Patterns of retinal hemorrhage associated with cardiac arrest and cardiopulmonary resuscitation

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BACKGROUND Hypoxia and cardiopulmonary resuscitation (CPR) have been proposed as causes of retinal hemorrhage (RH) in children evaluated for abusive head trauma (AHT). We sought to determine the prevalence and characteristics of RH in children who underwent CPR after cardiac arrest.

METHODS This was a prospective, single-center, consecutive observational study of 38 children (<18 years of age). Indirect ophthalmoscopic examination was completed by an ophthalmologist within 48 hours of CPR. Extensive medical records data were collected to assess for potential confounding factors. Outcomes included the presence and pattern of RH.

RESULTS Of the 38 children, 20 had in-hospital arrest; 18 had out-of-hospital arrest. The median duration of CPR was 10 minutes. Seven children had RH, of whom 6 had an RH pattern consistent with coexistent medical conditions: 4 AHT diagnosable with nonocular findings, including subdural and subarachnoid hemorrhage, rib fractures, abdominal injury (RH pattern: diffuse, numerous, intraretinal and/or multilayered RH); 1 septic shock (RH pattern: 1-2 posterior pole RH); 1 ruptured arteriovenous malformation (RH pattern: 4-8 peripapillary RH). The seventh child had unwitnessed cardiac arrest due to nonfatal drowning and a single superficial intraretinal peripapillary hemorrhage.

CONCLUSIONS CPR for cardiac arrest is rarely associated with RH, which, absent coexisting conditions causing retinal hemorrhage, are intraretinal, few in number, and located in the posterior pole. In children who have undergone CPR, when RH are multilayered, or are more than a few in number, or extend outside the posterior pole, another etiology for the RH should be sought. (J AAPOS 2021;25:324.e1-4)

Cardiopulomonary resuscitation (CPR) has been proposed as a cause of retinal hemorrhage (RH) in children.[1-5] This possibility is relevant to the diagnostic interpretation of retinal findings in young children being evaluated for abusive head trauma (AHT), because some of these children have received CPR.[6-8] Generally, published studies suggest that CPR uncommonly causes retinal hemorrhage, and, if so, the hemorrhages are mild in severity.[1,2] However, these studies have limitations, including confounding effects of coexisting diseases known to cause retinal hemorrhages, delayed or nonophthalmologist retinal examinations, inadequate examination techniques, such as the use of direct ophthalmoscopy or examination through undilated pupils, and inadequate description of retinal findings.[1-5,9] The pattern of retinal hemorrhage, including the number, types, and locations of hemorrhage and other findings, such as retinoschisis or retinal folds, are fundamentally important for the diagnostic interpretation of retinal findings, because the patterns associated with the many causes of RHs in infants and children are well described.[6,10-12] These patterns are most reliably identified and best described by an ophthalmologist using indirect ophthalmoscopy through dilated pupils.[6,11] To address these limitations, particularly confounding by coincident disease, Odom and colleagues[2] conducted a prospective study of in-hospital cardiac arrests and excluded children with a potential cause of retinal hemorrhage, such as head trauma. In a cohort of 43 children, 93% of whom were coagulopathic, only 1 child had small punctate posterior RHs after 60 minutes of CPR. This study involved ophthalmologist examinations, but children were examined only within a 96-hour window. Numerous

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intraretinal hemorrhages can resolve in the first few days following onset, so ideally examinations should be completed sooner to adequately describe the initial pattern of hemorrhage.[9] Pham and colleagues[1] examined 22 children during and 1 day after CPR, but they did not exclude children with other potential RH causes, which were present in 5 of 6 children with retinal hemorrhage. Due to the greater limitations of other studies, the studies by Odom and colleagues[2] and Pham and colleauges[1] provide the primary current evidence base on this subject, and additional data confirming or refuting their findings would be valuable to physicians performing child abuse evaluations. We sought to determine the prevalence and characteristics of retinal hemorrhage among children who underwent CPR following cardiac arrest in order to add to the limited evidence available, and in particular to account for potentially confounding coincident diseases that are associated with RH by considering the patterns of hemorrhage and other ocular findings that might be present.

Subjects and Methods

We conducted a prospective, cross-sectional study of consecutive children <18 years of age who received CPR and were admitted to the pediatric intensive care unit (PICU) or the cardiac intensive care unit (CICU) at the Children's Hospital of Philadelphia between January 1, 2013, and December 31, 2015. Exclusion criteria included previous enrollment in this study during the same hospitalization or previous arrest during the same hospitalization without subsequent retinal examination. We did not exclude children based on coincident medical diseases, even if those diseases were known to be potential causes of RH, so as not create a potential selection bias. All children who received CPR and were cared for in the PICU or CICU were screened by the cardiac arrest research team. Families meeting the inclusion criteria were approached for consent. This study was approved by the Children's Hospital of Philadelphia Institutional Review Board and was compliant with the US Health Insurance Portability and Accountability Act of 1996.

All eye examinations were completed by a pediatric ophthalmologist as soon as possible but at most within 48 hours of cardiac arrest. The number, type, location, and overall pattern of any RHs or other ocular findings were recorded on a standardized study form. Data collected from the medical record included age, sex, race, past medical history as well as cardiac arrest data and suspected or confirmed AHT or child abuse; physical examination findings of trauma; blood pressure (hypertension); and laboratory studies, medications, and imaging studies, including computed tomography (CT) and magnetic resonance imaging (MRI). If a patient was examined by an ophthalmologist as part of clinical care, retinal photographs were taken after the examination by an ophthalmologist if retinal findings were present. If such photographs were taken, the retinal photographs were collected from the medical record and evaluated as part of the study protocol as well. When retinal findings were identified only on research study examination, those findings were shared with the clinical team.

The primary outcomes were prevalence of RH and patterns of RH, including laterality, number, type(s), location(s), and general pattern. An a priori plan was made to account for potential confounding by the presence of coincident medical diseases that cause RHs in the following fashion. If RHs were identified in a study patient, the observed pattern of hemorrhage would be compared to known patterns associated with coincident diseases. If the patterns matched, then that observed case would not be considered conclusive for a pattern caused solely by CPR. If the patterns did not match, then the pattern could be interpreted as being at least in part due to CPR. If no coincident disease known to cause RH was present, then the pattern could be considered due to CPR.

Results

A total of 38 children were included (median age, 1.67 years; range, 1 week to 17 years): 0-1 years of age, 18 children; 2-5 years, 9 children; 6-10 years, 6 children; and 11-17 years, 5 children. Twenty children had an in-hospital cardiac arrest, and 18 had an out-of-hospital cardiac arrest. Twenty-five cardiac arrests were witnessed. Of 18 children with out-of-hospital cardiac arrest, 5 had bystander CPR, 3 had paramedic CPR, and 10 had both bystander and paramedic CPR. Four children had a repeat cardiac arrest. The causes of arrest included respiratory failure (14), hypotensive shock/sepsis (9), airway obstruction (6), drowning (5), trauma (5, all of which were AHT diagnosable based upon nonocular findings of trauma), arrhythmia (3), metabolic abnormality (2), acute life-threatening event (1), and unknown (3). Of the 32 children with a recorded CPR duration, the median duration of CPR was 10 minutes (IQR, 3-13.5 minutes; range, 0.5 to >40 minutes). Of 30 children with brain imaging, 4 had an intracranial hemorrhage (3 cases of AHT, 1 case of arteriovenous malformation rupture). The mean "highest prothrombin time" during the period between arrest and eye examination was 20.2 seconds (range, 12.8 to >125; approximate normal range, 11-14.5); mean highest partial thromboplastin time (PTT) was 68.6 seconds (25 to >250; approximate normal range 29-46). There were no significant differences between eyes with and without RH, with regard to mean prothrombin time or PTT ($P = 0.86$ and $P = 0.35$, resp.; two-tailed t tests).

The mean time to retinal examination was 22.9 hours (range, 0.5-46 hours). In 37 of 38 examinations the pupils were pharmacologically dilated, and in 1 examination the pupils were sufficiently dilated to provide adequate views of the retina without need for pharmacological dilation. No child had optic disk swelling; 3 children had mild optic disk pallor, the causes of which were congenital, mitochondrial, and idiopathic. Seven children had retinal hemorrhage (Table 1). Of these 7 children, 6 had a pattern of RH that was consistent with a coexistent medical condition and therefore could not be ascribed to CPR. Four of these 6

Table 1. Clinical features of 7 children who received cardiopulmonary resuscitation and had retinal hemorrhage

Case	CPR duration, Min	CPR performer	Medical history	RH pattern
1	0.5	BYST	AHT, SDH, SAH	Numerous diffuse posterior and peripheral multilayered RH, bilateral
2	4	MD	AHT, SDH	Numerous diffuse posterior and peripheral multilayered RH, bilateral
3	5	BYST, EMT	AHT, SDH, SAH, RibFx	Numerous diffuse posterior and peripheral intraretinal RH, unilateral
4	30	BYST, EMT	AHT, HII, SDH	Numerous diffuse posterior and peripheral multilayered RH, bilateral
5	9	MD	Septic shock	1-2 posterior pole intraretinal RH, bilateral
6	6	MD	Ruptured AVM, SAH	4-8 peripapillary intraretinal or preretinal hemorrhages, bilateral
7	10	BYST, EMT	Unwitnessed nonfatal drowning	Single peripapillary superficial intraretinal hemorrhage, unilateral

AHT, abusive head trauma; *AVM*, arteriovenous malformation; *BYST*, bystander; *CPR*, cardiopulmonary resuscitation; *EMT*, emergency medical services technician; *HII*, hypoxic ischemic brain injury; *MD*, medical doctor; *RibFx*, rib fractures; *RH*, retinal hemorrhage; *SAH*, subarachnoid hemorrhage; *SDH*, subdural hemorrhage.

children had AHT that was diagnosable based on nonocular findings: 1 child had hypoxic ischemic brain injury and abdominal injuries, and 3 children had subdural and subarachnoid hemorrhage, 1 of whom also had rib fractures. In these AHT cases, the RH pattern was of numerous, diffusely distributed, intraretinal and/or multilayered RHs. One of the 6 children had septic shock; the retinal hemorrhage pattern was a few (1-2) posterior pole intraretinal hemorrhages in each eye. Of the 6 children, 1 had a ruptured arteriovenous malformation; the RH pattern was a few (4-8) peripapillary RHs in each eye. Of the 7 children with retinal hemorrhage, only 1 child did not have a coincident medical condition known to cause RH; this child had an unwitnessed nonfatal drowning episode, and the retinal examination revealed a single superficial intraretinal peripapillary hemorrhage in one eye.

Discussion

We found that CPR rarely causes RH. Of 38 children examined after cardiac arrest and CPR, 7 had RH, but in 6 of those cases, there was a coincident recognized cause of RH. Furthermore, the observed RH pattern matched a pattern known to be associated with that coincident cause of RH; therefore, those RHs could not be ascribed to CPR. Excluding these 6 cases, only 1 (3.2%) of the remaining 32 children who received CPR had RH with no coincident cause, so that the observed RHs might be ascribed to cardiac arrest, CPR, and/or hypoxia. The pattern of these RHs was that of very few (one) intraretinal peripapillary hemorrhages.

Our findings are consistent with those of previous studies. In a well-designed prospective study, Odom and colleagues[2] found that only 1 of 43 children with CPR (2.3%) had a single punctate RH after having 60 minutes of CPR, despite the presence of coagulopathy in 93% of the children. Pham and colleagues[1] describe a series of 22 children examined by ophthalmologists during or immediately after CPR; 6 children had RH, but 5 had a known cause of RH (AHT, severe motor vehicle accident, and active retinopathy of prematurity [ROP]) and a matching RH pattern for that cause, leaving only 1 child who had a few peripapillary intraretinal hemorrhages and was found apneic by a baby sitter under unclear circumstances.[1] Our study adds to the evidence base from these two studies with regard to the prevalence and pattern of RH that may be ascribed to cardiac arrest and CPR. Pooling our data with results from these studies and excluding children who have RH and a coincident other cause of hemorrhage, the prevalence of RH following CPR is about 3.3% (3 of 92 children), and the pattern is a small number of posterior pole intraretinal hemorrhages.

Other studies addressed these questions, but their designs had important limitations. Gilliland and colleagues[5] reported a nonconsecutive case series of 131 postmortem examinations of children who received CPR. Examinations were not performed by an ophthalmologist, and although 61 children had RH, the hemorrhage patterns were not described, and all 61 children had coincident causes of RH, including 56 children with head trauma, so none could be clearly attributed to CPR.[5] Goetting and Sowa[4] described a series of 20 children who had CPR; 2 children were reported to have RH, but the examinations were not performed by an ophthalmologist; a provided photograph shows an optic disk splinter hemorrhage referred to by the authors as RH, and abuse was not clearly ruled out. Kanter[3] reported a series of 54 children with CPR examined by a nonophthalmologist through undilated pupils; 5 children had RH, but 4 of these cases had AHT, and the remaining child was reported to have "a [single] RH."

Hypoxia has been proposed as an alternative cause of RH in children evaluated for possible AHT.[13,14] We did not directly study RH patterns associated with hypoxia. However, it is plausible that some of the children who suffered cardiac arrest in our study and prior studies had a period of hypoxia, particularly those with out of hospital cardiac arrest. Consequently, our findings would suggest that hypoxia is not a significant cause of isolated RH, a conclusion well supported by consideration of the common retinal effects of acute and chronic hypoxia. Retinal whitening is seen with retinal artery occlusion, and retinal neovascularization is seen in diabetic retinopathy and ROP, but these findings are absent in AHT. High-altitude retinopathy involves chronic hypoxia, leading to dilation and tortuosity of retinal vessels, optic disk hyperemia, and at most a few posterior pole intraretinal hemorrhages.[15,16] Vascular changes and optic disk hyperemia are not reported findings in AHT. Carbon monoxide retinopathy features similar vascular and optic disk changes, as well as cotton wool spots, and a small number of posterior intraretinal hemorrhages.[17,18] RHs are not known to be associated with drowning-related hypoxia, as demonstrated in 14 drowning cases with no RHs in the study by Gilliland and colleauges,[5] and 5 drowning cases in our series, of which only 1 had a single intraretinal peripapillary hemorrhage. In a study of retinal findings in 159 critically ill children, respiratory failure was associated with a lower likelihood of having RH, and nontraumatic encephalopathy had no association with RH.[19] We previously examined the associations between hypoxic ischemic injury, intracranial hemorrhage, and RH severity, but our study did not have any cases of isolated hypoxic brain injury without trauma, so it was not possible to control for potential confounding.[20]

Strengths of our study include prospective enrollment of patients, ophthalmologist examinations performed through dilated pupils within a short time from cardiac arrest, and careful handling of the potential confounding posed by coincident causes of RH, including consideration of the patterns known to be associated with those causes. There are also limitations to consider. Our sample size was not large, but the consistency between our study results and those of Odom and colleagues[2] and Pham and colleagues[1] is reassuring, and pooling of those data improves the precision of our prevalence estimate. Selection bias was unlikely to be a factor, as we consecutively enrolled children with cardiac arrest regardless of cause and did not exclude children because of the etiology of the arrest. While some older children were included, the majority (71%) were 0-5 years of age. Circular reasoning with regard to the diagnosis of abuse and the presence of RHs was also not a factor, since there was clear nonocular evidence of trauma in the AHT cases with retinal hemorrhage.

CPR with chest compressions and hypoxia following out-of-hospital or in-hospital cardiac arrest are only rarely associated with RH in the absence of other causes of RH. When such hemorrhages are present, they are characteristically intraretinal, few in number, and located in the posterior pole. In children who had CPR, when RHs are multilayered, more than a few in number, or extend outside the posterior pole, another etiology for the hemorrhages should be sought.

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