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Impact of Different Initial Epinephrine Treatment Time Points on the Early Postresuscitative Hemodynamic Status of Children With Traumatic Out-of-hospital Cardiac Arrest

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Abstract: The postresuscitative hemodynamic status of children with traumatic out-of-hospital cardiac arrest (OHCA) might be impacted by the early administration of epinephrine, but this topic has not been well addressed. The aim of this study was to analyze the early postresuscitative hemodynamics, survival, and neurologic outcome according to different time points of first epinephrine treatment among children with traumatic OHCA.

Information on 388 children who presented to the emergency departments of 3 medical centers and who were treated with epinephrine for traumatic OHCA during the study period (2003–2012) was retrospectively collected. The early postresuscitative hemodynamic features (cardiac functions, end-organ perfusion, and consciousness), survival, and neurologic outcome according to different time points of first epinephrine treatment (early: <15, intermediate: 15–30, and late: >30 minutes after collapse) were analyzed.

Among 165 children who achieved sustained return of spontaneous circulation, 38 children (9.8%) survived to discharge and 12 children (3.1%) had good neurologic outcomes. Early epinephrine increased the postresuscitative heart rate and blood pressure in the first 30 minutes, but ultimately impaired end-organ perfusion (decreased urine output and initial creatinine clearance) (all $P < 0.05$). Early epinephrine treatment increased the chance of achieving sustained return of spontaneous circulation, but did not increase the rates of survival and good neurologic outcome.

Early epinephrine temporarily increased heart rate and blood pressure in the first 30 minutes of the postresuscitative period, but impaired end-organ perfusion. Most importantly, the rates of survival and good neurologic outcome were not significantly increased by early epinephrine administration.

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Abbreviations: APLS = advanced pediatric life support, ATLS = advanced trauma life support, BLS = basic life support, CPR = cardiopulmonary resuscitation, ECMO = extracorporeal membrane oxygenation, ED = emergency department, EMS = emergency medical system, GCS = Glasgow Coma Scale, MAP = mean arterial blood pressure, OHCA = out-of-hospital cardiac arrest, PCPCS = pediatric cerebral performance category scale, PEA = pulseless electrical activity, ROSC = return of spontaneous circulation, VF = ventricular fibrillation.

INTRODUCTION

Traumatic out-of-hospital cardiac arrest (OHCA) in children is rare, and its outcome is poor.[1–8] Previous studies reported a return of spontaneous circulation (ROSC) can be initially achieved in up to 21% of patients; most children with OHCA lose spontaneous circulation during the early postresuscitative phase.[5,9] Only 0.3% of patients survive to discharge with intact neurologic status.[2,4,5] Previous studies have reported factors that are associated with survival in children with traumatic OHCA, such as hypoxia-caused arrest, prehospital resuscitation course, witness presence, shorter transportation duration, and inhospital resuscitation.[1,2,5,9,10] However, the contribution of medication (ie, epinephrine) for pediatric resuscitation has not been well documented.

Clinically, epinephrine is an essential medication for treating both adult and pediatric OHCA during pre/inhospital resuscitation.[11–13] For adult OHCA patients, early treatment with epinephrine has been demonstrated to increase the chance of achieving ROSC, although it has no benefit in terms of survival or neurologic outcomes.[14,15] Moreover, the survival rates are lower in adult patients who have received prolonged or

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high doses of epinephrine.[16,17] The reasons for the potential adverse effects are not well understood. Animal studies have attempted to identify these reasons, and found that treatment with epinephrine might impair body microcirculation and decrease brain perfusion.[18,19]

Previous studies have demonstrated that the α-agonist effect of epinephrine is predominant (over the β-agonist effect) at high doses.[20,21] Furthermore, obvious decreases in renal blood flow were observed when vessel resistance was increased by α-agonists in some animal studies.[22,23] Therefore, we suspect that postresuscitative end-organ perfusion (ie, kidney perfusion) might decrease and result in a poor outcome because of early vessel constriction, impaired microcirculation, and blood loss (trauma cases). Physiologically, body circulation (heart rate, end-organ perfusion) and basal metabolism in children are higher than in adults because pediatric vital organs require greater oxygenation and higher blood supply.[24,25] Because the self-regulation ability of peripheral vessels is usually immature in young children,[26–29] it is reasonable to suspect that one of the effects of epinephrine treatment (ie, α-receptor-dependent vasoconstriction) in pediatric OHCA might be to potentially induce severe organ perfusion impairment, especially in patients who are hypovolemic or have undergone traumatic cardiac arrest.

Therefore, in children with traumatic OHCA, we suspect that early treatment with epinephrine might immediately increase the cardiac function (effect on β receptors) and the risk of impairing postresuscitation hemodynamic status and end-organ functions because of early organ perfusion impairment. However, the relationship between different epinephrine administration time points and outcomes in children with traumatic OHCA has not been well demonstrated. In this study, we aim to analyze early postresuscitation hemodynamic status, and also survival and neurologic outcomes of children with traumatic OHCA according to different initial epinephrine treatment time points.

METHODS

Study Design

During the period between January 1, 2003 and December 31, 2012, a total of 435 children (<19 years of age) presented with traumatic OHCA at one of the 3 emergency departments (EDs) of 3 medical centers (not including drowning accidents, burn injuries, or intoxication). Among these children, those who did not receive prehospital resuscitation or for whom the duration of prehospital resuscitation was unclear ($n = 18$) and those who did not receive any epinephrine during resuscitation ($n = 29$) were excluded. Finally, a total of 388 children who had been treated with epinephrine for resuscitation in the ED or before arriving to the hospital were included in this retrospective study. In this study, the association between the different initial epinephrine treatment time points (early: <15, intermediate: 15–30, late: >30 minutes from collapse), and the outcomes (early postresuscitation hemodynamic status, survival to discharge, and neurological outcomes) were analyzed.

Ethics Statement

The protocol was approved by the Institutional Review Board (IRB) of Changhua Christian Hospital (IRB code: 140909). Consent was specifically waived by the approving IRB.

Study Setting and Population

We retrospectively reviewed the medical records of 388 children aged <19 years, who presented with traumatic OHCA at the ED of one of 3 medical centers in northern, central, and southern Taiwan (3700, 2500, and 2500 beds, respectively). The incidence of traumatic OHCA is 1.8 per 100,000 pediatric individuals at the institutions. A population of 2,550,000 pediatric individuals is covered by these hospitals, and medical records (electronic) are shared between the hospitals. During the study period, the averageemergency medical system (EMS) response time was 5.6 ± 10.8 minutes, and the average transportation time was 11.2 ± 21.3 minutes.

Patients transferred by EMS were initially surveyed and treated by EMS personnel. The treatments included prehospital basic life support (BLS), bleeding control, and medication. Prehospital BLS performed by EMS personnel included the use of automated external defibrillation (AED), noninvasive ventilation, and chest compressions. The bleeding control provided by EMS included pressure over the site (or pulsation points), tourniquet use (for limb hemorrhage only), and fracture splinting. The medication (ie, epinephrine) was administered only under the supervision of ED physicians. Finally, the decision to stop EMS resuscitation (when successful resuscitation was not possible) was made by only ED physicians.

Furthermore, ED physicians could also decide to terminate resuscitation when patients received inhospital cardiopulmonary resuscitation (CPR) was over 1 hour without ROSC.

Study Protocol

Prehospital Resuscitative Phase

Information related to the prehospital resuscitation, including the period in which the children were treated at the scene and were transported to the hospital, witness statements regarding the collapse, and information related to the epinephrine treatment by EMS personnel were also obtained from the witness statements or public EMS records.

Patient Characteristics

Information related to patient characteristics and the ED-resuscitative phase (the time period from when the patients entered the ED to their arrival at the intensive care unit) was obtained from the medical chart records. In this study, patients were treated with advanced pediatric life support (APLS) and advanced trauma life support (ATLS) protocols by emergency medicine specialists in each medical center. The outcomes of this study adhered to the pediatric Utstein reporting system.[30] Patient demographics were gathered from medical records and included sex, age (infant: <1, toddler: 1–4, preschool: 5–9, school-age: 10–14, and adolescent: 15–19 years), main site of injury, location of arrest, mechanisms of injury, type of trauma (blunt or penetrating trauma), and presence of ED physician-diagnosed hypovolemia (critical bleeding). In addition, the main sites of injury were further divided into 4 groups according to the clinical evaluations, including head and neck injury, thoracic injury, abdominal injury, and multiple traumas (2 or more than 2 main sites of injuries).

ED-resuscitative Phase

The initial cardiac rhythm (upon presentation to the ED), inhospital CPR duration, epinephrine dosage, and administration route (intravenous or nonintravenous), and also the time between collapse and initial epinephrine treatment (early: <15, intermediate: 15–30, late: >30 minutes), were obtained. The initial cardiac rhythms included pulseless ventricular tachycardia, pulseless electrical activity (PEA), ventricular fibrillation (VF), and asystole. VF includes pulseless ventricular tachycardia in this study.

Postresuscitative Phase: Primary Outcomes (Early Hemodynamic Features and Laboratory Data)

The period after achieving a sustained ROSC is postresuscitative period. After ROSC was initially achieved, the children were admitted to the surgical intensive care unit (SICU) or sent to the operating room. The average stay duration in the ED was 60 minutes. During the first hour after the patients had achieved sustained ROSC, the early postresuscitative hemodynamic features were checked by their treating physicians (or nurses) every 10 to 20 minutes.

The details were obtained according to 1 previous pediatric OHCA study and are as follows[9]:

Cardiac rhythm (sinus or nonsinus rhythms) and heart rate (normal or tachycardia or bradycardia) were monitored by electrocardiograms. Heart rate was classified according to the baseline heart rate (expected) of the child's age groups. Idioventricular rhythms, junctional, ventricular, and premature atrial contractions were classified as nonsinus rhythms. The major postresuscitative rhythm and rate were chosen based on the most predominant cardiac rhythm and rate.[31]

Mean arterial blood pressure (MAP) was classified as hypertension or normal blood pressure or hypotension. The most predominant pressure was considered as the postresuscitative blood pressure. Patient blood pressure was classified using the baseline MAP according to their age.[32]

Urine output (>1 or 1–0.5 or <0.5 mL/kg/h) was obtained using urinary catheters inserted (immediately after achieving sustained ROSC). Postresuscitative urine output did not include residual urine.

Initial Glasgow Coma Scale (GCS; >7 or 7–4 or 3): We used the highest score during the first 1-hour interval after achieving sustained ROSC to analyze. In addition, the heart rates and the mean blood pressures were monitored for 4 time periods during the stay in ED (≦15 minutes, 16–30 minutes, 31–45 minutes, or 46–60 minutes) to analyze variations in the postresuscitative cardiac function of children who received an initial treatment of epinephrine at different time points.

When more than 1 measured data point per time period was collected for a patient, we calculated the mean value. Laboratory data during the first 24 hours of the postresuscitation period that might reflect oxygenation and organ perfusion, including initial hemoglobin, PaO_2, $PaCO_2$, pH, creatinine clearance, lactic acid, and potassium, were also obtained.

Postresuscitative Phase: Secondary Outcomes (Duration of Survival, Survival to Discharge, and Neurologic Outcomes)

The duration was defined from the time the patient achieved sustained ROSC in the ED until death in hospital or discharge. Pediatric Cerebral Performance Category Scale (PCPCS)[33] was used to survey neurologic outcomes (baseline and the time of discharge).

In this study, the survivors were classified into 2 groups according to their neurologic outcomes: the good (when PCPCS = 1 or 2) or the new-onset poor outcomes (when PCPCS ≧3). Finally, the relationships between different initial epinephrine treatment time points and the survival duration, the survival to discharge rate, and neurologic outcomes were analyzed.

Data Analysis

Chi-square, Fisher exact, Mann–Whitney *U*, and 1-way analysis of variance (ANOVA) tests were used in this study. The descriptive statistics of the independent variables (patient characteristics and information concerning prehospital/ED/postresuscitative phases) are reported as percentages or the mean ± standard deviation (SD). The variables (mentioned above) that were potentially associated with achieving sustained ROSC were analyzed using a *t* test, Fisher exact test, or a chi-square test. The total duration of CPR and the time from the initial administration of epinephrine until sustained ROSC were calculated, and differences in postresuscitative heart rate and MAP among different initial epinephrine treatment time points (<15 minutes, 15–30 minutes, >30 minutes from collapse) were analyzed using a 1-way ANOVA. In addition, primary outcomes (postresuscitative hemodynamic features and laboratory data) and secondary outcomes (survival to discharge and good neurologic outcomes) that might have been influenced by epinephrine were analyzed using chi-square, Fisher exact, and Mann–Whitney *U* tests. The most predominant treatment effects of epinephrine on postresuscitation hemodynamic features were adjusted using multinomial logistic regression analysis. Finally, the relationship between the epinephrine treatment time point and the duration of survival was calculated using Kaplan–Meier curves.

Finally, power calculation was performed for sample size (survival). A *P* value <0.05 was considered statistically significant. All of the analyses were performed using the SPSS statistical package (version 15.0, SPSS Inc., Chicago, IL).

RESULTS

Characteristics and Factors Associated With Achieving Sustained ROSC

The primary outcome results are presented in Figure 1. Information on 388 children was analyzed in this study, and most of the children (n = 223, 57.5%) received an initial dose of epinephrine in the period 15 to 30 minutes after collapse, followed by the time periods <15 minutes (n = 97, 25%) and >30 minutes (n = 68, 17.5%). A total of 38 children (9.8%) survived until discharge, and only 12 children (3.1%) presented with good neurologic outcomes at discharge. The characteristics and factors associated with sustained ROSC are presented in Table 1. Road traffic injuries (RTIs) and motor vehicle crashes (MVCs) were the major causes of traumatic OHCA. Prehospital BLS was performed in 99.7% of EMS-transported patients and in only 33.3% of non-EMS-transported patients. Nonintravenous epinephrine was initially administered to 67 children (17.3%). In this study, most (n = 373, 96.1%) of the patients suffered cardiac arrest at the scene, immediately after accident, and only 15 patients had initial measureable blood pressure or heart rate before or during transportation. All 15 patients had hypotension, and 12 patients presented bradycardia (the remainder presented tachycardia). Unfortunately, these 15 patients suffered cardiac arrest before arriving to the hospital. Among the 165 patients who achieved sustained ROSC in the ED, most patients (n = 162, 98.2%) survived more than 1 hour. Thirty-two children with

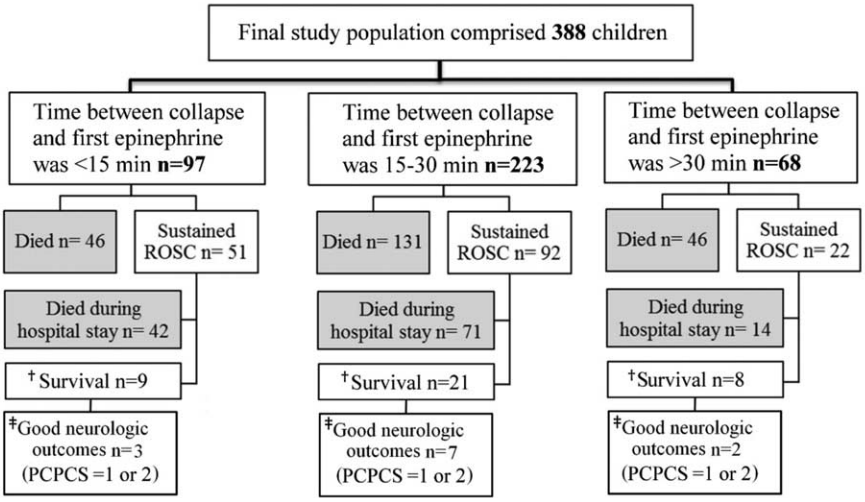

FIGURE 1. Primary outcomes of the patients. Superscript '†' indicates the survival to discharge rate ($P = 0.234$) and superscript '‡' indicates the frequency of good neurologic outcome ($P = 0.874$), which did not significantly differ among the 3 groups (chi-square test). ED = emergency department, EMS = emergency medical system, OHCA = out-of-hospital cardiac arrest, PCPCS = Pediatric Cerebral Performance Category Scale, ROSC = return of spontaneous circulation.

sustained ROSC received emergency surgery immediately, before being admitted to the SICU; the remaining 130 children were directly admitted to the SICU. The power calculation of our sample size was 0.86.

Early Epinephrine (<15 Minutes From Collapse) Increased the Chance of Achieving Sustained ROSC, But Did Not Shorten the After-injection Resuscitation Time

Among the 97 children who received early epinephrine, 52.6% (n = 51) achieved sustained ROSC. This percentage was significantly higher than for those who received intermediate (n = 92, 41.3%) and late (n = 22, 32.4%) epinephrine ($P = 0.030$). However, the resuscitation time (from initial epinephrine dose to sustained ROSC) was the shortest in patients who received intermediate epinephrine ($P < 0.05$) (Figure 2).

Early Postresuscitation Hemodynamic Status Was Related to Different Epinephrine Treatment Time Points

One hundred sixty-five children achieved sustained ROSC, and only 3 did not survive for more than 1 hour after achieving sustained ROSC. The early postresuscitation hemodynamic status at different epinephrine administration time points is shown in Table 2.

Cardiac Function (Heart Rate and Blood Pressure) Was Initially Increased by Early Epinephrine Treatment

Tachycardia (47.3%), hypotension (43.0%), and sinus rhythm (68.5%) were the most common heart-related features during the first hour after achieving sustained ROSC (all $P < 0.05$). Furthermore, we found that postresuscitation tachycardia was predominant in patients who received early and intermediate epinephrine relative to patients who received late epinephrine. However, postresuscitation hypertension was only predominant in patients who received early epinephrine treatment (Table 2). Finally, the variations in postresuscitation heart rate and blood pressure according to the different treatment time points were analyzed. The increased heart rate and blood pressure caused by early epinephrine administration was predominant only in the first half hour of the postresuscitation period (Figure 3).

End-organ Perfusion (Urine Output) Was Decreased by Early Epinephrine

In the first hour after achieving sustained ROSC, the majority of patients (41.8%) had a urine output of 1 to 0.5 mL/kg/h. However, most (43.1%) of the children who received early epinephrine had a urine output of <0.5 mL/kg/h. Finally, a urine output over 0.5 mL/kg/h was significantly more predominant patients who were first administered intermediate epinephrine (n = 73, 79.4%) relative to those treated with early (n = 29, 56.8%) or late (n = 14, 63.6%) epinephrine (Table 2).

Initial Brain Function (GCS) Was Not Associated With Different Epinephrine Treatment Time Points

The most common postresuscitation GCS score was 3 (48.5%). The initial GCS score did not differ significantly among the time points of initial treatment with epinephrine (Table 2).

Adjustment of Postresuscitation Hemodynamic Features With Regression Analysis

After performing an adjustment using a multinomial logistic regression analysis, we found that postresuscitation tachycardia was the predominant treatment effect caused by early administration of epinephrine (Table 3).

Early Epinephrine (<15 Minutes From Collapse) Increased Blood Acidification

The laboratory data related to the different initial epinephrine treatment time points and recorded over the first 24 hours of the postresuscitation period are shown in Table 4. Early initial treatment with epinephrine significantly increased the postresuscitation lactic acid concentration of the blood, and decreased blood pH and creatinine clearance (all $P < 0.05$).

TABLE 1. Characteristics and Factors Associated With Sustained ROSC in Patients Who Received Epinephrine During Resuscitation

		Sustained ROSC		
	Traumatic OHCA Children ($N = 388$), No. (%)	**Yes ($n = 165$), No. (%)**	**No ($n = 223$), No. (%)**	***P***
Patient characteristics				
Male	221 (57.0)	93 (56.4)	128 (57.4)	0.460
Age group				
Infant	19 (4.9)	6 (3.6)	13 (5.8)	0.414
Toddler	52 (13.4)	26 (15.8)	26 (11.7)	
Preschool	71 (18.3)	25 (15.2)	46 (20.6)	
School age	91 (23.5)	41 (24.8)	50 (22.4)	
Adolescence	155 (39.9)	67 (40.6)	88 (39.5)	
Major site of injury				
Head and neck	151 (38.9)	67 (40.6)	84 (37.7)	0.292
Thoracic	58 (14.9)	26 (15.8)	32 (14.3)	
Abdomen	73 (18.8)	35 (21.2)	38 (17.0)	
Multiple	106 (27.3)	37 (22.4)	69 (30.9)	
Location of cardiac arrest[*]				
Outside the home	259 (66.8)	121 (73.3)	138 (61.9)	0.012
Home	129 (33.2)	44 (26.7)	85 (38.1)	
Mechanisms of injury				
MVC or RTI	262 (67.5)	110 (66.7)	152 (68.2)	0.944
Falls	57 (14.7)	26 (15.8)	31 (13.9)	
Crush	35 (9.0)	14 (8.5)	21 (9.4)	
Others	34 (8.8)	15 (9.0)	19 (8.5)	
Type of trauma[*]				
Blunt trauma	365 (94.1)	160 (97.0)	205 (91.9)	0.028
Penetrating trauma	23 (5.9)	5 (3.0)	18 (8.1)	
ED physician-diagnosed hypovolemia[*]	282 (72.6)	102 (61.8)	180 (80.7)	<0.001
Prehospital resuscitative phase				
Period from scene to hospital[*], minutes	17.31 ± 9.58 (15)[†]	15.57 ± 8.11	18.53 ± 13.12	<0.001
EMS transportation[*]	355 (91.5)	159 (96.4)	196 (87.9)	0.002
Prehospital BLS[*]	365 (94.1)	162 (98.2)	203 (91.0)	0.002
Prehospital BLS duration[*] (mean ± SD), minutes	10.42 ± 4.73	9.12 ± 8.92	11.82 ± 7.56	<0.001
ED-resuscitative phase				
Initial cardiac rhythm[*]				
Asystole	210 (54.1)	77 (46.7)	133 (59.6)	0.003
PEA	115 (29.6)	64 (38.8)	51 (22.9)	
VF[‡]	63 (16.2)	24 (14.5)	39 (17.5)	
Inhospital CPR[*] duration[†] (mean ± SD), minutes	31.75 ± 17.56	13.78 ± 9.37	41.96 ± 26.44	<0.001
Epinephrine injections[*] (mean ± SD) (number)	8.46 ± 5.11	3.29 ± 2.50	11.26 ± 4.21	<0.001
First dose of epinephrine				
Intravenous	321 (82.7)	142 (86.1)	179 (80.3)	0.087
Nonintravenous	67 (17.3)	23 (13.9)	44 (19.7)	
Time between collapse and initial administration of epinephrine[*]				
Early (< 5 minutes)	97 (25.0)	51 (30.9)	46 (20.7)	0.030
Intermediate (15–30 minutes)	223 (57.5)	92 (55.8)	131 (58.7)	
Late (>30 minutes)	68 (17.5)	22 (13.3)	46 (20.6)	

BLS = basic life support, MVC = motor vehicle crash, RTI = road traffic injuries.

[*] Factors associated with achieving sustained ROSC.

[†] Number of patients with missing information.

[‡] VF includes patients with pulseless VT.

Survival Duration Rates and Neurological Outcomes

The total duration of survival (analyzed by Kaplan–Meier analysis) was not significantly different among the patients treated with epinephrine at different time points ($P = 0.832$). Additionally, significant differences were not observed in the survival until discharge rate or good neurological outcome status among the 3 different groups (Figure 1).

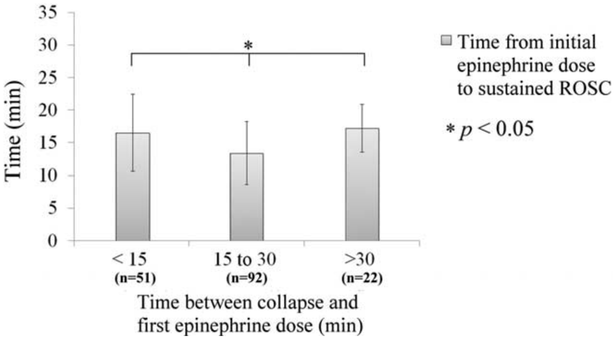

FIGURE 2. Among the patients with sustained ROSC (n = 165), the time from the initial epinephrine dose to sustained ROSC was shortest in the group of children administered intermediate epinephrine (15–30 minutes) ($P < 0.05$). ROSC = return of spontaneous circulation.

DISCUSSION

Clinically, cardiac output and systemic blood flow can be initially increased by treatment with epinephrine (a nonselective agonist of β-receptors), and epinephrine may facilitate ROSC during CPR.[18,34–38] However, in recent years, some unavoidable adverse effects of epinephrine treatment (ie, severe vasoconstriction and microcirculation impairment caused by α-agonist effects) have been discussed as causal factors underlying the low survival until discharge rates in adult OHCA.[18,34,35] Furthermore, a previous study investigated the duration between collapse and initial epinephrine treatment, and proposed that decreased durations might be beneficial in nontraumatic cardiac arrest in children.[39] However, the pattern in traumatic OHCA cases in children remains unclear. In this study, we aimed to analyze early postresuscitation hemodynamic status, and survival and neurologic outcomes according to different initial epinephrine treatment time points in children with traumatic OHCA.

We found that early treatment with epinephrine markedly influenced the outcomes of CPR. First, it increased the chance of achieving sustained ROSC. Compared with late treatment with epinephrine, early treatment resulted in a 20% higher chance of achieving sustained ROSC. Some previous studies reported that epinephrine may exert adverse effects during resuscitation, including myocardial dysfunction, increased oxygen requirements, and abnormal microcirculation.[20,36,40,41] In this study, we found that early treatment with epinephrine did not shorten the course of CPR. The mean time required for achieving sustained ROSC was 3 minutes longer in children receiving early treatment than in those receiving epinephrine at the intermediate stage. A possible reason for this result is that early treatment with epinephrine before inducing adequate body circulation (ie, CPR) might increase cardiac output, but impair oxygen/perfusion delivery (α-agonist effects, microcirculation obstruction).[18,19,42] Studies of cell biology have demonstrated that early reperfusion, adequate ion exchange, and a return to normal pH levels in the microcirculation are key factors for cell survival.[43,44] Therefore, achieving sufficient reperfusion and

TABLE 2. Hemodynamic Features Related to the Different Initial Epinephrine Treatment Time Points During the Early Postresuscitation Period

	Patients With Sustained ROSC (N = 165)				
		Time Between Collapse and First Epinephrine Dose			
	Total (N = 165) No. (%)	Early (<15 minutes, n = 51) No. (%)	Intermediate (15–30 minutes, n = 92) No. (%)	Late (>30 minutes, n = 22) No. (%)	*P*
Heart rate*					
Normal heart rate	49 (29.7)	21 (41.2)	21 (22.8)	7 (31.8)	0.023
Tachycardia	78 (47.3)	25 (49.0)	46 (50.0)	7 (31.8)	
Bradycardia	38 (23.0)	5 (9.8)	25 (27.2)	8 (36.4)	
Mean arterial blood pressure*					
Normal blood pressure	43 (26.1)	12 (23.5)	24 (26.1)	7 (31.8)	0.035
Hypertension	51 (30.9)	24 (47.1)	21 (22.8)	6 (27.3)	
Hypotension	71 (43.0)	15 (29.4)	47 (51.1)	9 (40.9)	
Type of cardiac rhythm					
Sinus rhythm	113 (68.5)	33 (64.7)	67 (72.8)	13 (59.1)	0.361
Nonsinus rhythm	52 (31.5)	18 (35.3)	25 (27.2)	9 (40.9)	
Urine output*					
>1 mL/kg/h	47 (28.5)	9 (17.6)	31 (33.7)	7 (31.8)	0.041
1–0.5 mL/kg/h	69 (41.8)	20 (39.2)	42 (45.7)	7 (31.8)	
<0.5 mL/kg/h	49 (29.7)	22 (43.1)	19 (20.6)	8 (36.4)	
Initial GCS					
>7	24 (14.5)	11 (21.6)	9 (9.8)	4 (18.2)	0.344
7–4	61 (37.0)	18 (35.3)	34 (37.0)	9 (40.9)	
3	80 (48.5)	22 (43.1)	49 (53.2)	9 (40.9)	

GCS = Glasgow Coma Scale, ROSC = return of spontaneous circulation.

* Significant hemodynamic features.

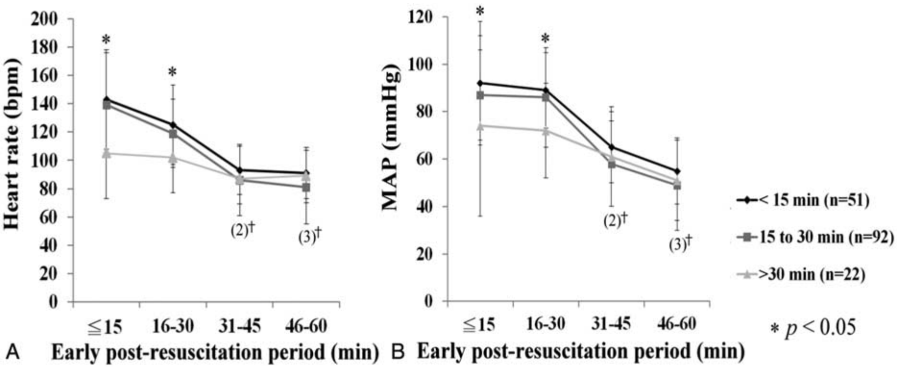

FIGURE 3. Variations in postresuscitation cardiac function. A, Heart rate and B, MAP were analyzed according to the different initial epinephrine treatment time points. The increased cardiac function caused by early and intermediate epinephrine (<15 minutes and 15–30 minutes from collapse) was predominant only during the first half hour of the postresuscitation period. Superscript '†' indicates number of patients with missing information. MAP = mean arterial blood pressure.

fluid supply should not be ignored in the early resuscitation period.

Although epinephrine is reported to cause potential postresuscitative myocardial dysfunction,[36,45,46] we found that early treatment with epinephrine temporarily improved the hemodynamic status in the early postresuscitation period. Compared with late epinephrine treatment, early treatment markedly increased the postresuscitative mean heart rate (by 10–25 bmp) and MAP (by 15–20 mm Hg) in the first 30 minutes of the postresuscitation period. Unfortunately, this cardiovascular elevation effect was not maintained over longer time periods. Therefore, emergency surgery, fluid resuscitation, and the cessation of bleeding should be aggressively pursued during this period as early treatment with epinephrine is not the only important factor in resuscitation.

TABLE 3. Multinomial Logistic Regression Analysis of the Predominant Epinephrine Treatment Effects on Postresuscitation Hemodynamic Features

	Time Between Collapse and Initial Epinephrine Treatment				
	Early (<15 minutes)		**Intermediate (15–30 minutes)**		
	OR	**95% CI**	**OR**	**95% CI**	**Late (>30 minutes)***
Heart rate					
Normal†	4.8	1.18–19.61	1.0	0.30–3.09	1
Tachycardia†	5.7	1.41–23.10	2.1	0.68–6.48	1
Bradycardia*	—	—	—	—	—
Mean arterial blood pressure					
Normal blood pressure	1.0	0.30–3.58	0.7	0.22–1.98	1
Hypertension	2.4	0.71–8.11	0.7	0.21–2.13	1
Hypotension*	—	—	—	—	—
Type of cardiac rhythm					
Sinus rhythm	1.3	0.46–3.54	1.9	0.71–4.88	1
Nonsinus rhythm*	—	—	—	—	—
Urine output					
>1 mL/kg/h	0.5	0.13–1.68	1.9	0.58–5.97	1
1–0.5 mL/kg/h	1.0	0.32–3.39	2.5	0.80–7.98	1
<0.5 mL/kg/h*	—	—	—	—	—
Initial GCS					
>7	1.1	0.28–4.48	0.4	0.10–2.49	1
7–4	0.8	0.27–2.49	0.7	0.25–1.93	1
3*	—	—	—	—	—

CI = confidence interval, GCS = Glasgow Coma Scale, OR = odds ratio.
* Reference group.
† Significant hemodynamic features.

TABLE 4. Laboratory Data Related to the Different Initial Epinephrine Treatment Time Points in the First 24 Hours of the Postresuscitation Period

	Patients With Sustained ROSC (N = 165)			
	Time Between Collapse and First Epinephrine Dose			
Initial Data in the First 24 Hours of the Postresuscitation Period	Early ($<$15 minutes, n = 51) No. (%)	Intermediate (15–30 minutes, n = 92) No. (%)	Late ($>$30 minutes, n = 22) No. (%)	*P*
Initial hemoglobin level (median), mmol/L (2)*	7.4	7.5	7.3	0.391
Initial K level (median), mmol/L (6)*	4.6	4.3	4.4	0.196
Initial pH level† (median) (16)*	7.18	7.19	7.20	0.008
Initial PaO_2 level† (median), mm Hg (16)*	134.5	121.3	127.8	0.005
Initial $PaCO_2$ level† (median), mm Hg (16)*	57.2	52.8	61.4	$<$0.001
Initial creatinine clearance† (median), m/min (14)*	52	64	58	$<$0.001
Initial lactic acid level† (median), mmol/L (25)*	3.4	2.8	3.6	$<$0.001

ROSC = return of spontaneous circulation.
[*] Number of patients with missing information.
[†] Significant laboratory data.

Previous studies have found that the α-agonist effect of epinephrine is predominant (over the β-agonist effect) at high doses.[20,21] Furthermore, in some animal studies, pronounced decreases in renal blood flow have been observed when the vessel resistance was increased by α-agonists.[22,23] Therefore, we hypothesized that early treatment with epinephrine (causing early vessel constriction) might decrease postresuscitative end-organ perfusion (ie, kidney perfusion), especially in patients with hypovolemic shock. In this study, 2 interesting findings support this hypothesis. First, early epinephrine caused a higher rate (6.7%) of oliguria (urine output $<$0.5 mg/kg/h) than did late epinephrine. Second, the initial 24-hour renal creatinine clearance in the early epinephrine group was lower than that in the other 2 groups (12 and 6 mL/min lower than in the intermediate and late epinephrine groups, respectively). Therefore, to preserve adequate blood flow to the kidneys, performing sufficient CPR may be needed before early epinephrine treatment.

In this study, the overall survival rate and the frequency of good neurologic outcomes (PCPCS = 1 or 2) were not significantly higher in the group receiving early epinephrine treatment. Some animal studies focusing on cardiac arrest have reported that epinephrine administration decreases postresuscitative cerebral perfusion.[18,47] One such study observed a decrease in cerebral cortical tissue oxygen tension and an increase in cortical tissue hypercarbia during and after CPR, which was performed subsequent to the administration of epinephrine.[18] As surmised above in discussing the kidneys, early treatment with epinephrine might not provide benefits to the end organs in traumatic cases.

Limitations

The treating effect of extracorporeal membrane oxygenation (ECMO) was not considered in this study because their measurement was not routine. Also, clinical evidence of these conditions in children with traumatic OHCA is lacking.[48–50] This study was also limited by the small number of survivors with good neurologic outcomes. One previous study mentioned 118 traumatic cardiac arrest children and reported only 6 (5%) survivors.[7] In this study, there were only 38 survivors, and 12 of them had good neurologic outcomes. Therefore, the analysis of the neurologic outcome among the 3 different time points of epinephrine treatment was limited. In addition, because only initial laboratory data were reported, sampling bias due to variation in the time of specimen collection might be present. Finally, other factors that were not evaluated in the present study may have influenced the results and the conclusions. In addition to the time of epinephrine administration, factors such as prehospital BLS, hypovolemia stage, and maneuvers during transportation might be associated with patient outcomes.

CONCLUSIONS

For children with traumatic OHCA, early treatment with epinephrine temporarily increased cardiac function during the first 30 minutes of the postresuscitative period, but impaired end-organ perfusion. Most importantly, the survival rate and the frequency of good neurologic outcome were not significantly increased by early epinephrine administration.

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