White blood cell count < 1500/ml	3 (1)	11 (1)	0.963 (0.445-2.085)	0.924
Renal failure	27 (11)	119 (12)	0.867 (0.674-1.116)	0.269
Hemofiltration required	80 (33)	268 (27)	1.486 (1.251-1.765)	**<0.001**
Metabolic complications, n (%)				
Arterial pH < 7.20	12 (5)	59 (6)	0.753 (0.524-1.082)	0.125
Arterial pH > 7.60	6 (3)	59 (6)	0.676 (0.466-0.980)	0.039
Blood glucose < 40 mg/dl	1 (0)	24 (2)	0.331 (0.158-0.692)	**0.003**
Blood glucose > 240 mg/dl	48 (20)	158 (15)	1.176 (0.953-1.452)	0.132
Hyperbilirubinemia**	13 (5)	61 (6)	0.777 (0.547-1.105)	0.160

* Hemolysis is defined as plasma-free hemoglobin >50 mg/dl; ** Hyperbilirubinemia is defined as direct bilirubin >2.0 mg/dl or total bilirubin >15.0 mg/dl. Missing data, n (LA+, LA-): [a] 55 (14, 41); [b] 102 (21, 81); [c] 104 (20,84). CNS: Central Nervous System; CPR: Cardio-pulmonary Resuscitation; ECMO: Extra-Corporeal Membrane Oxygenation; FiO2: Fraction of inspired Oxygen; LA: left atrial.

Supplemental Table 2. Univariate weighted logistic regression analysis of ECMO-related factors and ECMO complications, according to in-hospital adverse outcome (n total=1264)

Variable	Survivors without transplant on-ECMO nor conversion to VAD (n=605)	Non survivors, transplanted or converted to VAD (n=626)	OR (95% CI)	p value
ECMO pump flow rates (ml/kg/min), median (IQR)				
At 4h after ECMO initiation [a]	107 (91-130)	114 (97-137)	1.007 (1.004-1.010)	**<0.001**
At 24h after ECMO initiation [b]	109 (91-131)	119 (98-143)	1.011 (1.001-1.014)	**<0.001**
FiO2 at 24h after ECMO initiation (%)h[c]	40 (30-40)	40 (30-40)	1.001 (0.995-1.007)	0.731
ECMO support duration (h), median (IQR)	87 (61-129)	136 (69-216)	1.005 (1.004-1.006)	**<0.001**
Cardiac surgery on-ECMO, n (%)	63 (10)	87 (14)	1.530 (1.212-1.932)	**<0.001**
Cardiac surgery post-ECMO, n (%)	6 (1)	5 (1)	0.706 (0.355-1.403)	0.321
Multiple cardiac surgery, n (%)	68 (11)	91 (14)	1.496 (1.194-1.875)	**<0.001**
Invasive procedure on ECMO, others, n (%)	108 (17)	150 (23)	1.208 (0.998-1.462)	0.053
ECMO circuit complications, n (%)				
Mechanical problems	48 (8)	91 (14)	1.870 (1.436-2.435)	**<0.001**
Clots in ECMO circuit	127 (20)	214 (33)	2.235 (1.860-2.685)	**<0.001**
Air embolus	17 (3)	35 (5)	3.753 (2.374-5.935)	**<0.001**
Cannula problems	22 (3)	40 (6)	2.899 (1.7887-4.423)	**<0.001**
CNS complications, n (%)				
Seizures	25 (4)	56 (9)	2.489 (1.762-3.515)	**<0.001**
Cerebral infarction or intracranial hemorrhage	51 (8)	112 (18)	1.759 (1.395-2.216)	**<0.001**
Cardiac complications, n (%)				**<0.001**
Cardiac arrhythmia requiring treatment	80 (13)	160 (25)	2.967 (2.400-3.670)	**<0.001**
CPR on ECMO	8 (1)	30 (5)	7.111 (43.639 -13.896)	**<0.001**
Cardiac tamponade	60 (10)	79 (12)	0.940 (0.730-1.209)	0.630
Myocardial stun at echocardiography evaluation	46 (7)	78 (12)	1.095 (0.859-1.394)	0.465
Need for inotropic drugs	364 (58)	448 (70)	1.416 (1.202-1.667)	**<0.001**
Need for systemic vasodilators	111 (18)	98 (15)	0.828 (0.675-1.017)	0.072
Pulmonary complications, n (%)				
Pneumothorax requiring treatment	11 (2)	22 (3)	3.808(2.046-7.088)	**<0.001**
Pulmonary hemorrhage	33 (5)	99 (15)	3.543 (2.636-4.762)	**<0.001**
Hemorrhagic complications (other than pulmonary), n (%)				
Cannulation or surgical site bleeding	314 (50)	373 (58)	1.221 (1.042-1.431)	**0.014**
Gastrointestinal bleeding	4 (1)	12 (2)	4.704 (1.790-12.365)	**0.002**
Hemolysis*	64 (10)	93 (15)	1.624 (1.269-2.077)	**<0.001**
Disseminate intravascular coagulation	15 (2)	52 (8)	2.898 (1.933-4.346)	**<0.001**
Infectious complications, n (%)				
Culture proven infection	43 (7)	90 (14)	1.917 (1.452-2.530)	**<0.001**
White blood cell count < 1500/ml	3 (1)	11 (2)	6.289 (2.079-19.029)	**0.001**
Renal complications, n (%)				
Renal failure	44 (7)	102 (16)	2.600 (1.981-3.421)	**<0.001**
Hemofiltration required	124 (20)	224 (35)	1.858 (1.561-2.121)	**<0.001**
Metabolic complications, n (%)				
Arterial pH < 7.20	19 (3)	52 (8)	3.386 (2.232-5.138)	**<0.001**
Arterial pH > 7.60	36 (6)	29 (4)	1.499 (1.036-2.168)	**0.032**
Blood glucose < 40 mg/dl	9 (1)	16 (2)	2.613 (1.293-5.281)	**0.007**
Blood glucose > 240 mg/dl	100 (16)	106 (17)	1.018 (0.825-1.257)	0.865
Hyperbilirubinemia**	34 (5)	40 (6)	1.335 (0.939-1.8976)	0.107

* Hemolysis is defined as plasma-free hemoglobin >50 mg/dl; ** Hyperbilirubinemia is defined as direct bilirubin >2.0 mg/dl or total bilirubin >15.0 mg/dl. Missing data, n (adverse outcome, no adverse outcome): [a] 55 (22, 33); [b] 102 (47, 55); [c] 104 (43, 61). CNS: Central Nervous System; CPR: Cardio-pulmonary Resuscitation; ECMO: Extra-Corporeal Membrane Oxygenation; FiO2: Fraction of inspired Oxygen; LA: left atrial.

Project 6

Treat

Safety of inhaled Hydrogen gas mixture in healthy individuals: a New Drug, Phase I, FDA-approved trial

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Abstract

Background: Ischemia-reperfusion injury (IRI) is common in critically ill patients, and directed therapies are lacking. Inhaled hydrogen gas (H2) diminishes IRI in models of shock, stroke, and cardiac arrest. The purpose of this study was to investigate the safety of inhaled H2 at doses required for a clinical efficacy study.

Design: Prospective, single-arm study**. Setting:** Tertiary care hospital **Patients/Subjects:** Eight healthy adult participants. **Interventions:** Subjects underwent hospitalized exposure to 2.4% H2 in medical air via high flow nasal cannula (15 LPM) for 24 (n=2), 48 (n=2), or 72 (n=4) hours.

Measurements and Main Results: Endpoints included vital signs, patient- and nurse- reported signs and symptoms (stratified according to clinical significance), pulmonary function testing (PFT), 12-lead EKG, mini-mental state exams (MMSE), neurologic exam, and serologic testing prior to and following exposure. All adverse events were verified by two clinicians external to the study team and an external Data and Safety Monitoring Board. All eight participants (18-30 years; 50% female; 62% non-Caucasian) completed the study without early termination. No clinically significant adverse events occurred in any patient. Compared with baseline measures, there were no clinically significant changes over time in vital signs, PFT results, MMSE scores, neurologic exam findings, EKG measurements or serologic tests for hematologic (except for clinically insignificant increases in hematocrit and platelet counts), renal, hepatic, pancreatic, or cardiac injury associated with H2 inhalation.

Conclusions: Inhalation of 2.4% H2 gas does not appear to cause clinically significant adverse effects in healthy adults. While these data suggest that inhaled H2 may be well tolerated, future studies need to be powered to further evaluate safety. These data will be foundational to future interventional studies of inhaled H2 in injury states, including following cardiac arrest.

Background and Significance

Ischemia-reperfusion injury (IRI) results in end-organ injury in a number of clinical scenarios, including myocardial infarction, stroke, and cardiac arrest, leading to significant morbidity in surviving patients (163). Care paradigms for these illnesses focus on timely restoration of optimal perfusion and the prevention of secondary injury; therapies that target IRI itself are generally lacking. One notable exception is targeted temperature management, an approach that has not demonstrated a consistent therapeutic advantage in randomized controlled trials in older children and adults (147). The need for targeted therapies addressing IRI is significant.

Recently, it has been discovered that hydrogen gas (i.e. molecular dihydrogen, H2) has therapeutic benefits by selectively reducing the hydroxyl radical (•OH) in vivo (141, 164), a mediator that results from excess oxygen free radical formation during reperfusion injury and directly damages DNA and lipid membranes. H2 administration has been shown to decrease nuclear factor of activated T-cells (NFAT)-activated calcium signaling (central to apoptosis), activate the Nrf2 pathway (upregulates production of protective proteins, such as glutathione and catalase), and downregulates proinflammatory cytokines (e.g. IL1, TNF-a) (165, 166). There are numerous preclinical studies demonstrating that peri-injury H2 inhalation results in clinically important improvements in animal models of cardiac arrest (167–172), cardiopulmonary bypass (100), stroke (141, 173), hypoxic-ischemic encephalopathy (174), and sepsis (175, 176).

To date, a rigorous clinical study of the safety of H2 is lacking. Previously, our group found that mice exposed continuously to 2.4% hydrogen in air for 72 hours experienced no clinically significant changes in neurologic or pulmonary function compared with controls exposed to medical air (99). Further, there have been numerous reports of clinical H2 exposure in early phase clinical trials, including in cardiac arrest (177), stroke (178), coronary reintervention (179), colorectal cancer (180), and lung cancer (181). Although reports of adverse events among these studies are rare, the H2 dosing and duration of H2 administration varies widely among them, often limited to several hours per day. Further, because these patients were otherwise ill, the identification of H2-related findings may have been confounded by disease-related findings. Finally, although each of these studies was well-conducted, none mention Good Clinical Practice rigor, nor were they intended to be screening studies for adverse events. The purpose of this study was to rigorously screen for adverse effects associated with H2 exposure in healthy subjects at the dose and duration that we intend to use for a future efficacy study.

Methods

Study design

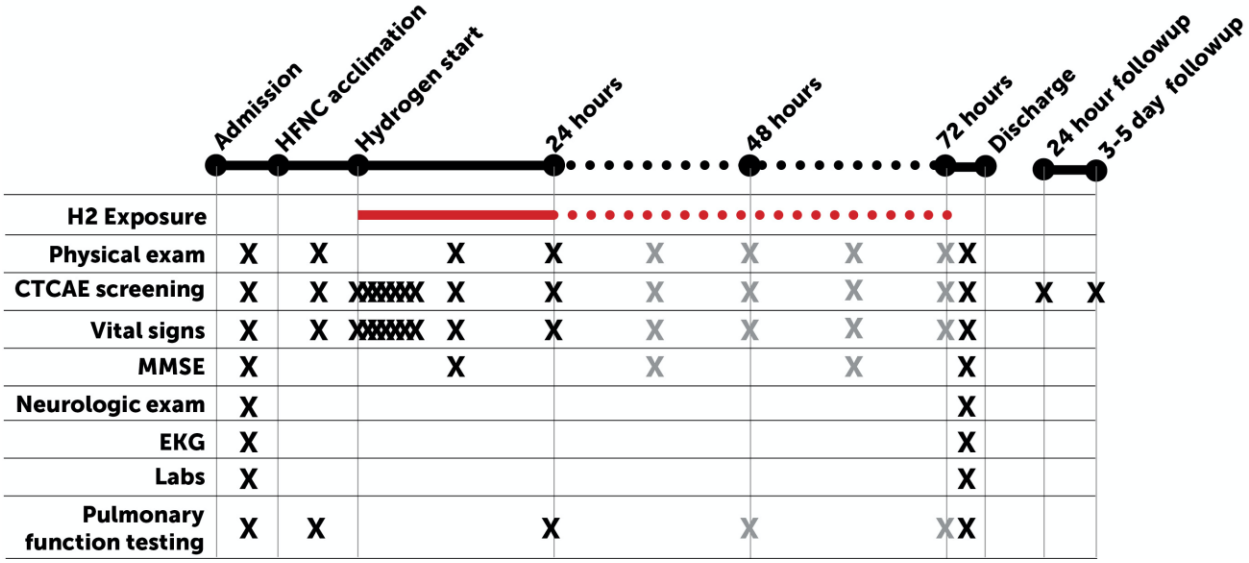
The study was performed under an investigator-initiated Investigational New Drug application (IND 146967), was approved by the Institutional Review Board of Boston Children's Hospital (IRB-P00031196), was registered on clinicaltrials.gov (NCT04046211), and was performed according to Good Clinical Practice guidelines. The study was monitored by an independent DSMB. Eligible subjects were 18 to 35 years of age and otherwise healthy; subjects with a history of chronic or recent illness, including COVID-19 or respiratory disorders such as asthma, COPD, prior ALI/ARDS, inflammatory disorders, known heritable disorders, nasal septal or sinus disease, history of tobacco use, recent blood transfusions, or the regular use of prescription medications (excepting contraceptives) were excluded. Subjects were recruited using an advertisement at a local university and on

clinicaltrials.gov. Financial compensation was provided for participation. All respondents were screened via email for inclusion and exclusion criteria. Participants were then randomly selected (but with a targeted 50/50 gender distribution) for phone screening. Assenting participants then underwent an in-person physical examination, testing for pregnancy and COVID-19, and an in-person, written informed consent. Consenting eligible subjects then proceeded to study participation during an inpatient admission.

Study protocol

At the start of the inpatient admission, a complete physical examination, neurologic examination, pulmonary function testing, EKG, and baseline serologic testing were completed (**Figure 1**). Thereafter, subjects underwent a 4-hour acclimation period to the high-flow nasal cannula (HFNC; 15 liters/minute, 21% oxygen, no hydrogen) to distinguish any symptoms arising from the HFNC itself. Participants were then assigned to either 24 (n=2), 48 (n=2), or 72 hours (n=4) (sequential dose escalating design with 50/50 within-group sex assignment) of exposure to inhaled 2.4% hydrogen via HFNC (15 LPM, in 21% oxygen, balance nitrogen) during an inpatient stay. Gas mixtures were premixed using a GMP process and certified (Airgas Specialty Gases, part number Z03NI76T15A0000, Plumsteadville, Pennsylvania), regulated via medical air flowmeter (AmVex, part number FMAA07442FH), and administered with heat and humidification (Fisher & Paykel Healthcare, part number MR850JHU). Proper placement of the HFNC within the nares was observed at least hourly by a staff nurse. At this flow rate, we expected alveoli to be saturated with the inhaled gas (i.e. 2.4% H2) given that subjects were at rest and generally exhibited closed mouth breathing (182).

Figure 1. Schematic of study treatment and testing. Upon hospital admission, subjects underwent a physical exam, mini-mental state exam (MMSE), a separate, detailed neurologic exam, 12-lead electrocardiogram (EKG), pulmonary function testing, and baseline labs. Subjects were then acclimated to high flow nasal cannula (HFNC) for 4 hours, after which they were exposed to hydrogen gas (H2) for up to 72 hours. Subjects were regularly screened for signs and symptoms, which were graded according to the Common Terminology of Clinical Adverse Events (CTCAE). Following exposure, measurements were repeated prior to discharge. A follow-up phone call took place at 24 hours and 3-5 days following discharge.



During the exposure period, subjects were observed for several endpoints as described subsequently. Broadly, our choice of endpoints was intended to represent a comprehensive screening for possible symptoms of H2 administration. Since there have been no consistent reports of adverse findings in clinical exposures, we began with a comprehensive screening tool frequently used to codify adverse events: National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. We also screened specifically for symptoms that might be expected from an inhaled gas (i.e. respiratory findings, such as wheezing or bronchospasm based on spirometry) or one with known clinical neurologic effects (i.e. neurologic examination). Given that we had previously described a decrease in locomotor activity following H2 exposure (albeit an isolated finding among a large battery of neurologic endpoints), we also performed a detailed neurologic examination to interrogate this finding in humans. Given that H2 exhibits rapid plasma transport and elimination within hours, the timing of the following endpoints were more frequent early in the exposure period and decreased over time. Following exposure, subjects underwent the same testing as at baseline. Follow-up phone interviews were conducted 1 day and 3-5 days after H2 exposure.

Adverse event screening

Adverse symptoms and signs were collected by the bedside nurse and separately by study team members at predefined intervals (i.e. during each vital sign measurements, as well as during the 1 day and 3-5 day followup phone calls). Any adverse effects (AEs) were graded by the study team according to the CTCAE. A physical examination was performed by the bedside nurse at least every 12 hours and by a physician on the study team at least every 24 hours, including a respiratory, cardiovascular, and neurologic assessment. A mini mental status examination (MMSE) was conducted at baseline and every 24 hours by a member of the study team. A comprehensive neurologic examination (including deep tendon reflexes, strength, coordination, fine motor skills, rapid alternating movements, and short-term memory) was separately performed by an attending neurologist once prior to and once following H2 exposure (prior to discharge). AE severity assignments were separately reviewed by both a physician and nurse removed from the study team, and all AEs were reported to the DSMB. All grade II and higher AEs, and clinically significant grade I AEs (e.g. those which required treatment) were reported.

Pulmonary function testing

Pulmonary function testing was conducted every 24 hours using a calibrated bedside spirometer (Vyaire Medical, Micro I spirometer). Percent predicted forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, and peak expiratory flow rate (PEFR) were recorded for each of three blows at each time point, and the blow with the highest FEV1 was chosen as representative of each time point.

12-lead electrocardiogram

A 12-lead electrocardiogram was performed prior to and following the H2 exposure period. Standard intervals were compared over time. All EKGs were interpreted by a board-certified cardiologist and abnormalities reported as adverse events.

Serological testing

A pre-defined battery of laboratory testing was analyzed prior to and within 2 hours following the completion of H2 exposure. All testing was performed in the hospital's core lab, including a complete blood count (CBC), chemistry panel 10, liver function tests, amylase and lipase levels, coagulation panel, and cardiac troponin.

Statistical analysis

Patient characteristics and clinical measurements were summarized using mean and standard deviation, median and interquartile range, and frequency and percentage. Serial measures of vital signs, mini-mental state exam, and pulmonary function testing were compared to baseline measurements (when relevant, the baseline was taken while the patient was breathing medical air without hydrogen added via HFNC) using a mixed effects analysis of variance model (random subject, fixed time points) with a compound symmetry covariance structure; these analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). Comparisons of lab measurements and EKG findings pre- versus post-exposure were carried out using Wilcoxon matched-pairs signed rank testing. These analyses were performed in (and all graphs created in) GraphPad Prism 9.1 (GraphPad Software, San Diego, California USA). A P value less than 0.05 was defined as statistically significant for all tests. Normal values for each lab are displayed on each figure below for reference; values shown for adult females (LabCorp reference values).

Results

Of the nine subjects screened, eight met all eligibility criteria and provided written informed consent. All participants completed the study protocol as described without early termination (**Table 1**).

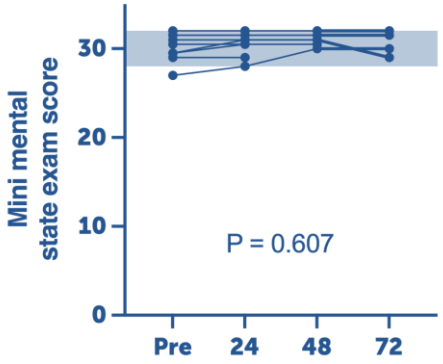
Table 1. Demographics of study participants.

Characteristics		n(%)
Sex	Male	4 (50%)
	Female	4 (50%)
Ethnicity	Hispanic or Latino	0 (0%)
	Not Hispanic or Latino	8 (100%)
	Unknown or not reported	0 (0%)
Race	White	3 (38%)
	Black/African American	2 (25%)
	Asian	1 (13%)
	Native American/ Alaskan Native	0 (0%)
	Native Hawaiian/ Other Pacific Islander	0 (0%)
	Multi-racial	2 (25%)
	Other	0 (0%)
	Unknown	0 (0%)
Weight (kg)	Mean	73.9
	Median	76.7
	Standard Deviation	11.0
	Minimum	56.7
	Maximum	86.5
Age at enrollment (years)	Mean	22.1
	Median	20.8
	Standard Deviation	4.1
	Minimum	18.5
	Maximum	30.7

The study cohort was 20.8±4.1 years old and 50% were male. One subject was observed to have a cannula displacement for less than 1 hour during sleep, and the exposure period was extended by an additional hour. No

environmental hazard events occurred during the study. No clinically significant symptoms or adverse events occurred in any patient. Specifically, there were no complaints of respiratory distress, chest tightness, no findings of wheezing or tachypnea. There were also no clinically significant changes noted in neurologic examination (pre vs post-exposure) nor in MMSE score over time (P=0.607, **Figure 2**). There were no complaints of headache, malaise, fatigue, or other constitutional symptoms during or following H2 exposure through the follow-up periods.

Figure 2. Mini-mental state exam (MMSE) scores during H2 exposure did not differ from baseline values. Points are individual replicates; green shading represents reference range.



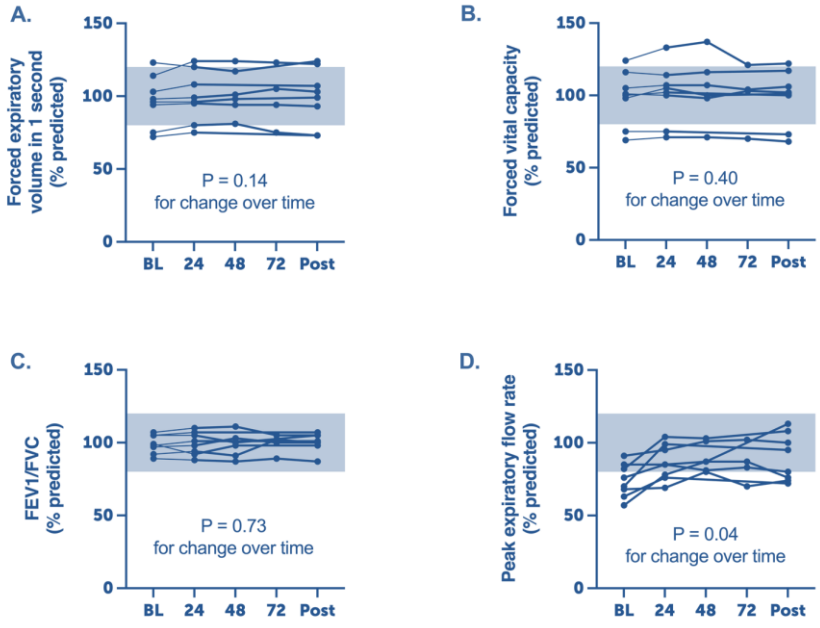
Vital signs and electrocardiogram

Compared with baseline findings (HFNC breathing), there were no significant changes in systolic or diastolic blood pressure, respiratory rate or oxygen saturation over time (**Supplemental Figure 1**). There was a statistically significant, but clinically insignificant decrease in heart rate over time (P<0.05). There was no evidence of ectopic rhythm or conduction abnormality in any patient on telemetry or 12-lead EKG (**Supplemental Figure 2**).

Spirometry

Compared with HFNC breathing, there were no changes over time in percent predicted FEV1, FVC, or FEV1/FVC ratio (**Figure 3**). There was a statistically significant, but clinically insignificant increase in PEFR over time during and following H2 breathing (P=0.038).

Figure 3. Pulmonary function testing. Compared with baseline (BL) measurements, there were no significant changes in percent predicted forced expiratory volume in 1 second (FEV1, **A**), forced vital capacity (FVC, **B**), or FEV1/FVC ratio (**C**) during and following H2 administration. There was a clinically insignificant increase in peak expiratory flow rate over time, perhaps related to improving technique over time. Points are individual replicates; green shading represents reference range.



Laboratory findings

Compared with baseline findings, there were no significant changes in white blood cell count. There were statistically significant, but clinically insignificant pre- versus post-exposure increases in hemoglobin (mean increase 1.3 [95% CI 0.8,1.7] g/dL), hematocrit (mean increase 4.0 [2.4, 5.6]%), and platelet count (mean increase 22 [4,41] cells/uL) (**Supplemental Figure 3A-D**). Compared with baseline findings, there were no significant changes in serum chemistry profile (**Supplemental Figure 3E-N**). There was a decrease in serum chloride by 2.0 [0.27, 3.7] mmol/L, P=0.0391. Similarly, there were no significant changes in hepatic or pancreatic enzymes, coagulation profile, or cardiac troponin (**Supplemental Figure 3O-AA**).

Discussion

We have shown that the administration of 2.4% H2 via HFNC appears to be safe and well tolerated, without clinically significant adverse effects in healthy participants. Subjects did not describe any odor or sensation, nor any respiratory signs or symptoms. There were no clinically detectable changes in neurologic function, including attention, memory, fine motor skills, and coordination associated with H2 inhalation. This was reassuring given our prior (likely artifactual) finding of diminished locomotor activity (one of many subsets of a battery of tests) in hydrogen-exposed mice (99). There was also no evidence that prolonged exposure to hydrogen in healthy subjects causes any clinically significant organ injury as evidenced by serologic testing. There was no evidence of clinically significant leukodepression. It is likely that the increases we found in hemoglobin, hematocrit, and platelet concentrations following H2 exposure were related to a mild dehydration in the hospitalized subjects; it is also possible that H2 stimulated bone marrow to increase production across cell lines or decreased erythrocyte and platelet destruction, though these seem less likely. The statistically significant decrease in heart rate over time (always within the clinically normal range) may have been related to mild, transient anxiety early on in the study, particularly since there were no signs of arrhythmia on telemetry and no hemodynamic compromise. Similarly, the statistically significant improvement in peak expiratory flow rate was most likely related to improvements in spirometry technique over time, rather than a true H2 effect. Given that there were no meaningful changes in other spirometric endpoints, it is unlikely that this reflects a true H2 effect. The strength of this work was study rigor, including redundancy in examining for important endpoints (e.g. respiratory and neurologic symptoms), layers of quality control and endpoint adjudication, direct observation of hydrogen administration, and good clinical practice. This gives us confidence that the lack of positive findings in this study reflects a reassuring safety screening study.

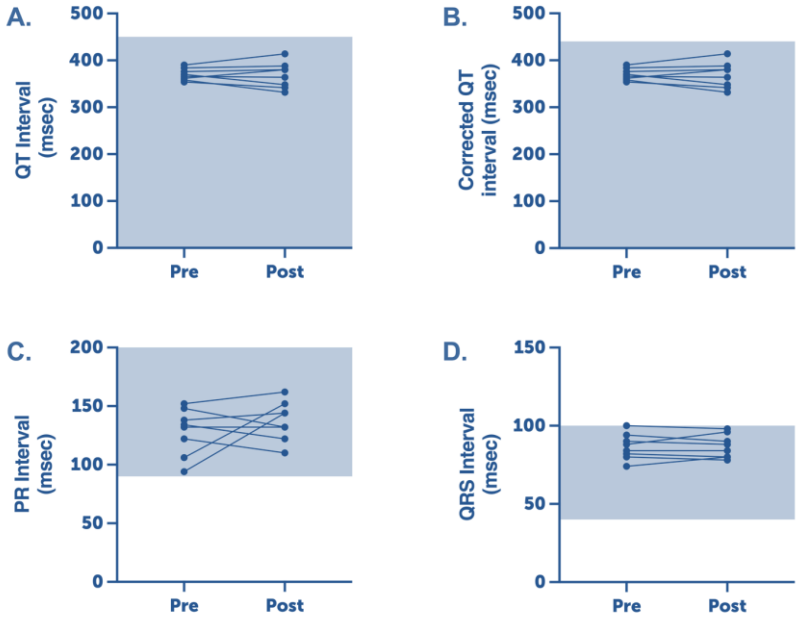
These results are consistent with prior reports of hydrogen exposure in adult patients in illness, although dosing regimens in published studies vary. Perhaps the most rigorous study to date found that hematologic, liver, kidney, pancreas, cardiac enzymes, and electrolyte profiles did not significantly change in stroke patients breathing 3% H2 via non-rebreathing face mask for 1 hour twice daily for 7 days (178). Another study described no environmental safety hazards, no renal injury, and no constitutional symptoms (specifically dizziness, rash, constipation or cystitis) in a small number of patients receiving peri-procedural 1.3% H2 via face mask during percutaneous coronary reintervention (179). Similarly, another pilot study described no environmental hazards and no major attributable AEs following 18 hours of continuous delivery of 2% H2 via mechanical ventilator in a small number of post-CA patients (177).

We note the following limitations to our study. Given the low number of subjects in this safety, our study was limited to the identification of frequent AEs and was underpowered to detect findings that may be less common. Further, we intentionally enrolled healthy subjects for this initial study; the AE profile of H2 in illness may differ. Relatedly, the neurologic findings were requisitely measured using a different battery of tests than were used in the prior mouse study (since there is no direct correlate). As such, the lack of positive neurologic findings cannot be completely reassuring. Second, although we ensured H2 exposure by direct observation of cannula placement and of gas flow, we did not quantify serum H2 concentrations, as there is no GLP-validated instrument to do so. However, we administered H2 at a flow rate (15 LPM) at which we expected alveoli to be saturated with the inhaled gas with minimal air entrainment given that subjects were at rest and generally exhibited closed mouth breathing (182). Thirdly, this was a single-arm study in which the study team was not blinded to treatment allocation. However, most of the endpoints were objective, and subjective endpoints (e.g. neurologic findings) were confirmed by more than one observer.

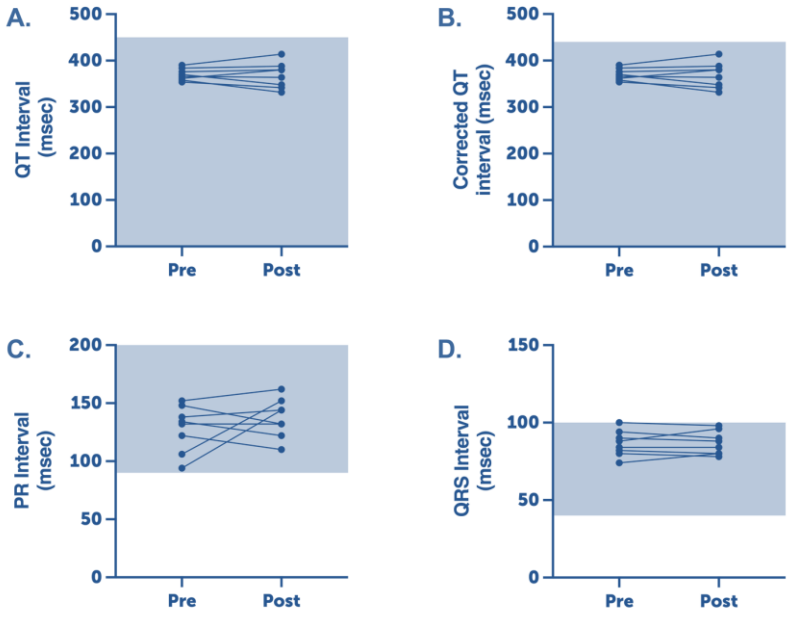
Conclusion

Inhalation of 2.4% H2 appears to be well tolerated with no clinically significant adverse effects. Compared with baseline measures, there were no clinically significant changes in vital signs, neurologic examination, pulmonary function testing, or EKG changes, nor in any lab parameters associated with up to 72 hours of H2 inhalation. While these data suggest that inhaled H2 may be well tolerated, future studies need to be powered to further evaluate safety. These data should enable future studies of inhaled H2 in injury states.

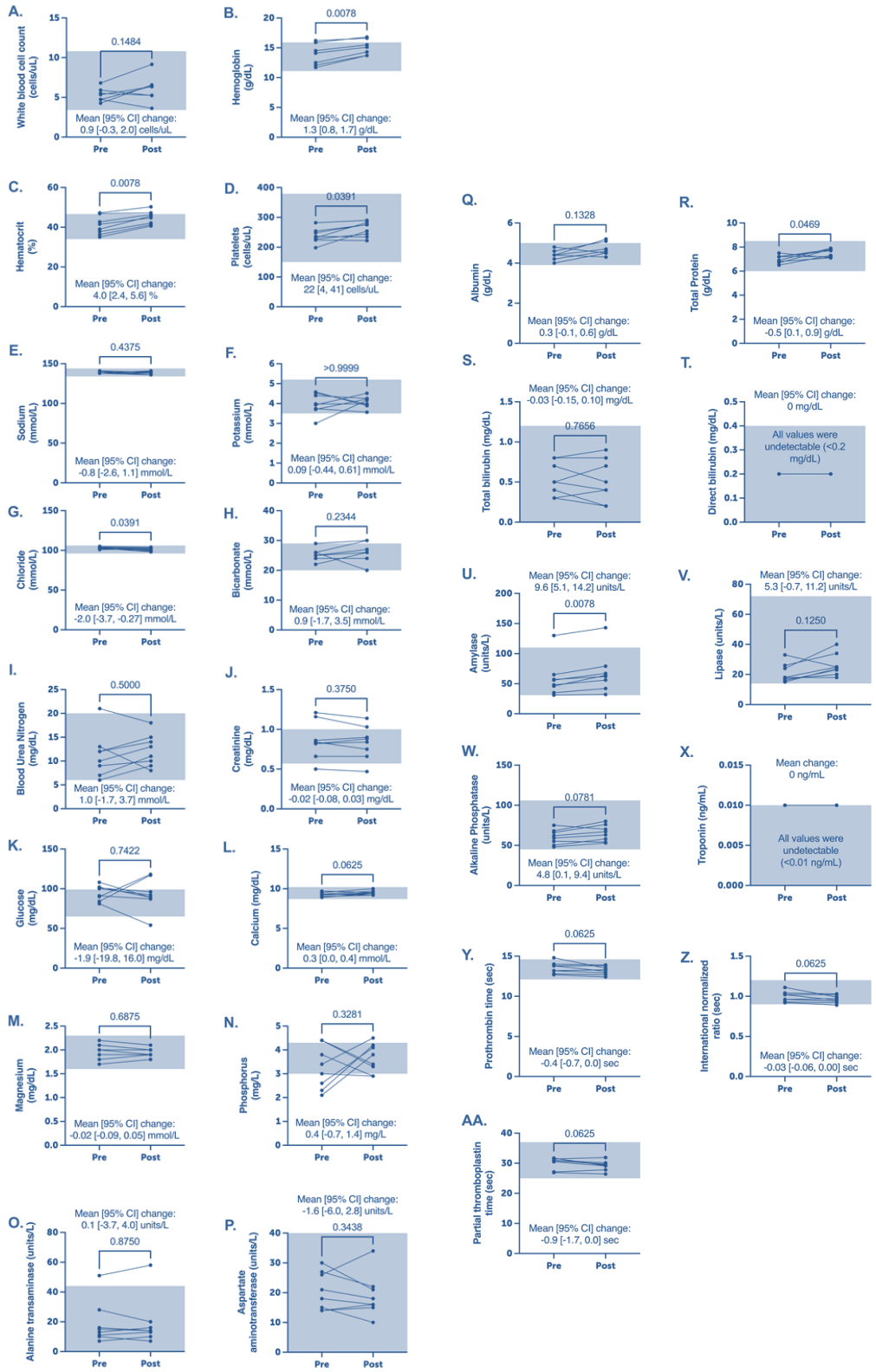
Supplemental Figure 1. Vital signs findings. Compared to baseline (BL), there were no significant changes in systolic blood pressure (**A**) or diastolic blood pressure (**B**) during H2 exposure. There was a statistically significant decrease in heart rate over time ($P<0.05$, **C**), though this remained within the clinically normal range and was not clinically significant. There were also no changes in oxygen saturation by photoplethysmography (**D**) or respiratory rate (**E**) during H2 exposure.



Supplemental Figure 2. Electrocardiogram findings. Compared to pre-H2 exposure measurements (Pre), there were also no changes in PR interval (**F**), QRS interval (**G**), QT interval (**H**) or corrected QT interval (**I**) following H2 exposure (Post). Points are individual replicates; green shading represents reference range.



Supplemental Figure 3. Serologic measurements. Pre- (Pre) and post-H2 exposure (Post) white blood cell count (**A**), hemoglobin (**B**), hematocrit (**C**), platelet count (**D**), serum sodium (**E**), potassium (**F**), chloride (**G**), bicarbonate (**H**), blood urea nitrogen (**I**), creatinine (**J**), glucose (**K**), calcium (**L**), magnesium (**M**), phosphorus (**N**), alanine transaminase (**O**), aspartate aminotransferase (**P**), albumin (**Q**), total protein (**R**), total bilirubin (**S**), direct bilirubin (**T**), amylase (**U**), lipase (**V**), alkaline phosphatase (**W**), cardiac troponin (**X**), prothrombin time (**Y**), international normalized ratio (**Z**), and partial thromboplastin time (**AA**). Points are individual replicates; green shading represents normal measurements for adult females.



Discussion

Throughout these multiple projects, we have shown that resuscitation in critically ill pediatric cardiac patients remains one of the biggest challenges for the pediatric cardiologist and intensivist, but multiple opportunities exist to improve care and outcomes - from big data, to bench, to bedside.

PROJECT 1

In **Project 1**, we have systematically reviewed the current data on incidence, risk factors, and outcomes for CA and associated mortality in this population. Summarizing the data by random-effects meta-analysis, we have shown that a non-negligible proportion of cardiac pediatric patients admitted to the intensive care units (5%, CI95%: 4-7%) require resuscitation at least once during their stay. Very interestingly, this proportion showed a trend of improvement over time, with a calculated 8% incidence (CI95% 7-9%) when including studies before 2010, and an incidence of 3% (CI95% 3-3) when including only studies after 2010. In centers with ECMO expertise, a pooled proportion of 21% (CI95%: 15-28%) of patients were supported with ECPR. Overall, 35% of patients who were resuscitated (CI95%: 27-44%) did not reach ROSC and died shortly thereafter. The overall pooled mortality rate was high at 54% (CI95%: 47-62%). However, similarly to the incidence of CA, studies showed a trend of improved survival over time, with a decrease in mortality rate from 67% (CI95%: 52-79%) to 51% (CI95%: 44-57%) before and after 2010, respectively.

Overall, a significant number of patients with cardiac disease experience CA, and outcome following resuscitation remains poor. It is clear that a strong emphasis must be placed on the prearrest phase to prevent CA. In Project 1 we have identified some of the important risk factors for CA in this population: neonatal age, univentricular physiology, a condition of acute heart failure, significant arrhythmias, and higher surgical complexity. Interestingly, the presence of an arterial line and an expert attending decreased the risk of CA.

PROJECT 2

In **Project 2**, we aimed to investigate a new prediction algorithm that included both clinical characteristics and hemodynamic data, derived by arterial and central venous lines. The model was able to use hemodynamic summary measures, computed based on a *big data*-set of hemodynamic data (vital signs extracted every 5 seconds from the patient's bedside monitor) to predict a resuscitation event. Specifically, we have analyzed data of 4,161 critically ill cardiac patients who underwent cardiac surgery and were admitted to the ICU. Using vital signs of the first 24h of admission, we computed three novel hemodynamic indices (i.e. SI, CPP, and RPP) and we tested them as predictors of major adverse outcomes within the first 7 days of admission. Adverse outcomes included were the need for CPR, ECPR, ECMO or VAD support, heart transplantation, death, or unplanned surgery.

In the first 7 days of admission, 7% of the included patients met the outcome, in a median time of 1.2 days (IQR 0.3-3.6). By analyzing their hemodynamic profile, we have shown that HR and SBP over the first 24 hours of admission – even in isolation - are quite predictive of a meaningful short-term outcome. Although the concept seems straightforward and the association expected, surprisingly this has not been previously reported for this cohort of patients. This may be due to the fact that, so far, only single or limited timepoints of hemodynamic data have been

studied as predictors of outcome (e.g. those included in the PIM-3 score (125)), and these may be not representative of the hemodynamic state of the first 24 hours. In fact, vital signs may express different conditions that range from inadequate sedation or over-sedation, pain not well controlled, response to medications, and hemodynamic instability; thus, single time-points may not truly represent the hemodynamic status of the patient. Differently, in this study, we have used all the vital signs extracted every 5 seconds in the first 24h of admission, and summarized them with a centrality measure (median) that may have been more clinically meaningful than a single time-point.

In this study, we have also shown that the median SI and CPP are strongly associated with the short-term outcome following congenital heart surgery in children. Previous studies, in different contexts and populations, have shown that these variables may have potential in predicting hemodynamic deterioration. For example, a SI > 0.9 in adults has been associated with mortality and the need for massive transfusion following major trauma (114). In children, an age-adjusted SI has been predictive of morbidity and mortality in trauma patients (126–129) and in patients with septic shock (130–132). Similarly, CPP >15 mmHg during CPR is known to be a predictor of both acute resuscitative success (115) and 24-hour survival (133). However, to date, none of these variables were tested in pediatric critically ill patients with cardiac disease, and none of the previous studies have used *big data* to compute the median hemodynamic summary measure. These new predictors have the potential to be easily used by the bedside provider to assess the hemodynamic status of the patient. Moreover, in the future, an algorithm integrated into the bedside monitor may automatically calculate these predictors, opening a new window of opportunity in the prediction – and prevention - of CA. Specifically, these predictors may allow the early identification of patients at high risk of CA, both in the cardiac ward and in the PICU/CICU. An alarm may sound when definite cut-offs are meet, driving the staff's attention to the patient promptly so that a careful evaluation (clinical and serological) and specific interventions (as fluid boluses, inotropic support, ventilation adjustments) may take place. This would be extremely important especially in the setting of full capacity and short staffing. In the future, and likely with the help of artificial intelligence, this prediction may reach very high accuracy and serve as an important support tool for the physician's practice.

The identification of strong predictors is pivotal not only for preventing a resuscitation event, but also for predicting - and modifying – its associated outcome. As shown in Project 1, outcomes after resuscitation in pediatric cardiac patients remain poor. By random-effect meta-analysis, 35% percent of patients (CI95%: 27-44%) did not reach ROSC, and the overall pooled in-hospital mortality rate was 54% (CI95%: 47-62%). Similarly, in-hospital mortality after cardiac ECMO of all indications - reported in a recent ELSO International Summary - ranges from 52% in pediatric cardiac ECMO to 55% in the neonatal cardiac population (33). Given these poor outcomes, the identification of new predictors of survival after resuscitation remains crucial.

Main risk factors for in-hospital mortality after CA identified in Project 1 were univentricular physiology, renal failure, cerebral damage, higher vasoactive-inotropic-score, longer CPR, CA during the weekend, and limited nurse experience, while admission to a CICU was associated with a decreased risk of mortality. In **Project 3**, we have investigated outcomes and associated risk factors of one of the cohorts at highest risk of mortality after resuscitation, i.e. patients who required to be supported with ECMO after failure to wean (FTW) from CPB. Specifically, we have analyzed multicenter data extracted from the ELSO Registry. These patients face imminent mortality without ECMO support, and decisions regarding use of ECMO in these patients have to be made rapidly,

often without optimal clinical and/or imaging information. ECMO deployment in these circumstances may provide resuscitation and the consequent opportunity for a careful evaluation of reversible conditions that may be amenable for correction (e.g. residual lesions).

In our study, we confirmed that mortality in this setting is high (55%), but similar to mortality reported for cardiac ECMO support of all indications (34). Further, we have developed a model able to predict in-hospital mortality with relatively good accuracy. This model may be able to help to assess prognosis in these high-risk patients and identify risk factors that may be amenable to intervention. The final model showed that neonatal age, comorbid conditions, complex congenital cardiac surgery (higher RACHS-1 score), duration of CPB, and significant ECMO complications were all independent predictors of in-hospital mortality. Although factors as neonatal age and genetic/congenital anomalies offer little opportunity for improvement, other factors identified by the model may be at least partially controlled. For example, complex cardiac surgical procedures and longer CPB duration were both independently associated with mortality in our cohort. Since residual lesions are one of the most important causes of FTW from CPB in these patients, prompt diagnosis and correction of these lesions are essential to improve ECMO survival. (48). Repair of these residual lesions at the time of the operation may provide optimal hemodynamics for successful ECMO support; however, this would require a long CPB duration or repeated exposures to CPB and may worsen outcomes for those who require post-operative ECMO support. (137) Therefore, any decision regarding duration of CPB should be made after weighing the consequences of continuing CPB or deploying ECMO to provide a period of stability and attempting correction at a later time.

Interestingly, at the multivariable model including ECMO-related factors only, left atrial decompression with left atrial cannulation was identified as a protective factor for mortality. Because ECMO does not decompress the left ventricle, draining the left atrium can reduce left ventricular distension allowing myocardial rest and recovery. Furthermore, it can also protect from lung injury due to cardiogenic pulmonary edema or hemorrhage from severe left atrial hypertension (69, 74). Even though statistical independence was not confirmed in the final model, we believe that patients with left atrial hypertension could benefit from left-heart decompression. Project 5 will investigate the role of LA decompression in this population. Additionally, Project 3 showed that patients receiving heart transplantation on-ECMO had significantly improved survival, as previously suggested (44). Thus, when there are no signs of recovery on ECMO support, early evaluation and listing for cardiac transplantation can be considered as an exit strategy. Finally, ECMO complications, e.g. surgical bleeding, represent other factors significantly associated with mortality, that may be amenable to prevention or intervention. Reduction of surgical bleeding complications with aggressive modification of anticoagulation protocols, use of hemostatic agents, and surgical intervention for hemostasis may be used to improve outcomes for these patients.

In **Project 4**, we have investigated a relatively large cohort of patients who underwent cardiopulmonary resuscitation with ECMO (ECPR) at BCH in the last 10 years (n=182), their outcome, and factors associated with either mortality or severe functional impairment at discharge. We have shown that 52% of cardiac patients undergoing ECPR either died or experienced severe functional impairment (irreversible coma or vegetative state, FSS≥16) at the time of hospital discharge. This is on par with results from the THAPCA trial and other studies of ECMO rescue of in-hospital pediatric CA. (62, 83, 147, 148). Remarkably, survivors at 6 months had n FSS median score of 6 (IQR 6-8), which corresponds to a good cerebral performance by PCPC categories. (146)

PROJECT 4

In this study, we modeled mortality and unfavorable neurologic outcome at hospital discharge and at 6 months, reaching remarkable accuracy (AUC >0.9). Factors found to independently predict the adverse outcome were FSS on admission, ECMO duration, and detailed scoring of both organ dysfunction – using the validated PELOD-2 score - and neurologic injury - graded with the novel ASPECTS score. PELOD-2 score was calculated every day for each patient for the first 28 days of admission. This methodological choice allowed us to achieve granularity on the degree of organ dysfunction. Subsequently, summary measures such as mean, median, and worst PELOD-2 values were modeled to achieve the best accuracy in predicting the outcome. Higher mean PELOD-2 was found to be associated with adverse outcome both at discharge and at 6 months. To grade the amount of neurologic injury, we used, for the first time in pediatrics, a validated score for hypoxic-ischemic injury, the mASPECTS score (or ASPECTS-DWI for magnetic resonance) as well as a quantification of brain hemorrhages. As PELOD-score for organ damage, the use of the ASPECTS score allowed us to achieve granularity, which we incorporated into the predictive model, significantly improving its accuracy and prognostic value. Future steps of this project may include creating a model able to predict the precise FSS score at discharge or six months, or even specified components of the score, permitting a more granular prediction of neurologic and functional outcome.

As highlighted before, the identification of predictors of mortality or severe functional outcome is crucial, not only for defining prognosis, but also for identifying modifiable factors that may change the outcome. Whether or not the amelioration of these potentially modifiable factors - as the treatment of the left atrial hypertension in Project 3, the PELOD-2 components and the ASPECTS score in Project 4– may modify this association and therefore the outcome in a sub-category of patients, this can only be determined by ad-hoc studies. In the last part of this Ph.D. Thesis, we have investigated two different interventions on modifiable factors in patients undergoing resuscitation, which may be able to modify the outcome.

In **Project 5**, we have investigated the role of the left atrial decompression, an invasive procedure, in a subset of patients with biventricular physiology supported with ECMO. As previously mentioned, while VA-ECMO effectively supports organ perfusion in the setting of a failing heart, it increases the LV afterload which rises LV end-diastolic pressure and causes LV dilation. Additionally, LA hypertension may cause significant pulmonary edema which can negatively affect the right ventricular function and the respiratory gas exchange. In this setting, LA decompression, either surgical or transcatheter, has been proposed as a mean to mitigate these adverse events both in adults and pediatric patients (70–73, 75, 76, 155). However, studies in pediatric populations are scarce and include small samples. Ideally, a randomized controlled trial would represent the perfect design to assess the value and effectiveness of treatment. However, randomization of critically ill patients in a trial evaluating an invasive procedure is significantly challenging. In this setting, the use of advanced statistical techniques – i.e. the propensity-score approach – is considered highly valuable, since it is able to adjust for treatment-related baseline differences, resembling the randomization process.

In our large multicenter cohort of pediatric patients with biventricular physiology supported with ECMO, we have shown, using a propensity-score-weighted analysis, that LA decompression was independently associated with decreased in-hospital adverse outcome (mortality, transplantation, or conversion to VAD), suggesting that these patients may benefit from LA decompression.

Certainly, this is a selected population of patients who required ECMO support due to severe LV impairment, with 60% of them supported with more than 100 ml/kg/min of ECMO flow at 4 hours. Likely, these high ECMO flows may have also contributed to increased LV afterload. (162) Consistently, ECMO flows at 4h was retained in the final logistic regression model as an independent risk factor for adverse outcome - with higher ORs at increased flows - while LA decompression and use of systemic vasodilators were identified as protective. Other risk factors for adverse outcome identified by our model may all be related to either insufficient decompression of the LV or insufficient ECMO flow: pulmonary hemorrhage (likely related to LA hypertension), cardiac arrhythmias (possibly related to high filling pressures), renal failure (likely secondary to either right ventricular failure of insufficient ECMO flow), hypoglycemia (likely related to liver failure secondary to right ventricular failure), and acidosis (likely secondary to insufficient ECMO flows).

To the best of our knowledge, this study represents the largest reported cohort of pediatric patients on VA-ECMO who underwent LA decompression, and the first propensity-score adjusted analysis to access its association with in-hospital adverse outcome. Although prospective studies may be more powerful to confirm the results, we think that this analysis may significantly help to clarify the role of this intervention in patients supported with ECMO for a failing heart, and help to guide the medical decision-making.

Our final Project - **Project 6** - represents the first step of a bigger, ambitious, journey. Our group has recently shown that administration of inhaled hydrogen (H2) during reperfusion following an experimental global ischemic injury in an animal model significantly decreases the degree of neurologic and renal injury (100), mainly through chemical reduction of the hydroxyl radical (141). These results opened a real window of opportunity for the use of H2 in patients who suffers from ischemia – and consequently of ischemia-reperfusion injury - during the resuscitation event, as CA or ECPR. Following these promising results, our group conducted the first New Drug, FDA-approved, Phase 1 trial assessing the safety of the inhaled 2.4% H2 in healthy adult volunteers, which is reported in this Thesis as Project 6.

In this Phase 1 trial, we have shown that the administration of 2.4% H2 via HFNC appears to be safe and well-tolerated, without clinically significant adverse effects in healthy participants. Compared with baseline measures, there were no clinically significant changes in vital signs, neurologic examination, pulmonary function testing, or EKG changes, nor in any lab parameters –markers of organ failure and hemato-immunologic tests - associated with up to 72 hours of H2 inhalation. Certainly, future studies will require to be powered for safety to confirm these important results. However, the demonstration that H2 is safe in healthy subjects represents a crucial step in the pathway towards the use of this new drug as a therapeutical strategy during ischemia events.

This study lay officially the groundwork of a multicenter randomized controlled trial, which will be conducted in a pediatric population of cardiac patients who underwent ECPR at Boston Children's Hospital and in other two tertiary-care centers. Specifically, using data from Project 4, we have designed a feasibility and safety multicenter, partially-blind, randomized controlled trial of H2 gas administration in pediatric ECPR patients with congenital heart disease. We have hypothesized that the administration of H2 gas in ECPR patients will be feasible, with H2 being administered for >95% of the first 72 post-arrest hours, and will be environmentally safe; additionally, we have hypothesized that the number of clinically unexpected adverse events (adjudicated by an

external review board blinded to treatment allocation) will not be higher in H2-treated patients compared with those treated according to standard of care. As a secondary aim, guided by Project 4, we will explore whether serial portable brain MRI evaluations may help improving the predictive accuracy for functional status (evaluated by FSS) at discharge and 6 months following ECPR. Of note, the study protocol has been recently approved by the FDA, which has defined Project 6 as pivotal for the design of these future steps. This randomized control trial will represent the next step forward of this Ph.D. Project.

Conclusion

With this Ph.D. Project, we have provided new insight into resuscitation and outcomes in critically ill pediatric patients with cardiac disease. We have explored different opportunities of data definition, event prediction, and treatment investigation to prevent resuscitation and improve outcomes in this high-risk population - from big data, to bench, to bedside.

In the first part of this Thesis, we have defined the incidence and outcomes of resuscitation events in the overall cardiac pediatric population admitted to the CICU/PICU, as well as in different high-risk populations such as post-operative cardiac patients, patients who failed to wean from CPB, and patients who underwent ECPR. Overall, the incidence of CA in the cardiac pediatric population remains not negligible, however, the trend seems to be improving over time. In the last decades, an intense effort has been made to identify risk factors and therefore to predict any adverse events in this high-risk population. In this Thesis, we have shown that advanced monitoring and associated technologies – e.g. the *big data* that are constantly recorded by our monitors, as well as some novel easily computable hemodynamic indices - may significantly help in predicting resuscitation events in this high-risk population. In the future, artificial intelligence techniques may be integrated into the bedside monitor, which may automatically and real-time compute these values as a support tool for the prediction of adverse outcomes.

Further, we have shown that outcomes of resuscitation in the cardiac pediatric population remain poor. By random-effect meta-analysis of literature data, we have shown that the overall pooled mortality rate after cardiac arrest was high at 54% (CI95%: 47-62%). Similarly, mortality among patients supported with ECMO for FTW from CPB after cardiac surgery or after ECPR were 55% and 52%, respectively. To define patients at higher risk and to identify potentially modifiable risk factors, we have developed models able to predict with high accuracy the adverse outcome. In the cohort of patients who failed to wean from CPB, we have shown that younger age, genetic abnormalities, comorbid conditions, complex cardiac surgical procedures, as well as longer ECMO support and ECMO complications were all independent risk factors for in-hospital mortality. Additionally, LA decompression was identified as a risk factor in the model including ECMO-related factors only. In the cohort of patients who underwent ECPR, we have shown that single ventricle physiology, FSS at admission, longer ECMO duration, the degree of organ dysfunction measured with the PELOD-2 score, as well as the degree of neurologic damage assessed with the novel mASPECTS score, were all independently associated with death or severe functional impairment at discharge. Overall, these high-accuracy models may significantly help prognostication in this population. Most importantly, they were essential for the identification of potentially modifiable risk factors for adverse outcomes, which we have further investigated in the last part of our Thesis.

In the final section of this Ph.D. Project, we have investigated two interventions that address two of these modifiable factors. In Project 5, we have shown, by propensity-score adjusted analysis, that LA decompression

independently decreased the risk of in-hospital adverse outcomes in pediatric cardiac patients with biventricular physiology supported with ECMO. Although only a randomized controlled trial would effectively confirm this evidence, we believe this result may add more evidence in supporting LA decompression in this category of patients and may help design future higher-evidence trials. In Project 6, we have investigated the safety of a new FDA-approved drug, the inhaled H2, potentially able to modify the degree of brain ischemia-reperfusion injury. In this Phase-1 FDA-approved study, we have shown that inhalation of 2.4% H2 is well tolerated with no clinically significant adverse effects. Our group is currently leading a multicenter randomized controlled trial aimed to assess the feasibility and safety of inhaled H2 in pediatric cardiac patients who undergo ECPR, which will serve as a pilot study for a larger randomized controlled trial to prove H2 efficacy. The study protocol of this randomized controlled trial has recently received full approval by the FDA and will represent the future step of this Ph.D. Project.

Overall, although outcomes after resuscitation in pediatric cardiac patients remain poor, we have shown that there are multiple opportunities to act (to define, predict, treat – from big data, to bench, to bedside), which are all sharing the final aim to improve the quality of care of these patients, as well as the quality of life and their overall outcome. Future efforts may be directed on the improvement of data sharing, multicenter collaborations, artificial intelligence application, and further application of innovative translational research projects, as the use of inhaled H2 in randomized controlled trials.

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