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Myocardial injury in children following resuscitation after cardiac arrest

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Abstract

Background: Myocardial dysfunction occurs immediately after successful cardiac resuscitation. Our purpose was to determine whether measurement of cardiac troponin I in children with acute out-of-hospital cardiac arrest predicts the severity of myocardial injury. *Methods and results:* This prospective, observational study was performed in the Pediatric Intensive Care Unit (PICU) on 24 patients following arrest, ranging in age from 8 months to 17 years. Troponin measurements were obtained on admission, and at 12, 24, and 48 h. Transthoracic echocardiograms were performed within 24 h after admission. Survival to hospital discharge was 29% (7/24). The mean age was 5.9 ± 4.6 years for survivors and 4.2 ± 5.3 years for non-survivors. The median (range) duration of cardiac arrest times for survivors was 6 min (3 to 63 min) versus 34 min (4 to 70 min) for nonsurvivors ($P = 0.02$). Survivors received 1.3 ± 2.2 doses of epinephrine (adrenaline) compared with 2.9 ± 1.6 doses for non-survivors ($P = 0.02$). Only one patient had ventricular fibrillation and defibrillation was unsuccessful. The ejection fraction for survivors averaged $73.2 \pm 11.2\%$, but for nonsurvivors only $55.4 \pm 19.8\%$ ($P = 0.04$). Ejection fraction correlated inversely with troponin at 12 h ($r = -0.54$, $P = 0.01$) and at 24 h ($r = -0.59$, $P = 0.02$). Circumferential fiber shortening for survivors was 37.5 ± 7.8 and $25.5 \pm 10.7\%$ for nonsurvivors ($P = 0.02$). It also correlated inversely with troponin ($r = -0.46$, $P = 0.03$ for survivors and $r = -0.65$, $P = 0.01$, for nonsurvivors). *Conclusion:* After cardiac arrest and resuscitation in pediatric patients, the severity of myocardial dysfunction was reflected in troponin I levels.

Keywords: Pediatric resuscitation; Cardiac arrest; Cardiopulmonary resuscitation; Echocardiography

Resumo

Contexto: A seguir à reanimação com sucesso de paragem cardíaca ocorre disfunção miocárdica. O nosso objectivo foi determinar se a troponina I cardíaca medida em crianças com paragem cardíaca fora do Hospital prediz a gravidade da lesão do miocárdio. *Método e resultados:* Estudo prospectivo e observacional realizado na PICU (Unidade de Cuidados Intensivos Pediátrica) em 24 vítimas de PCR, com idades entre os 8 meses e os 17 anos. A troponina foi doseada à admissão, às 12h, 24h, e 48 h. Foi realizado ecocardiograma transtorácico nas 24 horas após a admissão. A sobrevivência à alta hospitalar foi 29% (7/24). A idade média foi 5.9 ± 4.6 Anos para os sobreviventes e 4.2 ± 5.3 anos para os não sobreviventes. A mediana de duração da paragem cardíaca para os sobreviventes foi 6 min (3 a 63 min) versus 34 min (4 a 70 min) para os não sobreviventes ($P = 0.02$). Os sobreviventes receberam 1.3 ± 2.2 de epinefrina comparada com 2.9 ± 1.6 doses para os não sobreviventes ($P = 0.02$). Só um paciente teve paragem em fibrilhação ventricular e a desfibrilhação não teve sucesso. A fracção de ejecção para os sobreviventes foi em média de $73.2 \pm 11.2\%$, mas para os não sobreviventes apenas $55.4 \pm 19.8\%$ ($P = 0.04$). A fracção de ejecção correlaciona-se inversamente

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com a troponina às 12 h ($r = -0.54$, $P = 0.01$) e às 24 h ($r = -0.59$, $P = 0.02$). O encurtamento das fibras circunferenciais foi de 37.5 ± 7.8 para os sobreviventes e $25.5 \pm 10.7\%$ para os não sobreviventes ($P = 0.02$). Este também se correlaciona inversamente com a troponina $r = -0.46$, $P = 0.03$ para os sobreviventes e $r = -0.65$, $P = 0.01$, para os não sobreviventes). *Conclusão:* A gravidade da disfunção miocárdica após reanimação por paragem cardíaca em doentes pediátricos, correlaciona-se com o nível de troponina I.

Palavras chave: Reanimação pediátrica; Paragem cardíaca; Reanimação cardiopulmonar; Ecocardiografia

Resumen

Antecedentes: La disfunción miocárdica ocurre inmediatamente después de reanimación cardiopulmonar exitosa. Nuestro propósito fue determinar si acaso la medición de troponina I cardíaca en niños con paro cardiorrespiratorio agudo prehospitalario predice la severidad de la lesión miocárdica. *Métodos y resultados:* este estudio observacional prospectivo fue realizado en la Unidad de Cuidados Intensivos Pediátricos en 24 pacientes después de un paro cardíaco, cuyas edades estaban entre 8 meses y 17 años. Se obtuvieron mediciones de troponina al momento de admisión, a las 12, 24 y 48 horas. Se realizaron ecocardiogramas transtorácicos dentro de las 24 horas de admisión. La sobrevida al alta fue 29% (7/24). La edad promedio fue 5.9 ± 4.6 años para los sobrevivientes y $4.2 + 5.3$ años para los que no sobrevivieron. La mediana (rango) de duración de paro cardíaco en los sobrevivientes fue 6 minutos (3 a 63min) versus 34 (4 a 70 min) para los no sobrevivientes ($P = 0.02$). Solo un paciente tenía fibrilación ventricular y la desfibrilación fue no- exitosa. La fracción de eyección de los sobrevivientes promediaba $73.2 \pm 11.2\%$, pero para los no sobrevivientes solo $55.4\% \pm 19.8\%$ ($P = 0.04$). La fracción de eyección se correlacionó inversamente con la troponina a las 12 horas ($r = -0.54$, $P = 0.01$) y a las 24 horas ($r = -0.59$, $P = 0.02$). El acortamiento de fibra circunferencial en los sobrevivientes fue 37.5 ± 7.8 y $25.5 \pm 10.7\%$ para los no sobrevivientes ($P = 0.02$). También se correlacionó inversamente con la troponina ($r = -0.46$, $P = 0.03$ para los sobrevivientes y $r = -0.65$, $P = 0.01$, para los no sobrevivientes). *Conclusión:* Después de paro cardíaco y reanimación en pacientes pediátricos, la severidad de la disfunción miocárdica fue reflejada en los niveles de troponina I.

Palabras clave: Reanimación pediátrica; Paro cardíaco; Reanimación cardiopulmonar; Ecocardiografía

1. Introduction

Shock commonly occurs following cardiac arrest in children in the absence of preexisting cardiovascular disease [1]. Cardiac index is decreased and both systemic and pulmonary vascular resistances are increased together with increased right and left sided filling pressures. Systolic and diastolic myocardial dysfunction is progressive in the first hour that follows restoration of spontaneous circulation [2]. In young children, myocardial dysfunction reverses over intervals of 24 h during which more normal levels of cardiac output and both systemic and pulmonary vascular resistances are restored [1]. The myocardial injury is attributed to the global hypoxic-ischemic injury to the heart itself during the no-flow interval of cardiac arrest.

The measurement of serum levels of cardiac troponin I, provides a sensitive and specific marker of myocardial injury, in both adults and children, [3–5] in settings of acute myocardial infarction, [6] myocarditis, [7] cardiopulmonary bypass triggered myocardial injury, [8] and during the course of systemic sepsis [9].

In the current study, we hypothesized that cardiac troponin levels in children who survive an acute out-of-hospital cardiac arrest would reflect the severity of ventricular dysfunction.

2. Methods

Our prospective, observational study was approved by the Institutional Review Board of Loma Linda University and informed consent was obtained. All children who were admitted to the Loma Linda University Medical Center after out-of-hospital cardiopulmonary arrest and who received cardiopulmonary resuscitation (CPR) prior to arrival to the Emergency Department (ED) within the geographic area covered by Loma Linda University Children's Hospital were evaluated. Only patients who were admitted to the Pediatric Intensive Care Unit (PICU), regardless of underlying cause, were included in the study.

CPR was initiated by either bystanders or medical personnel. Patients were eligible regardless of etiology of arrest (i.e. drowning, sepsis, or respiratory distress). Patients with congenital heart disease were excluded. The cause of cardiac arrest was established retrospectively, based on both pre-hospital and in-hospital records and the results of post mortem examination.

2.1. Troponin measurements

Cardiac troponin was measured on admission to the PICU, and repeated after 12, 24, and 48 h. The assays

were performed with the aid of the Abbott Axsym® (Abbott Diagnostics, North Chicago, IL) in accord with the manufacturer's recommendations. This cardiac troponin I assay is a two-site immunoassay in which the troponin concentration of serum is captured by an antibody incorporated in a paper solid phase. Following washing to elute contaminants, radial partition chromatography was used after adding excess antibody with a fluorescent label to form a double monoclonal cardiac troponin I sandwich. Cardiac troponin I is quantitated fluorometrically. The results are interpreted as follows: ≤ 0.3 ng/ml represents the normal range; 0.4–2.3 ng/ml is the range suggestive of cardiac damage; and > 2.3 ng/ml is regarded as diagnostic of acute myocardial infarction.

2.2. Echocardiograph measurements

Echocardiograms were performed within 24 h of admission, using the Hewlett–Packard/Agilent Sonos 5500 system with 4, 8, and/or 12 MHz transducers. Standard pediatric echocardiographic views were performed from the parasternal long and short axes, apical, subxyphoid and suprasternal areas. Two-dimensional, spectral Doppler and color-flow Doppler recordings were obtained in each instance. Circumferential fiber shortening and ejection fractions were measured, including M-mode analysis in the parasternal long axis view inferior to the level of the mitral valve. Two pediatric cardiologists who were blinded to both troponin measurements and outcomes interpreted the echocardiograms.

2.3. Electrocardiograph measurements

Recordings of rhythms during resuscitation and/or immediately following return of spontaneous electrical cardiac activity were reviewed. A12-lead electrocardiograms and subsequent rhythm strips recorded in the Emergency Department were interpreted. Finally, a 12-lead electrocardiogram was performed on all patients on admission to the PICU within the first 24 h. A pediatric electrophysiologist who was blinded to the clinical status of the patient and the troponin measurements interpreted these tracings.

2.4. Statistical analysis

Statistical software SAS version 8 (SAS Institute, Inc., Cary, NC) results are reported as mean $\pm$ S.D. or median and range. Comparisons between survivors and non-survivors utilized the two-sided t-test or Mann–Whitney U-test when the continuous variables were not normally distributed. Pearson's product moment correlation was employed to relate troponin I measurements to the time intervals at baseline, 12, 24, and 48 h, for both and ejection fraction and fiber shortening.

3. Results

A total of 24 patients were available for study between December 1, 2000 and December 31, 2001. Seven of 24 victims survived (29%). The mean age of survivors was 5.9 ± 4.6 and of non-survivors, 4.2 ± 5.3 years, ($P = 0.13$). Nineteen of the 24 patients, and all seven survivors, were males.

3.1. Arrest and resuscitation data

The median duration of cardiac arrest times for the group of 24 patients was 31 min (range = 3–70 min); and for seven survivors, 6 min (range 3–63 min). The median arrest time was 34 min (range 4–70 min) for nonsurvivors ($P = 0.02$). Epinephrine administered to the entire group averaged 2.4 ± 1.9 doses (range 0–6), but survivors received only 1.3 ± 2.2 doses compared with 2.9 ± 1.6 doses for non-survivors ($P = 0.02$). Only one patient presented with ventricular fibrillation in the Emergency Department, but this patient was not resuscitated. No patients were defibrillated in the prehospital setting. Etiologies of arrest are listed in Table 1.

Table 1
Etiologies of out-of-hospital cardiopulmonary arrest

Patient	Etiology
Survivors	
1	Near-Drowning
2	Near-Drowning
3	Near-Drowning
4	Near-Drowning
5	Trauma
6	Near-Drowning
7	Trauma
Nonsurvivors	
8	NAT
9	Drowning
10	Drowning
11	Drowning
12	Drowning
13	Accidental hanging
14	Pneumonia/sepsis
15	Drowning
16	Drowning
17	Smoke inhalation
18	Drowning
19	SIDS
20	Trauma
21	Pneumonia/sepsis
22	Pneumonia/sepsis
23	Collapsed while running
24	Pneumonia/sepsis

NAT, non-accidental trauma; SIDS, sudden infant death syndrome.

No patient suffered obvious chest trauma. There was no association found between the etiology of arrest (i.e. severe CNS insult) and myocardial dysfunction. Additionally, there was no association found between CNS function as measured by initial Glasgow Coma Score and myocardial injury measurements.

3.2. Troponin measurements

The average values of troponin I are shown in Fig. 1. Significantly greater concentrations were observed in non-survivors at admission and 12 h later. Maximal troponin values in non-survivors were observed at 12 h after admission. This association was found between mean concentrations. There was not a threshold value with predictive power of mortality in this population.

3.3. Echocardiograph correlations

The circumferential shortening was reduced in relationship to increases in troponin when quantified at 12 and 24 h (($r = -0.46$, $P = 0.03$ and $r = -0.65$, $P = 0.01$, respectively). This negative association also applied to ejection fraction at 12 and 24 h ($r = -0.54$, $P = 0.01$ and $r = -0.59$, $P = 0.02$, respectively). Both ejection fractions and fiber shortening were greater in survivors as shown in Fig. 2.

3.4. Electrocardiograph results

Except for the one patient already cited, electrocardiographic rhythm strips recorded by out-of-hospital rescue personnel or on arrival in the Emergency Department demonstrated asystole or sinus bradycardia. Standard 12-lead electrocardiograms, performed on all patients after admission to the PICU revealed normal sinus rhythm. In 13 patients T wave abnormalities were identified and in three patients prolongation of the QTc interval (Table 2).

4. Discussion

We report an association between initial troponin values and mortality following cardiac arrest, predominantly of asphyxial causes, in children. This demonstration of a highly significant association between troponin values and echocardiograph findings of ventricular dysfunction following the global ischemia of cardiac arrest is in a pediatric population in the absence of coronary artery disease.

In adult patients, a correlation between cardiac troponin measurements and the duration of CPR had already been established [10,11]. Serum troponin levels in these studies were related to infarct size and ventricular dysfunction following myocardial infarction

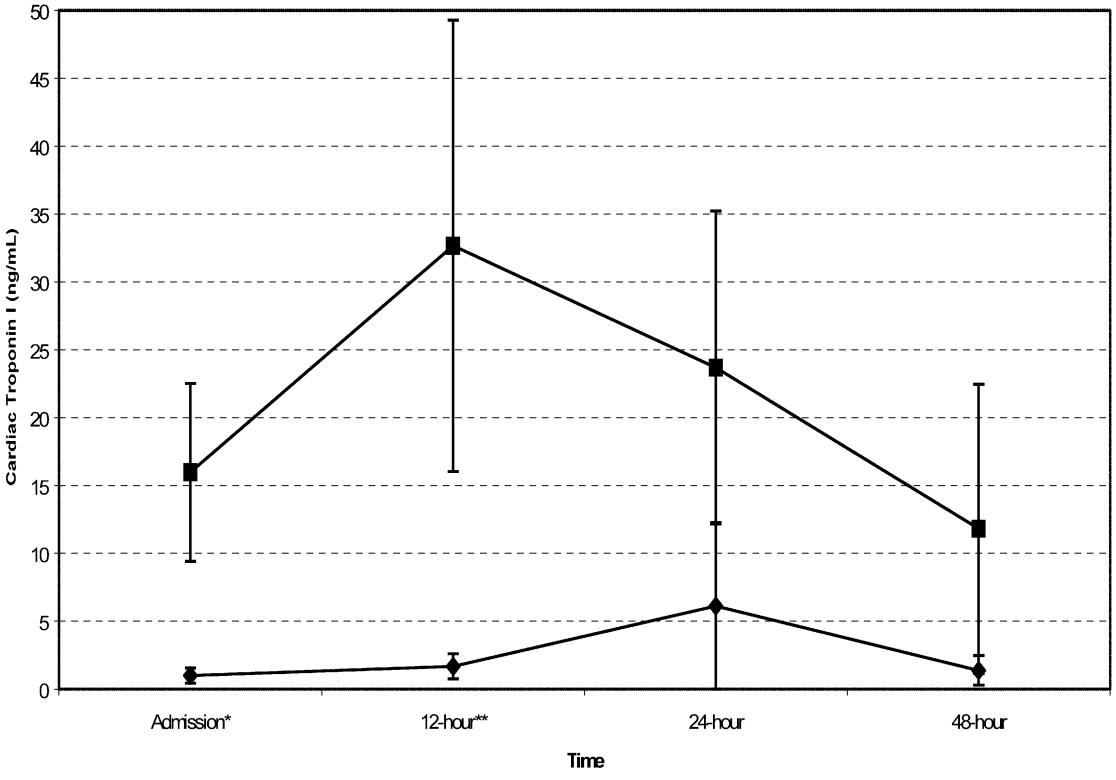

Fig. 1. Mean ± S.D. cardiac troponin I measurements (ng/ml) by survival status at different times of testing. Squares, non-survivors; diamonds, survivors. *$P = 0.02$, **$P = 0.04$.

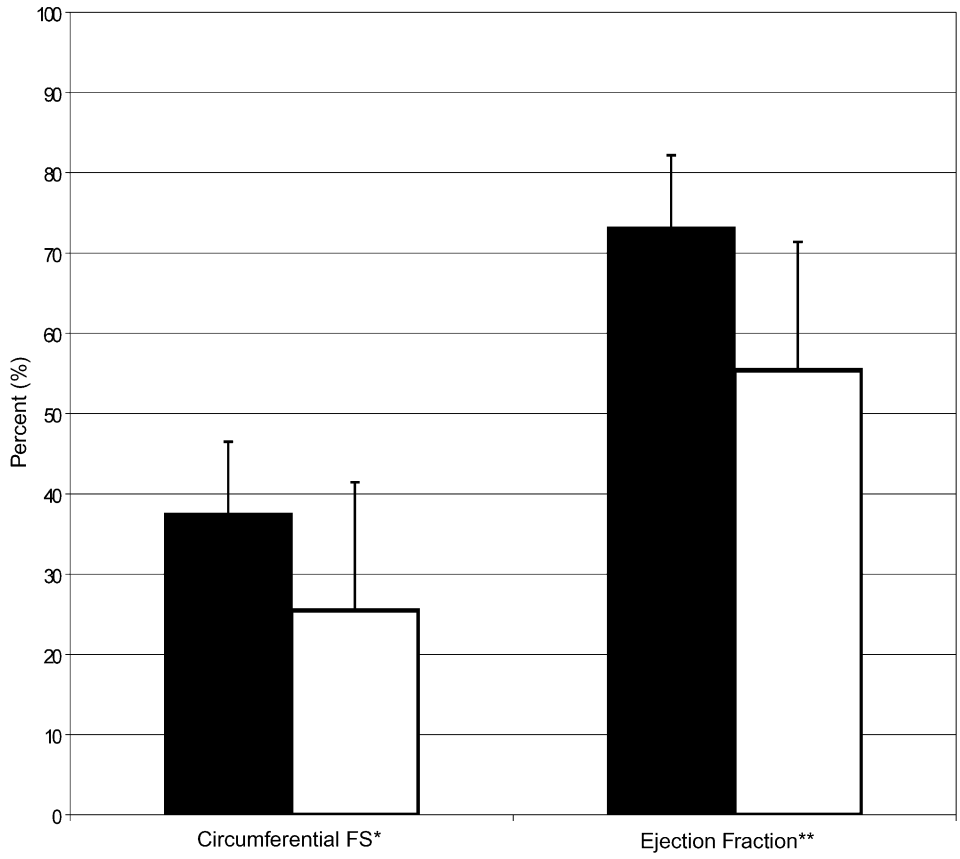

Fig. 2. Mean (±S.D.) circumferential fiber shortening and ejection fractions of survivors vs. non-survivors. Solid bar, survivors; Open bar, non-survivors. *$P = 0.02$, **$P = 0.04$.

[12–15]. A correlation between troponin elevation and perioperative myocardial damage following cardiopulmonary bypass was also documented [16–19]. In each of these studies pre-existing coronary artery disease or acute myocardial infarction were implicated. In the pediatric population herein reported, previously healthy children sustained cardiac arrest as a consequence of asphyxia and, therefore, global myocardial ischemia.

Serum measurements of cardiac troponin serve to quantify myocardial injury in both adult and in pediatric settings [4]. More specifically, troponin measurements serve as the basis for diagnosis of myocardial injury in neonates, [20–22] and in children suffering from Kawasaki Disease [23]. Additionally, troponin measurements have been used extensively in the diagnosis of myocardial injury during the course of cardiac surgery using cardiopulmonary bypass in children [5,8,24–27]. Hirsch et al. [28], for instance, analyzed troponin levels in 55 children following repair of atrial septal defects, ventricular septal defects, and tetralogy of Fallot. The severity of troponin elevation correlated with the duration of aortic cross clamping. Immer et al. confirmed that increases in troponin at 4 h following admission to the intensive care unit after open heart surgery in children predicted post-operative complications, including the frequency of inotropic support, the severity of renal dysfunction, and duration of intubation and mechanical ventilation [27]. In the present study, troponin distinguished between survivors and non-survivors; however, there was not a specific threshold level.

Several limitations are inherent in the current study. Our study is necessarily observational since no baseline measurements of ventricular function were available prior to cardiac arrest. However, the incidence of preexisting myocardial dysfunction in this general population of children is expected to be only 0.6–1.1 per 100 000 [29]. In addition, animal studies after cardiac arrest demonstrated progressive myocardial dysfunction in piglets over the initial 3 h with full recovery at the end of 72 h [30]. In the present study, only a single non-invasive measurement of ventricular function was obtained.

We conclude that the measurement of cardiac troponin in children with acute out-of-hospital cardiac arrest predicts the severity of hypoxic-ischemic myocardial injury, based on objective echocardiographic estimates of ventricular dysfunction. This study provides more

Table 2
Electrocardiographic observations

Patient	ECG Interpretation
Survivors	
1	NSR, NSTWC
2	NSR
3	NSR, QTc = 0.49 s
4	NSR
5	NSR
6	NSR, NSTWC
7	NSR
Nonsurvivors	
8	NSR, QTc = 0.48 s, NSTWC
9	NSR, NSTWC
10	NSR, QTc = 0.48 s, NSTWC
11	NSR, NSTWC
12	NSR, ST Flattening
13	NSR
14	NSR
15	NSR, NSTWC, Left atrial hypertrophy
16	NSR
17	NSR, NSTWC
18	NSR
19	NSR, NSTWC
20	NSR, NSTWC
21	NSR, NSTWC
22	NSR
23	RAD, LBBB, NSTWC
24	ST Depression inferior lateral

NSR, normal sinus rhythm; NSTWC, nonspecific T wave changes; QTc, corrected QT segment measurement; RAD, right axis deviation; LBBB, left bundle branch block.

secure evidence of post resuscitation dysfunction after asphyxial cardiac arrest, not only primary cardiac arrest due to structural or coronary artery disease. Finally, the troponin elevation, as in postoperative cardiac settings in children, is associated with mortality after out-of-hospital cardiac arrest.

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