Pediatric survivors of out-of-hospital ventricular fibrillation: Etiologies and outcomes

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BACKGROUND In general, the prognosis is poor for pediatric patients who experience out-of-hospital (OOH) cardiac arrest, with survival rates of 12% to 29%.

OBJECTIVE The purpose of this study was to describe the causes and outcomes of pediatric patients with documented ventricular fibrillation (VF) at resuscitation from OOH cardiac arrest with sustained return of spontaneous circulation after defibrillation and survival to hospital admission.

METHODS Retrospective analysis of OOH-VF patients <19 years of age evaluated between 2004 and 2016 was performed. Primary outcome measures included demographics, arrest and resuscitation parameters, cardiac diagnoses, survival, and neurologic outcome.

RESULTS Forty-five patients fulfilled study criteria (median age 12 years; range 2 months to 18 years). Cardiac arrest occurred in public in 68% of cases, with bystander cardiopulmonary resuscitation in 42% before arrival of emergency medical services. All patients underwent defibrillation (1–6 shocks) with return of spontaneous circulation and survival to hospital admission. Underlying etiologies were primary electrical disease (33%), cardiomyopathy (27%), congenital heart disease (11%), other (13%), and unknown (16%). Before arrest, 40% of patients had a cardiac diagnosis and 26% had symptoms. Ultimately, 40 of 45 patients (89%) survived resuscitation to hospital discharge. During 72 ± 37 months of follow-up, 38% of survivors had a normal neurologic outcome, whereas 32% had mild neurologic impairment and 30% had moderate-to-severe neurologic impairment.

CONCLUSION In pediatric patients resuscitated from OOH-VF, a cardiovascular cause was identified in >80%. Regardless of cause, survival and neurologic prognosis appear improved compared to patients with asystole or pulseless electrical activity. These findings support early rhythm assessment and advanced cardiopulmonary resuscitation protocols in pediatric cardiac arrest victims.

KEYWORDS Cardiac arrest; Pediatrics; Resuscitation; Sudden death; Ventricular fibrillation

ABBREVIATIONS **CPR** = cardiopulmonary resuscitation; **EMS** = emergency medical services; **ICD** = implantable cardioverter–defibrillator; **OOH** = out of hospital; **ROSC** = return of spontaneous circulation; **SCA** = sudden cardiac arrest; **VF** = ventricular fibrillation

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Introduction

Out-of hospital (OOH) cardiac arrest in pediatric patients is associated with a poor prognosis for survival and meaningful neurologic outcome. A 2005 meta-analysis of studies of childhood survivors of OOH cardiac arrest reported an overall survival rate of 12.4%, with a neurologically intact status of 4%.[1] However, recent reports have indicated improved survival, with rates approaching 30%, as bystander cardiopulmonary resuscitation (CPR) and rapid response emergency services have become increasingly prevalent.[2,3]

Although the initial rhythm at attempted resuscitation in the majority of pediatric patients is either asystole (78%) or pulseless electrical activity (13%), ventricular fibrillation (VF) has been reported in 5%–8%.[1,3] As VF may indicate a shorter interval of loss of myocardial and end-organ perfusion than asystole, it may be associated with an improved outcome.[4] Therefore, the purpose of this study was to assess the causes and long-term outcomes of patients <19 years of age who were resuscitated from OOH-VF with sustained return of spontaneous circulation (ROSC) after defibrillation and survival to transfer to a tertiary medical center.

Methods

This study was conducted as a retrospective case series analysis of all patients evaluated at a large urban tertiary hospital between January 2004 and April 2016 who fulfilled the following criteria: (1) witnessed OOH sudden cardiac arrest (SCA), defined as "malfunction or cessation of the electrical and mechanical activity of the heart, resulting in near instantaneous loss of consciousness and collapse"[5]; (2) documentation of VF at the time of initial resuscitation ECG by

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emergency medical service providers; (3) defibrillation with sustained ROSC maintained during hospital transfer; and (4) age <19 years at time of event.

Exclusion criteria were (1) patients in whom SCA occurred but without clearly documented VF; and (2) patients with a terminal noncardiac illness or SCA due to trauma or violence.

An initial database of possible study patients was derived from the hospital administrative database with the primary query "ventricular fibrillation" between the years 2004 and April 2016. The initial report identified 176 potential patients with a discharge diagnosis of VF. Review of each chart was performed, with a final total of 53 patients included after resuscitation from OOH-VF. Further review of the charts excluded 11 patients because of inadequate or inconclusive documentation of OOH-VF.

A secondary search was performed using the institutional cardiac rhythm device database to identify patients who received an implantable cardioverter–defibrillator (ICD) for secondary prevention, who were not included in the hospital administrative database but for whom resuscitation from OOH-VF was clearly documented. By this method, 3 additional patients were identified who fulfilled study entry criteria.

Independent assessments of study eligibility were made by 2 clinicians, followed by a consensus review. In the event of disagreement regarding the diagnosis or documentation of VF, the decision was adjudicated by a third physician.

The primary variables evaluated were demographics, setting and activity at time of the event, witnessed or unwitnessed cardiac arrest, bystander CPR provision, number of defibrillation attempts, and whether epinephrine was used. Responses to resuscitative efforts were classified according to the Utstein criteria.[6] Given the lack of documentation of time from collapse to defibrillation or ROSC, this variable could not be analyzed.

Variables evaluated postdefibrillation and hospital admission included postdefibrillation recurrence of VF, whether a form of cardiovascular disease was defined, whether an ICD was implanted, and whether there was postdischarge recurrence of VF. Evaluation for a potential cardiac cause included prior known diagnoses, ECG and continuous rhythm monitoring, echocardiography, and, when indicated, cardiac magnetic resonance imaging, programmed ventricular stimulation, or diagnostic cardiac catheterization with biopsy. In cases in which a primary electrical disease was suspected or the cause of the event was undefined, genetic testing for known mutations and copy number variants was performed, with further testing (whole exome or genetically elusive analyses) when the cause of the SCA remained undefined.

After resuscitation, the patient's neurologic status was evaluated using the standardized Neurologic Impairment Scale, which provides a basic assessment of both cognitive and physical function.[7] A score of 0 indicates normal function; 1 implies mild impairment, affecting high-level function only; 2 implies moderate impairment, with significant impairment but useful function; and 3 implies severe impairment of either cognitive or physical function, with limited rehabilitative potential. Patients who did not survive to hospital discharge were not included in this portion of the analysis. Neurologic evaluation also included assessment by the hospital rehabilitation service regarding the need for, and potential to respond favorably to, physical therapy. Given the evolution of recovery after acute brain injury, the neurologic status reported is based on the most recent evaluation.

The study was approved by the institutional review board of the Children's Hospital Los Angeles and the University of Southern California. Basic statistical analyses were performed using commercially available software (Microsoft Excel, Redmond, WA). Continuous variables are summarized as median (range) and categorical variables as number (percent). χ^2 Analysis with Yates correction was used unless the number in any cell was <5, in which case the Fisher exact test was used. A 2-sided $P < .05$ was considered statistically significant for all analyses.

Results

After critical review of all patients identified by the 2 databases, 45 patients ultimately fulfilled criteria for study inclusion. The basic demographic variables of the study patients are listed in Table 1. There were 27 male and 18 female patients (median age 12 years; range 2 months to 18 year) at the time of resuscitation from OOH-VF. The number of patients who fulfilled criteria for study inclusion ranged from 1 to 6 per year.

Before SCA, a cardiac diagnosis was known in 18 patients (40%), the most common being hypertrophic cardiomyopathy (n = 6), congenital heart disease (n = 5), and long QT syndrome (n = 4). Furthermore, a prior history of syncope was reported in 9 patients and palpitations in 4 patients. In 21 patients (46%), SCA was the first potential manifestation of cardiovascular disease, that is, no known prior symptoms or cardiovascular diagnosis and no significant family history suggesting risk for SCA.

Resuscitation parameters

The onset of cardiac arrest was directly witnessed in 42 of 45 patients. Three patients were found unresponsive within 1–3 minutes since last having been observed to be alert and responsive. Resuscitation and cardiac arrest parameters are given in Table 2. Bystander CPR was performed in 19 patients (42%), although the quality of CPR could not be evaluated. At the time of the cardiac arrest, 25 patients were active, 14 were sedentary or engaged in mild activities, and in 6 patients the state of activity was uncertain. Cardiac arrest occurred during jogging or physical education in 8 patients, organized or informal sports in 7 patients, and bike riding, swimming, playing, or working in 2 patients each. The most common settings for SCA were school (33%) and home (29%), with 68% of events occurring in a public setting (Table 2).

Table 1 Demographic data (N = 45)

Gender	
Male	27
Female	18
Age at time of arrest (years)	
0–5	10
6–10	5
11–14	16
15–18	14
Race	
Hispanic	28
Caucasian (non-Hispanic)	10
African American	4
Asian	3
Cardiac diagnosis before arrest	
Yes	18
Hypertrophic cardiomyopathy	6
Congenital heart defect	5
Long QT syndrome	4
Kawasaki (prior myocardial infarction)	1
Myocardial tumor	1
Myocarditis/AV block	1
No	27

OOH recording of VF and subsequent successful defibrillation was performed by emergency medical services (EMS) in 43 of 45 patients; 2 patients were successfully defibrillated using a school AED. Between 1 and 6 shocks were required to defibrillate the patients. Epinephrine was used in 16 patients. Recurrence of VF before hospital transfer was reported in 7 patients. After defibrillation and sustained ROSC, all patients were transferred either directly to Children's Hospital Los Angeles or to a local emergency department with subsequent transfer to our institution.

Table 2 Cardiac arrest and resuscitation data

Activity	
Active	25
Sedentary	14
Uncertain	6
Bystander cardiopulmonary resuscitation	
Yes	19
No	18
Uncertain	8
Setting of arrest	
School	15
Home	13
Park	8
Street	5
Water	3
Other	1
No. of shocks to defibrillate	
1	27
2	9
3	4
4	3
5	1
6	1

Cardiovascular evaluation

After admission, ECG and continuous rhythm monitoring were performed along with serial echocardiography to assess both cardiac anatomy and ventricular function. Antiarrhythmic therapy with intravenous amiodarone, lidocaine, or esmolol was used as needed, based on the presence of complex ventricular arrhythmias and status of ventricular function. Recurrence of VF occurred in 8 patients within 24 hours after admission.

Based on prior known diagnoses as well as subsequent evaluation after admission, the following diagnostic categories were determined: primary electrical disease (15), cardiomyopathy (12), congenital heart defect (5), other (6), and unknown (7). Two patients, initially discharged with an unknown cause of OOH-VF, were subsequently determined to have catecholaminergic polymorphic ventricular tachycardia based on clinical phenotype in 1 and genetic testing in the second, which demonstrated compound pathogenic heterozygous triadin mutations. The final major diagnostic classifications and distribution among age groups are shown in Figure 1. Furthermore, 2 patients with near-drowning subsequently were documented to have pathogenic KCNQ1 (long QT) mutations. The subtypes of diagnoses within the major diagnostic groups are listed in Table 3.

Clinical outcome

Of the 45 initial patients, 5 did not survive to discharge, primarily because of withdrawal of support due to profound neurologic injury. The 5 deaths included 2 patients <1 year of age, 1 with congenital aortic stenosis and a second with a massive myocardial tumor. The other 3 deaths occurred in a 7-year-old with prior repair of double-outlet right ventricle, a 14-year-old with unrecognized Wolff-Parkinson-White syndrome, and an 18-year-old with severe hypertrophic cardiomyopathy, who had previous implantation of a complex ICD lead system due to elevated defibrillation thresholds.[8]

Of the 40 remaining patients, 35 underwent insertion of an ICD. Five patients who did not receive an ICD: 1 with anomalous origin of the left coronary artery from the pulmonary artery who underwent coronary reimplantation, 1 with hydrocarbon inhalation defined as the cause of SCA, 1 whose family refused ICD insertion, and 2 in whom an ICD was not inserted because of profound neurologic injury. During mean follow-up of 72 $\pm$ 37 months, appropriate ICD discharges occurred in 11 of the 35 patients who received an ICD, including 3 with long QT syndromes, 4 with hypertrophic cardiomyopathy, 1 with catecholaminergic polymorphic ventricular tachycardia, and 2 with an unknown cause of VF.

The neurologic status of patients after admission was initially evaluated by intensive care physicians, with neurology and rehabilitation consultation as needed. Sixteen patients awoke quickly without apparent neurologic deficit and stable cardiovascular status, 13 required ventilation and sedation for 2–5 days, and 16 required >5 days of sedation

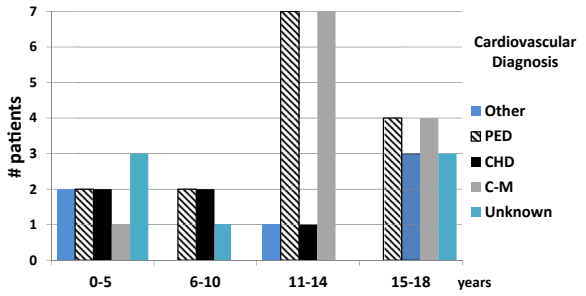

Figure 1 Frequency of cardiovascular diagnoses among the 4 patient age groups. These data represent all 45 patients. CHD = congenital heart disease; C-M = cardiomyopathy; PED = primary electrical disease; Unknown = cause of cardiac arrest has not been established.

and ventilation for either unstable cardiac rhythm status or depressed neurologic function.

Patients have been followed in the cardiac device program, which has allowed serial evaluation of both cardiovascular and neurologic status. Patients and their families are questioned regarding both physical and cognitive domains of function based on the Neurologic Impairment Scale. Based on this scale, 15 patients seem to have no residual neurologic impairment compared to pre-arrest status, whereas 13 are judged to have mild levels of impairment of either high=level cognitive or physical function. Moderate (n = 6) and severe (n = 6) levels of impairments are reported in 12 patients. The assessment reported is based on the most recent available clinical evaluation. The relationships between neurologic outcome and patient age at the time of SCA or cardiovascular diagnosis are shown in Figures 2 and 3.

The potential relationships between acute resuscitation variables and neurologic outcome are listed in Table 4. No specific resuscitation variable was identified that predicted a good or poor ultimate neurologic outcome. With regard to the etiology of OOH-VF, there was a trend toward improved outcome in patients with a primary electrical disease and a trend toward poor outcome in those with congenital heart disease, although these did not achieve statistical significance.

Patients with an undefined etiology of OOH-VF

A specific cardiovascular cause of the OOH-VF arrest remains undefined in 7 of the 45 patients (16%). As noted, evaluation has included rhythm monitoring, echocardiography, and genetic testing for known mutations and copy number variants associated with SCA. Of these 7 patients, none had reported recognition of any potential cardiac symptoms before to SCA. Further testing, based on possible causes of the arrest, has included cardiac magnetic resonance imaging or angiography and programmed stimulation or pharmacologic challenge for possible Brugada syndrome.

An ICD was inserted in 4 of these 7 patients with 3 exceptions: (1) a 2-month-old with VF within 24 hours of his immunizations; (2) a 2-year-old with a single episode of unexplained VF whose parents refused ICD insertion; and (3) a 17-year-old female with irreversible severe hypoxic–ischemic brain injury who was transferred to a chronic care facility. Of the 4 unknown etiology patients with ICD insertion, 2 have received appropriate ICD shocks for recurrence of VF.

Table 3 Identified causes of cardiac arrest

Cardiomyopathy	
Hypertrophic	11
Dilated	1
Primary electrical disease	
Long QT syndromes	10
Catecholaminergic polymorphic VT	4
Brugada syndrome	1
Congenital heart defect	
Total anomalous pulmonary venous return	2
Aortic stenosis	1
Double-outlet right ventricle	2
Other	
Kawasaki disease (post-MI)	1
Anomalous left coronary artery	1
Wolff-Parkinson-White syndrome	1
Myocardial tumor	1
Myocarditis	1
Hydrocarbon inhalation	1
Unknown	7

MI = myocardial infarction; VT = ventricular tachycardia.

Discussion

Before the 1990s, VF in children was considered an extremely rare event, with SCA considered to be primarily a respiratory event. During that era, resuscitation efforts were directed toward oxygenation and ventilation, with outcomes that were so dismal that some regarded attempted resuscitation in young patients to be futile or ethically indefensible.[9,10]

Coincident with the widespread adoption of automatic external defibrillators, Mogayzel et al[11] reported in 1995 that, contrary to prior reports, VF was documented during 19% of resuscitative efforts for SCA in children between the ages of 5 and 18 years. Furthermore, of those with VF, 17% were discharged with a good neurologic outcome compared to only 2% of those with asystole.

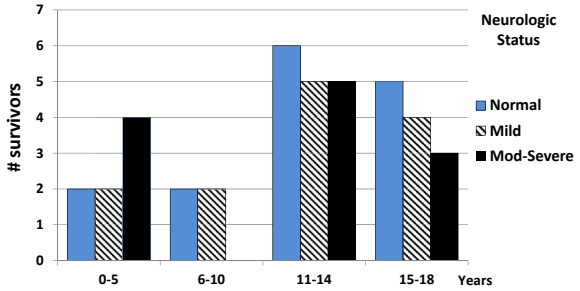

Figure 2 Neurologic outcome compared to patient age at sudden cardiac arrest. These data represent the 40 survivors to hospital discharge. Neurologic status is based on the most recent available evaluation based on the Neurologic Impairment Scale. Patients with moderate (Mod) and severe neurologic impairment are grouped together.

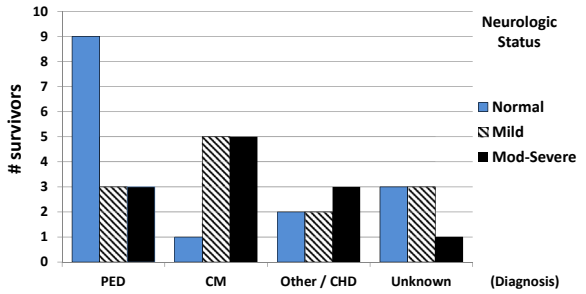

Figure 3 Neurologic outcome compared to cardiovascular diagnoses. These data represent the 40 survivors to hospital discharge. Patients with CHD and diagnoses other than PED and CM are grouped together. Of note, 4 of the 5 postadmission deaths occurred in patients in the Other/CHD diagnostic category. Abbreviations as in Figure 1.

Over the past 20 years, as awareness of SCA due to cardiovascular disease in young patients has increased, recommendations have evolved to emphasize the need for early assessment of the cardiac rhythm.[12] However, whether this has significantly improved the outcome of pediatric SCA victims remains a matter of debate.[2,3,13]

Several studies have focused on pediatric victims of sudden unexplained death (death within 24 hours of the onset of symptoms),[14] with an estimated annual incidence ranging between 1 and 6 per 100,000 patient-years.[15,16] However, these studies have been based on autopsy reports, with death as an endpoint. By definition, these studies underestimate the actual incidence of SCA in pediatric patients, which remains elusive because there is no mandatory reporting of deaths or attempted cardiac resuscitation in young patients. Furthermore, single-center prospective studies of pediatric SCA have been difficult to perform because of low event rates and limited population bases.[17]

Table 4 Final outcomes: survival to discharge/neurologic status

Resuscitation parameters vs outcome

Resuscitation parameters	Outcome				
	Good		Poor		
	Yes	No	Yes	No	*P* value
Bystander CPR	12	16	11	6	.155
Active at arrest	16	12	9	8	.783
Public site	20	8	13	4	.711
ROSC, first shock	17	11	8	9	.371

Age group vs outcome

Age (years)	Outcome		All others		
	Good	Poor	Good	Poor	*P* value
0–5	4	6 (2)	24	11	.143
6–10	4	1 (1)	24	16	.639
11–14	11	5	17	12	.541
15–18	9	5 (2)	19	7	.720

Cardiovascular diagnosis vs outcome

Cardiac diagnosis	Outcome		All others		
	Good	Poor	Good	Poor	*P* value
Primary electrical	12	3	15	15	.068
Cardiomyopathy	7	5 (1)	22	11	.501
Congenital	1	4 (2)	27	13	.059
Other	3	3 (2)	25	14	.658
Unknown	5	2	23	15	.693

Good outcome is defined as normal or only minimal impairment. Poor outcome is defined as death or moderate to severe neurologic impairment. Numbers in parentheses in poor column indicate patient deaths.

CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous circulation.

With regard to resuscitation from OOH-SCA, in 2012 Meyer et al[2] reported a marked improvement in the survival from all causes of SCA in patients 0–35 years of age, progressing from 13% in the era 1980–1989, to 25% in 1990–1999, to 40.2% in 2000–2009. The investigators proposed that the improvement could be attributed, at least in part, to advances in rapid-response EMS and modern resuscitation protocols. They noted the highest survival rates among victims between 3 and 13 years of age (40%) and 14 and 24 years of age (36.7%) in whom a primary arrhythmic disorder was the most frequent identified cause. Conversely, the survival rates among individuals aged 25–35 years decreased to 27.8%, with coronary artery disease reported as the most common etiology. The investigators also reported the prevalence of VF as the first reported cardiac rhythm in the initial era as 26%, increasing to 40% in the second era, followed by 60% in the most recent decade.

The patients reported in this study represent a highly select group of SCA victims, those with (1) documentation of VF, (2) ROSC after defibrillation, and (3) ROSC sustained with patient survival to admission, classifications suggested by the consensus Utstein guidelines.[6] Several selection factors may have contributed to the observed survival and outcomes in this cohort: first, the limited number of infants, in whom resuscitative outcomes are consistently poorest; second, the preponderance of witnessed SCA events; and third, VF rather than asystole as the presenting rhythm.[3,13] Furthermore, although specific response times were not available, the witnessed arrests in public settings as well as close proximity of EMS services may have contributed to the observed outcomes.[18,19]

We remain cautious in reporting the neurologic status of these patients, as subtle higher-order cognitive or neuromuscular deficits may not be apparent after an acute cerebral ischemic injury. Furthermore, assessment of higher-order neurologic status in infants and young children may not be reliable. However, we have been able to perform serial evaluation of the majority of these patients during cardiac/device follow-up, which has provided us with the ability to assess their overall functional status on a serial basis. Of note, the postdischarge functional and neurologic outcomes of patients in this study are comparable to those reported in 2015 for adult survivors of OOH-SCA.[20]

Many questions remain regarding the long-term care and prognosis for these patients. Particularly vexing are the individuals with an undefined cause of VF, who had a single event and no further arrhythmias or defined cardiovascular

disease. Whether these patients will require an ICD lifelong, particularly in view of lead failures, device malfunctions, and the increased risk of infection with each device replacement remains uncertain.[21] However, 2 of the 4 patients in this series with an unknown etiology of VF who underwent ICD insertion have received appropriate device shocks, suggesting continued ICD therapy is reasonable.

Study limitations

This is a retrospective study with the recognized limitations of incomplete data and potential selection bias. We have been selective in inclusion only of patients with VF documentation who survived to hospital admission after ROSC. We do not have data regarding the number of young patients with VF during the same era who did *not* survive or patients with OOH-VF who were possibly treated and discharged from other regional institutions. Although longitudinal neurologic outcome follow-up has been available for the majority of patients, some have transferred care to adult practitioners or have been lost to follow-up for a variety of reasons. Furthermore, as shown in Table 4, statistical analysis of risk and outcome in this study is limited by the small numbers of patients within the various diagnostic subgroups. Several categorical variables (congenital heart disease, diagnosis other than primary electrical disease) approached but did not achieve statistical significance for risk of a poor outcome ($P = .06–.07$).

Conclusion

In patients <19 years of age who experience OOH-SCA due to VF and are defibrillated with sustained ROSC, a specific cardiovascular cause can be identified in >80%. Recurrence of VF is common, immediately after resuscitation, after hospital admission, and during long-term follow after ICD placement. However, the survival and long-term neurologic prognosis for pediatric patients resuscitated from VF with ROSC appears considerably improved compared to previously reported outcomes for asystole or pulseless electrical activity. These findings support continued early assessment of the cardiac rhythm and advanced CPR protocols in pediatric victims of SCA.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2017.08.014.

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