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Neurol Clin 24 (2006) 147–158

NEUROLOGIC
CLINICS

Brain Injury from Cardiac Arrest in Children

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Many of the features of postischemic brain injury in children are similar to injury in adults; thus, much of this issue of the *Neurologic Clinics of North America* applies to children and adults. There are two important differences, however, that merit a separate section focused on pediatric injury. First, the mechanism of cardiac arrest in children differs, with respiratory causes far outnumbering cardiac causes (Tables 1 and 2). Second, the developing brain has different vulnerability and potential for repair compared with the mature brain. This article reviews these differences and the available clinical data relevant to pediatric brain injury following cardiac arrest.

Asphyxial cardiac arrest

The most common cause of nontraumatic cardiopulmonary arrest in children is airway compromise [1–3]. Although ventricular fibrillation (VF) or ventricular tachycardia (VT) occurs less commonly in children than in adults, it is not rare: approximately 5% to 15% of children with prehospital arrest have VF/VT [4–6].

Asphyxia can be clinically defined as airway obstruction or inadequate ventilation leading to hypoxemia and hypercarbia. Examples include drowning, choking, and coma accompanied by loss of airway patency. The typical progression of untreated asphyxia is hypertension and increased

This work was supported by the National Institutes of Health grant NIH KO8 HD40848 to Robert W. Hickey.

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doi:10.1016/j.ncl.2005.10.002

Table 1
Etiology of out-of-hospital cardiac arrest in children

Cause of arrest	n (%)
Sudden infant death syndrome	136 (23)
Trauma	118 (20)
Respiratory	96 (16)
Submersion	73 (12)
Cardiac	48 (8)
Central nervous system	35 (6)
Burn	6 (1)
Poisoning	6 (1)
Other	63 (10)
Unknown	20 (3)

Data from Young KD, Gausche-Hill M, McClung CD, et al. A prospective, population-based study of the epidemiology and outcome of out-of-hospital pediatric cardiopulmonary arrest. Pediatrics 2004;114(1):157–64.

work of breathing (where possible), followed by bradycardia, hypotension, pulseless electrical activity, and eventually, asystole.

Although both VF and asphyxial cardiac arrest result in global brain ischemia, the pattern of ischemia differs (Table 3). VF causes an abrupt cessation of cardiac output, whereas asphyxia causes an initial hypertension, followed by a gradual decrease in flow until pulseless electrical activity and, finally, asystole occur. Paradoxically, although low cerebral blood flow is better than no flow, a ''trickle'' of flow can be worse than no flow. This phenomenon was demonstrated in a study by Bottiger and colleagues [7] that showed worse postresuscitation cerebral reperfusion in rats that had 12-minute untreated VF plus 5-minute VF treated with cardiopulmonary resuscitation compared with rats subjected to 17-minute untreated VF. Theories for the damaging effect of trickle flow include (1) the continued delivery of substrate during conditions of anaerobic metabolism, causing worse tissue acidosis; and (2) the continued delivery of platelets and coagulation factors, causing worse microvascular plugging that would

Table 2
Characteristics of children with in-hospital cardiac arrest

Patient characteristic	n (%)
Cardiac arrest	176 (100)
No CPR (terminal phase of chronic disease)	47 (27)
CPR performed	129 (73)
Chronic disease in subset with CPR	92 (71)
Respiratory failure in subset with CPR	79 (61)
Circulatory shock in subset with CPR	37 (29)

Abbreviation: CPR, cardiopulmonary resusciation.

Data from Reis AG, Nadkarni V, Perondi MB, et al. A prospective investigation into the epidemiology of in-hospital pediatric cardiopulmonary resuscitation using the international Utstein reporting style. Pediatrics 2002;109(2):200–9.

Table 3
Comparison of injury from ventricular fibrillation versus asphyxial cardiac arrest

Injury	Ventricular fibrillation	Asphyxial cardiac arrest
Postresuscitation cardiac injury	Relatively more	Relatively less
Postresuscitation cerebral injury	Relatively less	Relatively more
Cerebral blood flow	Sudden complete ischemia	Trickle flow prior to complete ischemia
Scattered microinfarcts	No	Yes
Injury to basal ganglia	Relatively less	Relatively more
Selective vulnerability of CA1 hippocampus	Yes	Yes
Selective vulnerability of cerebellar Purkinje's cells	Yes	Yes

Comparisons are extrapolated from animal experiments.

impair reperfusion during resuscitation. Asphyxia, but not VF/VT, has an interval of trickle cerebral blood flow accompanied by profound hypoxemia.

The histology of cerebral injury following asphyxia differs from that seen in VF. Safar and colleagues [8,9] showed that brain damage from asphyxial cardiac arrest in dogs is worse than the damage found after equivalent periods of circulatory arrest from VF. In addition, asphyxiated brains had scattered microinfarcts and hemorrhage not seen in VF animals. Thus, laboratory experiments demonstrate that the severity and pattern of cerebral injury following asphyxial cardiac arrest differs from VF arrest. Clinical evidence of a difference in injury patterns is suggested by a report from Morimoto and colleagues [10] that described increased prevalence of brain edema (diagnosed by head CT) in adults remaining comatose following respiratory-induced cardiac arrest compared with cardiac arrhythmia–induced cardiac arrest.

Do the differences between asphyxial brain injury and "cardiac-mediated" brain injury have clinical relevance? They do to the extent that asphyxial injuries are more severe. Both injuries, however, demonstrate selective vulnerability and delayed neuronal death. Specifically, both mechanisms cause cell death that is "delayed" and is first seen on histology at 24 to 72 hours following reperfusion. The most prominent of these "selectively vulnerable" regions are the hippocampus and reticular thalamus. Thus, although an asphyxial injury may be more severe than a cardiac-mediated injury for an equivalent period of ischemia, asphyxial injuries should respond similarly to neuroprotective therapies.

The developing brain

Brain maturation entails a complex coordination of neuronal proliferation, migration, synaptic overgrowth, pruning, and myelination. Although proliferation and migration are complete in humans at birth, the remaining processes continue into early adulthood, with completion of the myelination

of long association pathways occurring in the third decade of life. Accordingly, the brain's vulnerability to injury is not constant across different age ranges [11]. For example, rodents are extraordinarily resistant to ischemic injury when first born and then go through a period of increased sensitivity to injury, followed by intermediate sensitivity that lasts into adulthood [12–15]. The period of increased vulnerability correlates with maturation of receptors for excitatory neurotransmitters and maximal synaptogenesis. Laboratory data also show that immature neurons and oligodendrocytes have a lower threshold for initiating programmed cell death (apoptosis) compared with mature cells [16–19]. These developmental events that determine susceptibility to brain injury in laboratory models also occur during normal human development [20]. Synaptogenesis in human striatal cortex accelerates between age 2 and 4 months, creating a condition of exuberant connectivity that is subsequently pruned by 40% between age 8 months and 11 years [21]. A second wave of synaptic formation and pruning, primarily in the frontal cortex, has now been identified in adolescence [22]. In addition, ^{31}P magnetic resonance spectroscopy shows that the metabolic rate for local cerebral regions is 190% to 226% of adult levels between age 3 and 8 years, and there is a peak in the phosphomonoester spectrum that is indicative of active myelination just before age 2 years [23].

Functional development

Coincident to maturation seen at the tissue and cellular layer, the functional capabilities of the brain also mature over time. The acquisitions of gross motor, fine motor, and cognitive skills during youth are well-recognized phenomena. Beyond early youth, brain growth continues into the twenties and is associated with maturation of executive functions. Perhaps not surprisingly, functional imaging studies show that risk-taking during adolescence is associated with an immature pattern of cerebral activity compared with adult activity.

Some skills can only be acquired during specific periods of development (''use it or lose it''). For example, temporary monocular occlusion in children at the time when visual cortical pathways are being established can result in permanent cortical blindness in the occluded eye. Likewise, patching the ''good eye'' in patients with strabismus improves vision in the ''weak eye'' only when patching is initiated at a young age. A more prosaic example is the ability of young children to speak a second language without accent.

There is also an age-dependent capacity for repair [24]. A dramatic example of plasticity is the recovery that can occur in young children, but not adults, undergoing hemispherectomy for intractable seizures [25,26]. Children who have had hemispherectomy are more capable than adults of reallocating functions from the removed hemisphere to the remaining hemisphere. Similarly, language deficits are less common in children suffering injury to the dominant hemisphere before age 8 years.

The impact of global brain ischemia on functional outcome during "developmentally sensitive" periods of skill acquisition and the role of plasticity in recovery from global ischemia has not been systematically studied. One challenge is that injury obtained in young patients may not become apparent until the functional correlates are required for normal behavior and are testable. For example, children who have learning disabilities are often not diagnosed until the requisite learning skills become necessary for school performance. A greater understanding of the dynamic between injury and development has considerable potential benefit for children who have ischemic brain injury.

Clinical experience

Young and Seidel [27] recently summarized the results from 44 studies reporting on 3094 pediatric patients with cardiopulmonary arrest. The data showed an overall survival rate from cardiopulmonary arrest of 13%, with in-hospital arrest rates being higher than out-of-hospital arrest rates (24% versus 9%). Most of the reviewed studies reported good neurologic outcome in approximately 60% of survivors; however, comparison between studies is difficult because of the differences in inclusion criteria and the definition of "good" neurologic outcome. Neurologic outcome assessments that target motor function and rudimentary life-skill tasks suggest that most patients have full recovery or severe disability [28–35]. Patients who have poor outcome have generally suffered a severe, acute asphyxial event. Among children with good neurologic outcome, assessments that measure IQ or psychocognitive function often reveal impaired performance [36–40]. Robertson and colleagues [39] recently published data on a cohort of 53 children younger than age 3 years admitted to an ICU who had traumatic brain injury ($n = 26$) or hypoxic ischemic (HI) brain injury ($n = 27$) and an initial Glasgow Coma Scale of 8 or less. Of the 23 children identified as having "good recovery" based on the Glasgow Outcome Scale, 15 (65%) had below-average scores on the Mental Developmental Index or Performance Developmental Index. These indices, however, have imperfect correlation with later cognitive assessments and it is possible that additional recovery may occur or that deficits may remain "dormant" until uncovered by increasingly complex cognitive demands associated with maturation. Additional studies are desirable to better define long-term psychocognitive outcome.

Specific patterns of functional deficits have been described; notably, memory deficits in adults who have global brain injury [41,42] and cerebral palsy in neonatal asphyxia [43,44]. Similarly, the neurodevelopmental outcomes of premature infants have been well characterized in a meta-analysis of 227 studies by Bhutta and colleages [45]. The infrastructure that directs high-risk neonatal ICU graduates into comprehensive assessment/treatment programs, however, does not exist for older children who have HI injury

and, thus, the functional outcome of children who have HI injury is less well characterized.

Prognosis

Recently, Mandel and colleagues [46] reported on clinical and electrophysiologic predictors of outcome in 42 pediatric patients who remained comatose or had impaired consciousness at 24 hours following an HI injury. Twelve patients had an eventual good outcome, 4 had mild to moderate disability, 7 had severe disability or survival in a persistent vegetative state, and 19 ultimately died (9 with brain death, 2 after failed repeated resuscitation attempts, 8 after withdrawal of therapy). The positive predictive value for poor outcome (severe disability, persistent vegetative state, or death; $n = 26$) was 91% for duration of initial cardiopulmonary resuscitation exceeding 10 minutes and 100% for (1) Glasgow Coma Scale scores less than 5, (2) absence of spontaneous respirations, or (3) absence of pupillary reflex at 24 hours. The positive predictive value for poor outcome was 100% for discontinuous electroencephalographic activity, epileptiform electroencephalographic activity, or bilateral absent N20 latency on sensory evoked potential. This study is in agreement with other studies that have found neurologic examination and electrophysiology studies to be good predictors of outcome [47]. The main limitations of many of these studies are the small sample sizes and the post hoc derivation of decision rules.

Imaging

Neuroimaging techniques have identified specific patterns of cerebral injury in adults and newborns with ischemic injury. Data from human neonates and experimental primate models of neonatal asphyxia reveal that imaging abnormalities correlate with the nature and duration of the insult and the maturational stage of the brain at time of injury [48]. The immature brain of premature neonates is more vulnerable to white matter injury, whereas the brain of term neonates is more vulnerable to gray matter injury [49]. Acute, total asphyxia tends to result in greater injury to the brainstem and thalamus, whereas prolonged, partial asphyxia results in greater injury to the cortex and subcortical regions [50]. Even so, full-term infants who have prolonged, partial ischemia have a different pattern of injury compared with premature infants who have prolonged, partial ischemia. Thus, there are different patterns of HI brain injury relative to gestational age in newborns. What is not known is whether there are different patterns of injury relative to age in children outside of the newborn period suffering ischemia.

MRI can be used to measure regional volume (morphometrics) and thus characterize brain injury/recovery during follow-up of HI injury. A series of 17 adults surviving cardiac arrest studied by MRI at 6 months following resuscitation reported reduced hippocampal volume and a global reduction in

brain volume [51]. The reduction in hippocampal volume is consistent with the specific cognitive memory impairments commonly documented in adults following cardiac arrest [52]. The reduction in global brain volume is consistent with the more widespread deficits in memory, visuospatial, and executive functions that have also been documented. Similarly, follow-up MRI for former low birth weight preterm infants demonstrates smaller regional cortical volumes [53] and selective loss of hippocampal volume [54] compared with control subjects. The volume losses in these former preterm infants is correlated with memory performance and full-scale, verbal, and performance IQ scores. Again, information on the predictive value and long-term changes seen in MRI imaging of older children who have HI is limited [55].

Kreis and colleagues [56] used proton spectroscopy to study 16 children suffering near-drowning from age 7 months to 6 years. Loss of N-acetylaspartate from gray matter preceded the loss observed in white matter and was more severe. There was a delayed second peak of lactate, similar to the delayed secondary energy failure documented in neonatal HI. A spectroscopic index was derived that predicted neurologic outcome in this small series with greater accuracy than published clinical criteria.

A contemporary variation of diffusion-weighted MRI (diffusion tensor imaging; DTI) analyzes vector forces of diffusion patterns. Diffusion patterns are highly dependent on development and orientation of axonal fibers and oligodendroglia; thus, DTI is a sensitive tool for detecting white matter development (myelination) and injury. DTI scans obtained from premature infants who have white matter injury demonstrate disorganized vector forces consistent with disrupted white matter tract development [57]. Furthermore, white matter injury has been shown to correlate with diminished volume in the associated gray matter. DTI studies on older children who have HI injury have not been reported; however, DTI and MRI studies of normal children at different ages confirm that myelination continues through the second decade of life in an age-dependent, region-specific fashion [58–62]. Thus, it is likely that patterns of white matter injury vary by age. If so, DTI may be useful for identifying white matter injury and directing rehabilitative therapy to the associated cortical (and functional) brain regions.

Treatment

Following resuscitation from cardiac arrest, there is a period of increased sensitivity of the brain to secondary injury. A review by Kochanek and colleagues [63] provided the known precipitants of secondary injury, which include hypotension, hypoxia, hyperglycemia, and hyperthermia. Early postresuscitative care should focus on avoiding these causes of secondary injury (Box 1). Detailed discussion of intensive care therapy is beyond the scope of this article. Instead, discussion is limited to hyperventilation and hypothermia (hyperventilation because it is a pervasive problem and hypothermia because it is the most promising neuroprotective strategy).

Box 1. Postresuscitation treatment priorities

- Avoid hypotension
- Maintain normoxia (avoid hypoxia and prolonged hyperoxia)
- Maintain euglycemia (avoid hyperglycemia and hypoglycemia)
- Avoid hyperventilation
- Avoid hyperthermia
- Avoid rewarming
- Consider induced hypothermia

One preventable cause of secondary injury is iatrogenic hyperventilation. Hyperventilation has been shown to cause vasoconstriction and significantly decreased cerebral blood flow in children following traumatic brain injury [64] and in adults recovering from cardiac arrest [65]. Hyperventilation can also decrease cerebral blood flow by increasing intrathoracic pressure, causing a decrease in cardiac output and cerebral venous return. In addition, respiratory alkalosis shifts the oxygen hemoglobin dissociation curve to the left, reducing oxygen delivery to tissue. These alterations are particularly dangerous early after resuscitation when there is prolonged, multifocal decreased cerebral blood flow [66]. Avoidance of hyperventilation is challenging—caregivers under stressful circumstances unintentionally but predictably hyperventilate patients [67,68]. Tobias and colleagues [69] published a study on pediatric patients transported from the ICU to the radiology suite by nurses and respiratory therapists blinded to end tidal CO_2 values: 23% of readings were less than 20 torr. Increased use of quantitative continuous CO_2 monitors throughout the health care system would decrease the potential for harm secondary to inadvertent hyperventilation.

Measurement and control of temperature following cardiac arrest is an important part of patient management. After arrest, children commonly have an initial period of spontaneous hypothermia followed by a delayed (approximately 24 hours) development of fever [69a]. These temperature changes are relevant because hypothermia is neuroprotective, whereas hyperthermia can exacerbate brain injury. Accordingly, routine warming of patients during initial hypothermia is no longer recommended. Rewarming can negate the neuroprotective effects of hypothermia and may cause an ''overshoot'' of temperature that contributes to subsequent fever. Intentional induction or maintenance of hypothermia (therapeutic hypothermia) has recently been shown to be beneficial in adults recovering from cardiac arrest and in newborns recovering from birth asphyxia [70–73]. Although the studies in adults excluded asphyxia (enrollment was limited to patients who had VF/VT), there are significant animal data to support the use of hypothermia in asphyxial arrest [74]. Thus, consideration should be given to actively cooling children who remain comatose following resuscitation

from cardiac arrest. In addition, temperature should be monitored closely and fever should be treated aggressively.

Knowledge gaps and future directions

There is an accumulating literature on neurologic outcome in adults resuscitated from cardiac arrest and newborns recovering from perinatal asphyxia. In contrast, there is very little information on children resuscitated from cardiac arrest. Animal models showing age-dependent susceptibility to injury and clinical data showing age-dependent windows for learning and plasticity suggest that extrapolating from neonatal or adult experience will be imperfect. Thus, there is a critical need for studies targeting the pediatric age range between these populations. Important areas of inquiry include

- Age-dependent susceptibilities for injury and repair
- Contemporary imaging strategies targeting white matter development, morphometric measurements, and functional imaging
- Clinical or laboratory markers for severity of the initial event
- Role of antiapoptotic neuroprotective strategies in children
- Induced hypothermia
- Rehabilitation strategies (eg, enriched environment, forced use) that target age-dependent injury/repair susceptibilities

Because of the infrequent occurrence of pediatric cardiac arrest and the number of confounding variables, advances in understanding will likely require multicenter and interdisciplinary collaborations. Although studies of brain injury in children across a range of developmental stages will be challenging, they will also be unique opportunities to increase our understanding of brain development, learning, and plasticity.

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