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Post-Cardiac Arrest Syndrome: Focus on the Brain

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Abstract

Purpose of review—The field of pediatric cardiac arrest (CA) experienced recent advances secondary to multicenter collaborations. This review summarizes developments during the last year and identifies areas for further research.

Recent findings—A large retrospective review demonstrated important differences in etiology, severity and outcome of in-hospital versus out-of-hospital pediatric CA. This distinction is relevant to interpretation of retrospective studies that may not distinguish between these entities, and in planning therapeutic clinical trials. Hypothermia was further evaluated as a treatment strategy after neonatal hypoxia and leaders in the field of neonatology recommend universal use of hypothermia in term neonates. In infants and children after CA, there are inadequate data to make a specific recommendation. Two retrospectives studies evaluating hypothermia in children after CA found that it tended to be administered more frequently to sicker patients. However, similar or worse outcomes of patients treated with hypothermia were observed. Use of extracorporeal membrane oxygenation (ECMO) is another emerging area of research in pediatric CA, and surprisingly good outcomes have been seen with this modality in some cases.

Summary—Therapeutic hypothermia and ECMO continue to be the only treatment modalities over and above conventional care for pediatric CA. New approaches to monitoring, treatment and rehabilitation after CA remain to be explored.

Keywords

Cardiac Arrest; Child; Hypothermia; ECMO

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Introduction

Pediatric cardiac arrest (CA) results from asphyxia in a majority of cases (80-90%). It is a distinct entity from adult CA, which is predominantly due to ventricular fibrillation. During asphyxia, a period of hypoxemia, bradycardia, and hypotension precede CA. The morphological pattern of brain damage is different in asphyxial and ventricular fibrillation CA, as demonstrated a decade ago by Dr. Safar and colleagues [1]. In spite of these proven differences, interventions during CPR and in the postresuscitation phase have been translated from adult studies, partly due to scarce clinical trials in the pediatric population.

Post-cardiac arrest (post-CA) syndrome include brain injury, myocardial dysfunction, as well as systemic ischemia/reperfusion (a sepsis-like state [2]). In this review, we summarize pediatric data published during in the last year regarding post-CA syndrome focusing on new developments in the area of brain injury post-CA.

Post-cardiac arrest syndrome

The four phases of resuscitation in CA are: pre-arrest (events leading to CA, i.e. hypoxia, bradycardia, hypovolemia, arrhythmia), arrest (no flow), resuscitation (chest compressions: low or no flow), and recovery post resuscitation [3]. Recovery post resuscitation is the focus of this review. Negovsky was the first to identify that a distinct phase of resuscitation with specific pathology begins after return of spontaneous circulation (ROSC) [4]. Recently, the term *post-cardiac arrest syndrome* was proposed in a scientific statement by the International Liaison Committee on Resuscitation, and four phases of this syndrome were identified: i) immediate post-arrest phase (first 20 min after ROSC), ii) early post-arrest phase (20 min to 6-12 h), iii) intermediate phase (6-12 h to 72 h) and iii) recovery phase (beyond 3 days). Therapy targeting each of these phases has a defined goal: interventions in the early phases focus on limiting further injury and vital support, while those in the later phases focus on prognostication and finally rehabilitation [** 5].

Incidence of cardiac arrest

Epidemiology and outcomes of out-of-hospital CA were reported in a prospective cohort of 624 infants and children who received CPR between 2005 and 2007. The incidence of CA in infants approaches that of adults (72.71 vs. 126 per 100 000 person years) and is higher compared with children and adolescents (3.73 and 6.37 per 100 000 person years, respectively) [* 6].

In-hospital versus out-of-hospital cardiac arrest

Pediatric CA can occur out of the hospital setting (out-of-hospital CA) or in hospital (in-hospital CA). A Retrospective review reported pre-arrest characteristics, post-arrest interventions, mortality and neurological outcome after in- and out-of-hospital CA and concluded that these represent discrete entities with respect to etiology, first monitored rhythm recorded, mortality during resuscitation and in the post-CA period, and neurological outcome. The difference in outcome between in- and out-of hospital CA may simply represent a shorter duration of no-flow and higher quality CPR for patients after in-hospital than out-of hospital CA. Thus, when evaluating different therapies, these groups of patients should be analyzed separately since they represent different degrees of disease severity [** 7]. A comparison of in- and out- of hospital CA from the previous reference is presented in Table 1.

Epidemiology of post-cardiac arrest syndrome: survival and neurological outcome

In a recent recent large prospective pediatric cohort study, overall survival from *out-of-hospital CA* was 6.4% (children 9.1%, adolescents 8.9%, and infants 3.3%). A subset analysis of patients who achieved ROSC demonstrated that those successfully resuscitated before hospital arrival had a higher rate of survival to hospital discharge compared with patients transported in CA (37% vs. 10%) [6]. Similarly, patients with ROSC after out-of-hospital CA in another study, had chance of survival to hospital discharge of 38%. Fifty six percent of these patients had good neurological outcome [7].

Patients with *in-hospital CA* have a better survival to hospital discharge compared with patients with out-of-hospital CA. Survival rates for in-hospital CA ranged from 16 to 38% in different studies published in the last decade [3]. Patients who achieved ROSC after in-hospital CA, had a rate of survival to discharge of 49%. Seventy eight percent of these patients had good neurological outcome [7].

Favorable neurological outcome is more often achieved in patients with in-hospital CA as compared with out of hospital CA (47% vs. 24%), in spite of patients with in-hospital CA having a higher frequency of abnormal pre-arrest neurological status (34 vs. 17%) and chronic preexisting conditions (88 vs. 49%) (table 1).

Mechanisms of brain damage

Pediatric asphyxia produces a state of hypoxemic hypotensive perfusion before CA. Pediatric and neonatal models of hypoxia-ischemia and asphyxia exist, and therapies, brain tissue monitoring, cerebral blood flow and outcomes can be studied using these models. Data related to mechanisms of brain damage from children after CA are limited. During ischemia, energy stores of the brain are depleted, and toxic metabolites accumulate (lactate, and hydrogen ion). Upon reperfusion, injury to the brain is secondary to excitotoxicity, calcium accumulation, protease activation, and formation of reactive oxygen and nitrogen species. The pathology of neuronal damage after CA is a combination of apoptosis, autophagy and necrosis, along with inflammation.

Cerebral blood flow, tissue oxygenation and biomarkers after CA

Post-resuscitation CBF in a pediatric model of asphyxial CA was recently shown to be highly dependent on both duration of CA and specific brain regions. Early after ROSC (5 to 15 min), hyperemia was limited to subcortical areas. Hypoperfusion of the cortex occurred after 15 min post-ROSC and was more pronounced for longer durations of CA, such as 9 to 12 min [8].

In clinical work, near infrared spectroscopy (NIRS) is a noninvasive tool that measures cortical regional oxyhemoglobin saturation as an indirect indicator of cortical brain oxygenation and CBF [9]. During cardiopulmonary bypass for congenital cardiac repairs, NIRS-derived cerebral oxygenation correlated with postoperative neurological changes [10]. To date there are no studies reporting its use in children post-CA. A report of one child monitored before and during a CA, demonstrated that the regional oxygen saturation decreased markedly during CA and CPR, and recovered after ROSC to levels below baseline [11]. Cerebral NIRS might also represent a potential early warning monitor to prevent progression to CA [12]. Electroencephalographic monitoring after CA is helpful in detecting seizures that may not be detectable by clinical examination [13].

Biomarkers have been studied after CA in adults with the aim of prognosticating neurological outcome. These biomarkers include neuronal specific enolase (NSE), S-100B, CPK-BB, and inflammatory markers. A review of this topic concluded that there are insufficient data supporting use of these biomarkers to predict outcome [14], although serum biomarkers have much more utility than simply prognostication, such as therapeutic monitoring or assessment of mechanistic targets or insult severity [15]. There are limited data evaluating these biomarkers in children after CA [16]. However, two recent studies show that biomarkers have great promise in pediatric CA- particularly NSE [17, 18].

Hypothermia

A multitude of therapies resulted in neuroprotection in animal models of CA and neonatal hypoxia-ischemia, however, only hypothermia was proven to offer clinical neuroprotection in term neonates after hypoxic ischemic events [19, 20] and in adults after CA [21, 22]. It is now universally accepted that early hypothermia, maintained for 24 to 72 hours, at brain temperatures of 32 to 34° C, improves neurological outcome in term neonates after hypoxia-ischemia and adults after ventricular fibrillation CA. There are insufficient data to make specific recommendation for use of hypothermia in infants and children.

In neonates with HIE, two large RCT published in 2005 suggested that hypothermia was associated with reduction in death and disability at 18 months after insult [19, 23]. Another large RCT of hypothermia after HIE was completed in the UK, along with follow up to 18 months, and data are under analysis at this time [24]. A RCT in the US proved that hypothermia is safe; there was also a trend in reducing death and decreasing disability at 18 to 22 months, but the study was not powered for this endpoint [*25]. Meta-analysis of studies published to date in the neonatal population reported a significant positive effect of hypothermia on disability and death [26-29]. Based on this evidence, leaders in the field of neonatology recommend universal use of hypothermia in neonates with hypoxic ischemic encephalopathy [**30].

There is a hiatus in studies of therapeutic hypothermia in infants and children after CA outside of the neonatal period. To date, only two retrospective studies have been published, along with a few case reports. One study, conducted by the Canadian Critical Care Trial Groups, reviewed clinical charts of patients treated after CA in four centers in Canada and one center in the UK from 2001 to 2003 [*31]. Patients treated with hypothermia had a greater severity of illness prior to initiating cooling compared with patients maintained normothermic (duration of CA: 30 min vs. 10 min, larger doses of epinephrine were required during resuscitation, greater use of ECMO, higher organ dysfunction scores on admission). Before adjusting for the severity of illness, mortality was higher after hypothermia. After adjusting for these variables, there was no difference in mortality between groups. Another study reviewed data from 181 pediatric patients treated with hypothermia (n=40) or normothermia (n=141) after CA from 2000 to 2006 at a single center in the US. There was no difference in mortality between the two groups. As in the previous study, patients treated with hypothermia tended to have a greater severity of illness (more unwittnessed CA, more doses of epinephrine administered until ROSC, and greater frequency of out of hospital CA) [32]. There are no prospective randomized trials published to date regarding therapeutic hypothermia in this population. There are two RCTs with active recruitment: Children's Hospital of Pittsburgh (USA) and Hospital for Sick Children (Canada) and two planned RCTs that will evaluate therapeutic hypothermia in children with out-of-hospital and in-hospital CA (http://clinicaltrials.gov).

Given that therapeutic hypothermia in the range of 33 to 34° is safe and potentially improves outcome, it should be considered in children with CA. The American Heart Association

guidelines recommend that therapeutic hypothermia be considered in infants and children after CA. However, a study conducted in 2004 assessing the knowledge of PICU physicians regarding hypothermia in the setting of CA reports that only 9% of participating physicians used hypothermia consistently in comatose children, and an additional 38% used it "sometimes". The hypothetical use of hypothermia was associated with the likelihood of post arrest recovery, and there was a wide variation in methodology and duration of hypothermia, originating from lack of evidence and protocols [33]. A recent report on methods of cooling demonstrated that a servo-controlled fan with feedback from an esophageal temperature probe was efficacious in 10 infants cooled to 33 to 34 degrees [34]. A detailed review of therapeutic hypothermia in children along with methods of cooling was recently published [35].

Finally, increased temperature after HIE or CA is associated with poor outcome. This may represent either noxious effect of hyperthermia on the injured brain, or a worse insult overall with multi-organ system failure [36]. As little as one degree of hyperthermia appears to be important.

Extracorporeal Membrane Oxygenation

Extracorporeal Membrane Oxygenation (ECMO) can be used as a rescue tool for pediatric patients with CA in whom ROSC cannot be obtained (extracorporeal cardiopulmonary resuscitation- ECPR), as a therapy for patients with extreme cardiovascular instability after ROSC, or as a tool to deliver hypothermia in one of these previous scenarios. Simply put, ECMO represents delivery of oxygenated blood in a continuous flow to the systemic circulation.

ECMO was first used for resuscitation from CA in a dog model of CA in late 1980s and shortly afterwards it was used in humans [37, 38]. From a technical standpoint, venous blood from the vena cava is directed to an oxygenator and the oxygenated blood is pumped into the aorta, providing oxygenation, CO_2 removal and hemodynamic support. Physiological advantages and disadvantages of ECMO are reviewed in detail in a recent pediatric publication [**39]. ECMO is an invasive therapy with the obvious benefit of possible resuscitation or survival in a patient who is unlikely to survive otherwise. Major risks include: 1) vascular injury with compromise of distal perfusion, 2) CNS complications (i.e. bleeding, ischemia), 3) myocardial stun, 4) pulmonary hemorrhage, 5) infections and 6) bleeding.

Initial reports of ECPR were limited to children after cardiac surgeries [40, 41]. In the last 5 years three studies presented experience related to ECPR in a variety of patients with primarily in-hospital CA [42 43, 44]. A meta analysis of pediatric patients who received ECPR from 1990 to 2007 included a majority of patients (75%) with CA in the perioperative period. The overall survival was 39.6%. Frequent complications included neurological (27%), renal (25%), and sepsis (17%). Mortality was highest in patients with neurological and renal complications and in patients with long deployment of ECMO system (greater than 30 min), and was lowest in patients with cardiomyopathies and myocarditis [*45]. A recent study from Taiwan that was not included in the pervious meta-analysis reports experience with 17 patients with in-hospital CA followed by ECPR. The overall survival for patients receiving ECPR was 41%; 10 out of 11 patients (91%) with good neurological outcome. Similar to previous studies, non survivors had longer CPR duration before institution of ECMO, and higher incidence of renal failure during ECMO support. This study describes in its methods the key elements of successful ECPR sequence: a) education of critical care personnel about the benefits of ECPR and encouragement of early consultation, b) early deployment of ECMO "if the patients did not have sustained ROSC

within 10-15 min and had no obvious contraindications [the physician] proceeded to ECPR", and c) preparedness of ECMO team, consisting of surgeon and ECMO technician [*46]. ECMO and hypothermia post CA can be combined as presented in recent a case series of two pediatric patients [47].

Future directions

As reviewed here, there are no current strategies for brain monitoring post CA. Neurological dysfunction is the principal limiting factor in the successful recovery of pediatric patients after CA. There appears to be a need for applying contemporary neurocritical care monitoring to patients after CA and for goal-directed resuscitation strategies.

Conclusions

Hypothermia and ECMO are the only treatment modalities available for improving brain recovery in the post-cardiac arrest syndrome. Recent advances in the field of pediatric CA were possible due to collaborative multi-center clinical studies. Many uncharted territories remain in brain monitoring, therapy and rehabilitation from pediatric CA. Well planned RCTs are underway to establish the role of hypothermia as a treatment modality for pediatric CA.

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Table 1

Patient characteristics of successfully resuscitated pediatric patients with *in-hospital* or *out-of-hospital* CA.

	Out of hospital CA	**In Hospital CA**
Initial rhythm	Asystole (46%)	Bradycardia (49%)
CPR duration (median)	31 min	9 min
Etiology	Respiratory (72%)	Cardiac (73%)
Initial pH (median)	7.03	7.20
Reactive pupils within 12h	32%	75%
Preexisting chronic conditions	49%	88%
PCPC unchanged at discharge	24%	44%
Good neurological outcome	24%	47%
Survival for 10 days post CA	42%	63%
Mortality rate	62%	51%
Neurological injury as the cause of mortality	69%	20%

Table adapted from [7]