Review Article

Pediatric Resuscitation: Outcome Effects of Location, Intervention, and Duration

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Received 24 September 2014; Accepted 24 December 2014

Academic Editor: Ming-Hwang Shyr

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Cardiopulmonary resuscitation (CPR) is performed in order to restore oxygen delivery and prevent multiorgan system failure and death. Prompt initiation of CPR with appropriate medical or surgical therapy may shorten arrest duration before irreversible organ injury occurs. The brain is most susceptible to irreversible anoxic injury. Survival data suggests that children are more likely than adults to survive and have good neurologic outcomes following cardiac arrest. In this review of pediatric resuscitation, we discuss important predictors of postarrest outcomes as well as advances in resuscitation science focusing on the critical importance of oxygen delivery during periarrest care.

1. Introduction

Oxygen delivery ($DO_2$) is the product of cardiac output (CO) and arterial oxygen content ($CaO_2$) as $DO_2 = CO \times CaO_2$. Cardiac arrest results in cessation of oxygen delivery and development of global oxygen debt. When oxygen delivery is not restored, multiorgan failure and death ensue [1]. Cardiopulmonary resuscitation (CPR) is performed in order to restore oxygen delivery and prevent cell death. When the etiology of cardiorespiratory failure is clear and recognizable, expedient initiation of CPR with appropriate medical or surgical therapy may shorten arrest duration before irreversible organ injury occurs. The brain is most susceptible to irreversible anoxic injury. Survival data suggests that the potential to rescue following cardiac arrest is greatest in children [2, 3].

According to the American Heart Association (AHA), the first use of mouth-to-mouth resuscitation occurred in the mid-1700s. The first documented chest compressions were performed in the early 1900s. Leonard Cobb organized the world's first mass citizen training in CPR in Seattle, Washington called Medic 2. More than 100,000 people were trained during the first two years of the program. While most early studies focused on adult resuscitation, attention to pediatric resuscitation has increased dramatically in the last quarter century.

Early statistics suggest that most pediatric arrest victims either die or have poor neurologic outcomes [2–11]. Efforts to improve outcomes are directed at augmenting oxygen delivery and mitigating oxygen debt during all phases of periarrest management. In this review of pediatric resuscitation, we discuss important predictors of postarrest outcomes as well as advances in resuscitation science focusing on the critical importance of normalization of oxygen delivery during periarrest care.

2. Predictors of Outcome

2.1. Location of Arrest

Location of arrest is highly predictive of morbidity and mortality. Cardiac arrests are broadly classified as in hospital (IHCA) or out of hospital (OHCA) cardiac arrests. Current life support algorithms are designed to help lay providers and healthcare professionals resuscitate arrest victims in any setting.

2.1.1. Out of Hospital Cardiac Arrest (OHCA)

According to the 2013 AHA Heart Disease and Stroke Statistics, approximately 360,000 patients suffer OHCA annually in the United States. In a comprehensive review of OHCA in children, Atkins et al. cited an incidence of 8 per 100,000 person years. The Resuscitation Outcomes Consortium (ROC) analyzed
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The incidence of OHCA in children aged 1–19 years is significantly less [3].

The ROC study documented overall post-OHCA survival of 6%. Infants and adults have the lowest survival rates of 3% and 6%, respectively. Children beyond infancy experience higher survival rates (9%) [3]. Most pediatric OHCA occur in males (56%) under one year of age (62%). Few pediatric arrests are witnessed (31%) or receive bystander CPR (30%) administered. Factors that seemed to favor hospital discharge include having a witnessed arrest with bystander CPR of short duration prior to return of spontaneous circulation (ROSC) [12, 13].

### 2.2. Perioperative Cardiac Arrest (POCA)

Perioperative cardiac arrest (POCA) is an outlier with significantly higher survival than other forms of IHCA and OHCA. These arrests typically occur in the operating room or recovery room. Common etiologies of POCA arrest include volatile and local anesthetic toxicity, hypovolemia, airway emergencies, venous air embolism, and anaphylaxis [18, 19].

The Pediatric Cardiac Arrest Registry study performed from 1994 to 1997 concluded that intraoperative arrests were frequently medication related and commonly associated with the volatile anesthetic agent Halothane [18]. Subsequent analyses suggest that medication related arrests have decreased over time. Volatile anesthetic associated cardiac arrest has declined with the reduction of halothane use [19].

A recent quality improvement database review of more than 217,000 anesthetics documented 160 cardiac arrests within a 24 h perioperative period. Approximately 25 percent of these arrests were directly attributed to anesthesia. Fourteen deaths were attributed to the anesthetic (an incidence of 0.6 per 10,000 anesthetics) [20]. Additionally, 23 of the 160 arrests were found to have anesthesia as a contributing factor (incidence of 1.1 per 10,000). Airway complications resulted in over 60 percent of the anesthesia related perioperative arrests with a mortality rate of nearly 30 percent [20].

Children with congenital heart disease who suffer POCA are at high risk of mortality based on severity of illness [21]. Following POCA, one-third of children with congenital heart disease die versus one-quarter of children without cardiac disease. Children with single ventricle physiology have the highest incidence of POCA, while those with cardiomyopathies experience the highest mortality [21]. Other risk factors include infancy (age less than 1 year), high ASA status, emergency surgery, and preexisting hematologic, oncologic, immunologic, genetic, or metabolic disease [7, 18, 22, 23].

While anesthetic agents are frequently implicated in POCA, it is important to remember that anesthetic effect may contribute to more favorable outcomes following ROSC. Most anesthetics decrease tissue oxygen metabolism resulting in lower DO₂ requirements, which may be protective after abrupt reductions in oxygen delivery as occurs in arrest scenarios [24].

### 2.3. Initial Cardiac Rhythm

The initial documented cardiac rhythm following cardiac arrest is a major predictor of survival [2]. Postarrest cardiac rhythms are divided into three subgroups: malignant ventricular dysrhythmias (ventricular fibrillation (VF) or ventricular tachycardia (VT)), asystole, and PEA. Arrhythmia incidence differs between pediatric and adult arrests [2]. Asystole is the predominant presenting rhythm in children followed by PEA [4]. Ventricular dysrhythmias (VF/VT) are least prevalent. However, ventricular dysrhythmias occur more commonly in the setting of IHCA, occurring in up to 25% of children [2, 5].

The timing of malignant ventricular dysrhythmia generation is predictive of postarrest survival. Primary VF/VT is associated with more than 30% survival to discharge [5]. Early defibrillation of VF/VT is associated with high rates of ROSC and favorable outcomes [25]. Secondary development of VF/VT has lower survival than primary VF/VT, pulseless electrical activity (PEA), or asystole [5]. Irrespective of rhythm survival to discharge, ROSC, and neurological recovery are all higher in children [2].

### 2.4. Compression Duration

The relationship of compression duration to survival has been studied extensively [2, 5, 7, 10, 26–28]. Early studies of pediatric resuscitation concluded that patients who received compressions for more than 20 minutes were irretrievable [26]. However, with improved pediatric arrest outcomes this conclusion has been refuted [10]. The impact of compression duration on pediatric arrest outcomes was evaluated in a multicenter study of 267 patients.
from 6 hospitals [28] (Figure 1). Children were stratified according to etiology of arrest (respiratory versus cardiac). In setting of respiratory failure induced cardiac arrest survival declined exponentially after 15 minutes of duration, but after cardiac failure induced cardiac arrest, many children survived with good neurologic outcomes with compression duration of up to one hour [28]. Matos et al. divided compression duration into three categories (1–15, 16–35, and greater than 35 minutes) and concluded that mortality and neurological disability varied directly with compression duration yet still observed 16.5% survival and favorable neurologic recovery with compressions greater than 35 minutes. In this study, cardiac surgical patients had the highest survival rate, more so in those receiving extracorporeal mechanical support (ECMO) rescue. Traumatic arrest patients had the lowest survival rates [10].

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3.1. Prearrest Interventions. Enhanced identification of evolving oxygen debt in the prearrest setting allows for goal directed interventions prior to arrest development. Multifocal efforts to aid provider management of at risk children include early warning system scores, medical emergency teams, and advanced noninvasive monitoring.

3.1.1. Early Warning System Scores. Standardized severity of illness scoring systems have been developed for early identification of at risk patients. Any effective scoring system must be reliable and reproducible. When critical abnormalities are identified there must also be an appropriate response [29]. The efficacy of any early warning system score is dependent on observers who are able to reliably assess and measure individual components of the score and initiate proper interventions [29].

The Pediatric Early Warning System (PEWS) Score incorporates heart rate, blood pressure, capillary refill time, respiratory rate, oxygen saturation, and need for supplemental oxygen [30]. Parshuram et al. conducted a multicenter case control study of bedside PEWS scores in more than 2000 children admitted to 4 hospitals in Canada and the UK. This study revealed a temporal association between escalation of bedside PEWS scores and unplanned ICU admission and code blue events [31].

Many institutions, including ours, routinely use early warning system scores in an effort to reduce cardiac and respiratory arrests. Unfortunately, there remains a lack of consensus on an accepted pediatric scoring system. Currently, at least nine scoring systems are in use throughout North America, Europe, and Australia [29]. Critics of standardized severity of illness scores cite high false positive rates as well as other methodological flaws [29, 32].

3.1.2. Medical Emergency Teams. Medical emergency teams (METs) or rapid response teams (RRTs) were developed for the urgent assessment of at risk patients. These teams may function as the efferent response to the critical afferent early warning score signal. MET models were initially developed for adult hospitals. Adult studies report reduced code blue incidence and in hospital mortality [33, 34]. This data has prompted pediatric centers to develop METs.

There is growing evidence that pediatric METs are effective in reducing clinical deterioration of at risk children resulting in lower code blue rates and in hospital mortality [35–38]. A meta-analysis of available pediatric METs revealed reduced in hospital mortality and cardiac arrest outside of the ICU [39]. These conclusions were bolstered by a Canadian multicenter pediatric MET study that showed lower PICU mortality [40]. Unplanned ICU admissions may increase following MET implementation [37]. Many METs function as separate entities from code blue teams limiting resource overextension in a large tertiary care pediatric hospitals. Simulation based MET training exercises have been linked to improved team performance and outcomes [41].

3.1.3. Advanced Monitoring. Excluding respiratory failure, shock is the most common cause of pediatric cardiac arrest [4, 42]. In biochemical shock, inadequate DO2 results in oxygen debt and anaerobic metabolism [1, 43]. The initial evaluation of a child with suspected shock includes an assessment of indices of perfusion including heart rate, blood pressure, capillary refill time, urine output, and mental status. These parameters do not correlate well with the severity of circulatory insufficiency or oxygen debt [42–47]. Modern goal directed shock resuscitation models incorporate systemic venous oxygen saturation (SvO2) measurement as a surrogate for oxygen delivery based on the Fick equation as $\text{SvO}_2 = \text{SaO}_2 - \frac{\text{VO}_2/\text{DO}_2}{4}$. However, SvO2 monitoring requires central venous access, which may not be feasible in many prearrest environments (i.e., hospital wards).

Near infrared spectroscopy (NIRS) represents an important method of assessing regional oxygen delivery in completely noninvasive manner. The NIRS derived regional oxygen saturation (rSO2) reflects tissue venous saturation. When compared with the arterial oxygen saturation this allows for
an estimation of regional oxygen metabolism based on a variation of the Fick relationship (\(rSO_2 = SaO_2 - VO_2/DO_2\)) [45, 47].

Two-site cerebral and somatic NIRS monitoring enables a more comprehensive assessment of \(SvO_2\) and systemic DO_2. Two-site cerebral and somatic NIRS monitoring measures regional oxygen delivery to the autoregulated cerebral and sympathetically mediated renal-somatic circulations. Under normal conditions, the renal somatic saturation (\(rSO_2 SC\)) is approximately 10 percent greater than the cerebral saturation (\(rSO_2 C\)) [48]. A reduction in this somatic to cerebral difference (\(\Delta rSO_2 SC\)) is associated with the development of somatic hypoperfusion and anaerobic metabolism [49].

Sympathetically mediated vasoconstriction with progressive shock results in renal hypoperfusion, reduced somatic regional saturation, and eventual loss of pulsatility. NIRS devices perform well in shock states when blood flow is nonpulsatile as occurs with profound tissue hypoperfusion. This lack of reliance of pulsatile flow makes NIRS monitoring ideal in periarrest situations. Using two site NIRS monitoring, earlier detection and goal directed therapy of shock is possible [49–52].

3.1.4. CPR Guidelines. The AHA recommendations for single and multiple provider CPR have evolved over time. The 2010 guidelines represented a philosophical shift to circulation-based resuscitation [53]. Historically, CPR proceeded according to the ABC sequence of airway-breathing-circulation (ABC). The 2010 recommendations were modified to circulation-airway-breathing (CAB) with compressions preceding other interventions. In fact, compression only CPR is recommended for single provider CPR of an adult as most adult arrests are primarily cardiac in origin, and generation of adequate coronary perfusion pressure is essential for ROSC [53–55]. Compression first and compression only CPR emphasize restoration of cardiac output (CO) to augment coronary perfusion pressure and coronary DO_2 to achieve ROSC [53].

While the AHA recommends compression only CPR for single providers during adult arrests, this is not true for pediatric CPR. Most pediatric cardiac arrests are asphyxial in nature. The reduction of arterial oxygen content of blood during the asphyxial period preceding arrest contributes to DO_2 limitation and increasing cellular oxygen debt prior to cessation of cardiac output. Thus, augmentation of the arterial oxygen content with assisted ventilation is critical following asphyxial pediatric arrest. There is data that suggests restoration of oxygenation and ventilation via conventional CPR following asphyxial arrest is associated with improved outcomes when compared to compression only CPR in pediatric OHCA [56]. This is further supported by animal studies of asphyxial cardiac arrest [57–60].

IHCA resuscitations generally involve healthcare providers performing multiprovider CPR. This lends itself to the performance of multiple tasks in parallel and the AHA acknowledges that there may be variation in the sequence which airway breathing and circulation are supported during in hospital multiprovider CPR [53]. The ability to simultaneously augment both cardiac output and arterial oxygen content results in cumulative improvement in oxygen delivery to ischemic tissues, which may contribute to improved IHCA outcomes.

3.1.5. Compression Quality. Appropriate compression rate and depth is critical to performance of high quality. The 2005 AHA/ILCOR guidelines increased the compression to ventilation ratio for single person CPR from 15:2 to 30:2 as higher compression to ventilation ratios have been shown to increase coronary perfusion pressure, diastolic blood pressure, and coronary DO_2 [53, 61, 62]. Hemodynamic goal directed CPR targeting coronary perfusion pressure of 20 mmHg has been shown to improve survival in porcine arrest models [63].

The current 2010 guidelines recommend a minimum rate of 100 compressions per minute and minimum depth of compression of 50 mm [53]. These recommendations replaced the 2005 recommendations of 38 mm compression depth. While the previous target has been shown to generate a systolic blood pressure of at least 80 mmHg and diastolic blood pressure of at least 30 mmHg, compression depth greater than 51 mm during CPR is associated with greater 24-hour survival rates [63]. However, a major criticism of the 2010 recommendations is difficulty achieving the appropriate compression rate and depth during actual code events [63]. Rolling bedside resuscitation refresher courses utilizing compression quality monitoring are ongoing [64].

3.1.6. Resuscitative Medications. The most commonly administered vasoactive medication following cardiac arrest is epinephrine. Epinephrine increases coronary perfusion pressure, which is essential to achieve ROSC. However, high dose (>100 mcg/kg) epinephrine inhibits oxygen transport resulting in reduced DO_2 [65]. Above this threshold, the cumulative epinephrine dose is directly related with the level of impairment of DO_2 [65]. Both high dose (≥100 mcg/kg) and standard dose (10 mcg/kg) regimens of epinephrine have been utilized during pediatric code events. Studies evaluating the use of high dose epinephrine have failed to demonstrate improved survival or neurologic outcomes. Animal studies comparing 200 mcg/kg versus 20 mcg/kg doses during resuscitation after cardiac arrest reveal increased mortality with high dose epinephrine [66, 67].

In a randomized control trial of pediatric IHCA, Peroni et al. compared 100 mcg/kg and 10 mcg/kg dose epinephrine and demonstrated reduced survival at 24 hours after arrest with high dose epinephrine [68]. Retrospective analyses of pediatric IHCA and OHCA pediatric arrest have failed to show a benefit to high dose epinephrine [69, 70]. Similarly, less frequent epinephrine dosing following cardiac arrest has been linked to improved survival when compared to recommended dosing interval of every 3–5 minutes [71].

Bicarbonate and calcium administration during neonatal and pediatric resuscitations remain a source of controversy. Neither medication has been shown to be associated with improved survival following cardiac arrest. The most recent review of pediatric resuscitations from the GWTG Registry linked that both medications to reduced survival...
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According GWTG and AHA guidelines, the only clear indications for calcium administration are hyperkalemia, hypocalcemia, or calcium channel blocker toxicity [42, 72]. Calcium administration has been linked to decreased odds of survival and worse outcomes in pediatric VF/VT arrest [5, 73]. Bicarbonate administration is only indicated during arrest secondary to hyperkalemia or toxin ingestions such as tricyclic antidepressants [42, 72].

3.1.7. Mechanical Support. Extracorporeal membrane oxygenation (ECMO) support may be utilized for refractory circulatory or respiratory failure [74]. All mechanical support devices consist of a pump and an oxygenator allowing for augmentation of cardiac output and arterial oxygen content. There are veno-veno (VV) and venoarterial (VA) modalities of ECMO. Veno-Venous ECMO is indicated for respiratory failure with preserved myocardial pump function, while VA ECMO is required for combined cardiorespiratory failure. Cannulation for mechanical support is typically performed in either the intensive care unit or in the operating room. Many pediatric centers, including ours, have rapid response ECMO teams in place so to shorten arrest duration when the need for mechanical support has been identified [75]. Acceptable survival and neurologic outcomes may be achieved following ECMO rescue, even in the setting of prolonged resuscitation, especially children with preexisting cardiac disease [76–78]. Survival in children with cardiac disease who require ECMO rescue may approach 50% [79].

3.2. Postresuscitation Interventions

3.2.1. Therapeutic Hypothermia. Neuronal cell death following cardiac arrest occurs within minutes. Secondary injury develops during the ischemia reperfusion phase and evolves in the days following the injury. Mechanisms involved in postreperfusion secondary injury include cytotoxic cerebral edema, seizures, excitotoxicity, free radical production, and neuronal apoptosis [80]. The severity of these destructive processes determines whether at risk neurons within the ischemic penumbra survive. Therapeutic hypothermia (TH) has been shown to inhibit many of these processes. Induction of hypothermia also serves to optimize cerebral oxygen economy by reducing cerebral metabolic rate and cerebral oxygen consumption [80, 81]. Methods utilized include surface cooling (blankets, ice packs, pads, and immersion) and core cooling.

The patient populations with the most published data supporting therapeutic hypothermia are infants with hypoxic ischemic encephalopathy (HIE) and adults with cardiac arrest. Cochrane Database Reviews of neonates with HIE have reduced mortality and neurologic disability at 18 months when treated with TH [82]. Similarly, TH is also associated with improved neurologic outcomes in adults following OHCA [83–88]. There is insufficient data at this time regarding the efficacy of TH in pediatric patients following cardiac arrest [89].

Whether or not TH is utilized following cardiac arrest, it is clear that fever following arrest is associated with worse outcome [90–92]. Current recommendations include avoidance of fever and aggressive treatment of hyperthermia post cardiac arrest given this linkage to poor outcomes [93].

3.2.2. Electroencephalogram Monitoring. Cerebral hypoxic ischemic injuries lower the seizure threshold in children following cardiac arrest. Untreated seizures increase cerebral oxygen consumption and exacerbate secondary brain injury. Continuous electroencephalogram (EEG) monitoring is useful to detect epileptiform activity in children who may have subclinical seizures or who may be under neuromuscular blockade. Studies of EEG monitoring in children report a high incidence of postarrest seizure activity and status epilepticus [94]. Seizures in critically ill children are predictive of decreased survival and worse neurologic outcomes [95]. Continuous EEG monitoring may also provide important prognostic information as reduced EEG activity and reactivity portend poor neurological outcomes [96].

4. Summary

While pediatric arrest outcomes remain suboptimal, maintaining effective oxygen economy at each phase of care may improve survival and neurological status. Arrest location and initial cardiac rhythm remain significant predictors of mortality. Witnessed, out-of-hospital arrests followed by prompt by-passer intervention improve survival to hospital discharge. Early warning systems, medical emergency teams, and advanced noninvasive monitoring improve identification of at risk patients in the in-hospital prearrest setting. CPR guidelines have continued to evolve, with current focus on compression quality and pharmacotherapy. Finally, in the postarrest setting, favorable cerebral oxygen metabolism is maintained to optimize neurologic outcome. It is imperative that providers focus on all aspects of periarrest care in order to achieve favorable neurologic recovery and survival.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

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