

ORIGINAL ARTICLE

# A Comparison of High-Dose and Standard-Dose Epinephrine in Children with Cardiac Arrest

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ABSTRACT

**BACKGROUND**

When efforts to resuscitate a child after cardiac arrest are unsuccessful despite the administration of an initial dose of epinephrine, it is unclear whether the next dose of epinephrine (i.e., the rescue dose) should be the same (standard) dose or a higher dose.

**METHODS**

We performed a prospective, randomized, double-blind trial to compare high-dose epinephrine (0.1 mg per kilogram of body weight) with standard-dose epinephrine (0.01 mg per kilogram) as rescue therapy for in-hospital cardiac arrest in children after failure of an initial, standard dose of epinephrine. The trial included 68 children, and Utstein-style reporting guidelines were used. The primary outcome measure was survival 24 hours after the arrest.

**RESULTS**

The rate of survival at 24 hours was lower in the group assigned to a high dose of epinephrine as rescue therapy than in the group assigned to a standard dose: 1 of the 34 patients in the high-dose group survived for 24 hours, as compared with 7 of the 34 patients in the standard-dose group (unadjusted odds ratio for death with the high dose, 8.6; 97.5 percent confidence interval, 1.0 to 397.0;  $P=0.05$ ). After adjustment by multiple logistic-regression analysis for differences in the groups at the time of arrest, the high-dose group tended to have a lower 24-hour survival rate (odds ratio for death, 7.9; 97.5 percent confidence interval, 0.9 to 72.5;  $P=0.08$ ). The two treatment groups did not differ significantly in terms of the rate of return of spontaneous circulation (which occurred in 20 patients in the high-dose group and 21 of those in the standard-dose group; odds ratio, 1.1; 97.5 percent confidence interval, 0.4 to 3.0). None of the patients in the high-dose group, as compared with four of those in the standard-dose group, survived to hospital discharge. Among the 30 patients whose cardiac arrest was precipitated by asphyxia, none of the 12 who were assigned to high-dose epinephrine were alive at 24 hours, as compared with 7 of the 18 who were assigned to a standard dose ( $P=0.02$ ).

**CONCLUSIONS**

We did not find any benefit of high-dose epinephrine rescue therapy for in-hospital cardiac arrest in children after failure of an initial standard dose of epinephrine. The data suggest that high-dose therapy may be worse than standard-dose therapy.

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ADMINISTRATION OF EPINEPHRINE during cardiopulmonary resuscitation (CPR) consistently improves coronary and cerebral perfusion.<sup>1</sup> Doses of epinephrine ranging from 0.05 to 0.2 mg per kilogram of body weight increase coronary and cerebral perfusion during CPR more than does the lower, standard dose, which is 0.01 mg per kilogram.<sup>2-7</sup> The American Heart Association guidelines for pediatric advanced life support recommend use of the standard dose of epinephrine, given intravenously, as the initial dose for children with cardiac arrest.<sup>1</sup> However, if subsequent doses are necessary, the guidelines recommend use of either the standard dose or a higher dose (0.1 mg per kilogram).

Previously, in 1992, the American Heart Association recommended that second and subsequent epinephrine doses in children "should be 0.1 mg per kilogram,"<sup>8</sup> largely on the basis of a retrospective study of children with in-hospital cardiac arrest.<sup>9</sup> The rationale for higher-dose epinephrine as rescue therapy was further supported by the nearly uniformly fatal outcomes in other studies after the administration of more than two standard doses of epinephrine in children.<sup>10</sup> Moreover, the pharmacokinetics and pharmacodynamics of catecholamines in settings other than cardiac arrest were reported to be highly variable: a dose that is effective in one patient may be ineffective in another.<sup>1,11-13</sup> It was therefore reasonable to surmise that when a dose of 0.01 mg of epinephrine per kilogram is unsuccessful, a higher dose may be more effective and that patients receiving catecholamine infusions before a cardiac arrest may also need a higher dose.

Subsequently, however, multiple studies in adults, children, and animals failed to show improved outcomes with high-dose epinephrine as compared with standard-dose epinephrine.<sup>1,6,14-22</sup> Although the issue of rescue therapy was not well studied, the consistent lack of a benefit of high-dose epinephrine influenced the American Heart Association in 1997 to change its recommendation for second and subsequent doses of epinephrine during cardiac arrest in children to include either standard- or high-dose epinephrine.<sup>23</sup>

In a previous investigation at the Children's Institute of the University of São Paulo School of Medicine, 61 percent of the cardiac arrests were precipitated by asphyxia, and 36 percent occurred in children who had received catecholamine infusions before the arrest.<sup>24</sup> The Children's Institute is a 122-bed, tertiary-care children's hospital that ad-

mits more than 6000 patients each year. Cardiac surgery and trauma care are not provided. In this setting, we hypothesized that in children who had an in-hospital cardiac arrest, rescue therapy with high-dose epinephrine, as compared with continued use of the standard dose, would improve the rate of survival at 24 hours. We further hypothesized that the differences would be most clearly demonstrable in the subgroup of patients with asphyxia-precipitated arrests, who are more homogeneous and have a better response to therapy than the group as a whole.

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## METHODS

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### PATIENTS AND PROTOCOL

In a double-blind study conducted at the Children's Institute, we randomly assigned children who remained in cardiac arrest despite CPR and an initial, standard dose of epinephrine (0.01 mg per kilogram) to receive either standard-dose epinephrine or high-dose epinephrine (0.1 mg per kilogram). From October 31, 1999, to September 30, 2001, all such children were eligible for entry into the study except for neonates, children with sustained trauma, those whose cardiac arrest had commenced outside the hospital, and those with do-not-resuscitate orders. Cardiac arrest was defined as the cessation of mechanical cardiac activity, determined on the basis of the absence of a palpable central pulse and the presence of unresponsiveness and apnea. In children who had more than one cardiac arrest, only the initial cardiac arrest was evaluated.

Randomization was performed by a single pharmacist, who prepared the treatment packages, each containing 10 1-ml vials of epinephrine in a solution of 1:1000 or 1:10,000. She labeled the treatment packages with consecutive numbers provided by a random-number generator to ensure consistency with the randomization scheme. Patients who remained in cardiac arrest after CPR and the administration of the initial, standard dose of epinephrine from the routinely stocked solution received 0.1 ml of the experimental solution per kilogram, which provided a dose of 0.01 mg per kilogram if it was the 1:10,000 solution or 0.1 mg per kilogram if it was the 1:1000 solution. All further doses were provided from the same treatment package (such that all subsequent rescue doses of epinephrine were the same as the first rescue dose in a given patient). Only the study pharmacist had access to information pertaining to the epinephrine concentration in each package.

Residents, nurses, and faculty members provided CPR according to American Heart Association guidelines, without interference from the observing research team. Members of the pediatric intensive care and emergency medicine faculty were in the hospital 24 hours a day and were available to participate on the cardiac-resuscitation team. Postresuscitation hypothermia and extracorporeal membrane oxygenation were not provided to any of the enrolled patients. The data-collection form was adapted from the in-hospital, Utstein-style guidelines, as we have previously reported.<sup>24</sup>

The Commission on Ethics in Research of the Children's Institute approved this prospective investigation. Because of the unexpected and sudden nature of the cardiac events and because both dose strategies are recommended by the American Heart Association and the International Liaison Committee on Resuscitation, the commission accepted the concept of presumed consent and approved exemption from the requirement for informed consent.<sup>25</sup> However, informed consent was deemed necessary, and was obtained from the parents or legal guardians of all the patients, for continued participation in data collection and follow-up after hospital discharge.

#### SAMPLE SIZE

On the basis of our previous experience, a two-year recruitment period was expected to yield approximately 70 patients for enrollment.<sup>24</sup> In our previous study, the 24-hour survival rate after two standard doses of epinephrine was approximately 20 percent.<sup>24</sup> In an earlier study based on historical controls, rescue therapy with high-dose epinephrine increased the 24-hour survival rate from 0 percent to approximately 50 percent.<sup>9</sup> With 34 children in each group, the power to detect an improvement from 20 to 50 percent in the 24-hour survival rate (with a two-sided *P* value of 0.05) was 75 percent.

#### STATISTICAL ANALYSIS

Data from all the enrolled patients were analyzed on an intention-to-treat basis. The primary outcome measure was survival at 24 hours. Because we had previously shown that only patients with asphyxia-precipitated arrests had 24-hour survival rates that were greater than 10 percent (and that patients in shock had much worse outcomes), we analyzed the data for such patients separately.<sup>24</sup> Data analyses were performed with StatView 5.0 and Stata 7.0 software. Differences between the two treatment

groups were assessed by chi-square analysis or Fisher's exact test for discrete variables and by unpaired *t*-tests for continuous variables. All reported *P* values are two-sided.

Differences between the groups in the rate of 24-hour survival were further evaluated by multiple logistic-regression analysis, including all base-line factors for which the two groups differed at a level of *P*<0.10. Because of the emergency nature of cardiac arrest, protocol violations occasionally occurred. Additional analyses were conducted after the exclusion of data from patients whose treatment involved protocol violations.

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## RESULTS

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### PATIENTS AND PROTOCOL VIOLATIONS

During the 23-month investigation, cardiac arrests occurred in 185 children (Fig. 1). A total of 117 children met the exclusion criteria, in 67 cases because of orders not to attempt resuscitation. The remaining 68 children were randomly assigned to the high-dose treatment regimen (34 patients) or the standard regimen (34 patients).

Protocol violations occurred in 18 of these 68 cases. Because of the need for immediate intervention in cardiac arrest, inadvertent deviations from the research protocol in terms of dosing occurred in 10 of the 68 patients: 3 assigned to the standard-dose group, and 7 to the high-dose group. The doses in these 10 patients ranged from 0.002 to 0.06 mg per kilogram. The other eight protocol violations occurred because patients who had been assigned to the standard-dose group were given high-dose epinephrine at some point during resuscitative efforts; seven of these eight patients weighed more than 20 kg and thus received much larger volumes of medication than infants or toddlers. All eight were inadvertently treated with high-dose epinephrine after their experimental standard-dose vials had been emptied because the epinephrine routinely stocked at this hospital is the 1:1000 solution. Therefore, continued use of the same milligram-per-kilogram dose resulted in a 10-fold dose increase in these patients after the experimental vials containing epinephrine in a 1:10,000 solution had been emptied.

In general, the two groups were similar before the cardiac arrest (Table 1). Nearly all the arrests (96 percent) were witnessed. Before the arrest, the majority of the patients were being monitored electrocardiographically (78 percent), were receiving

mechanical ventilation (68 percent), or were being treated with catecholamine infusions (53 percent). Resuscitative efforts during cardiac arrest were similar in the two groups, although more patients in the high-dose group than in the standard-dose group received only two or three doses of epinephrine, and more patients in the standard-dose group received more than six doses (Table 2).

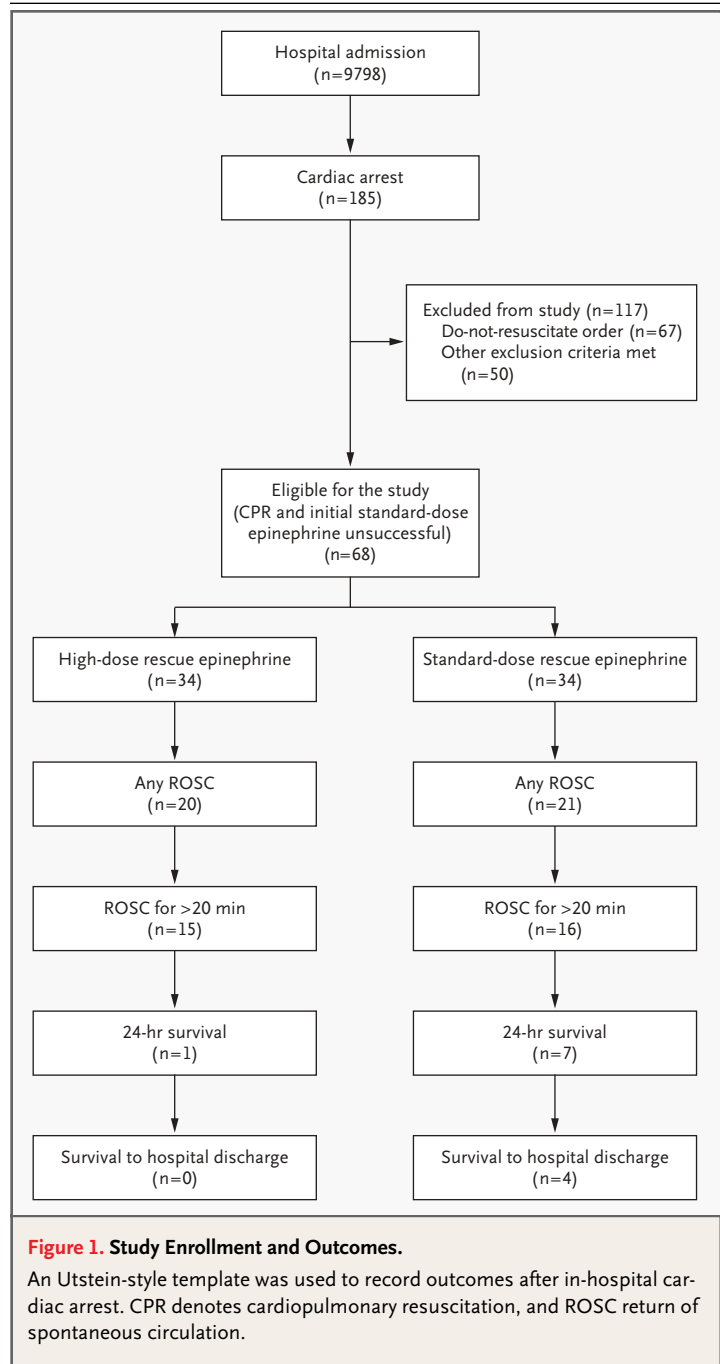
#### OUTCOME

The rate of survival at 24 hours was lower in the high-dose group than in the standard-dose group: 1 of the 34 patients assigned to the high dose of rescue epinephrine survived at 24 hours, as compared with 7 of the 34 patients assigned to the standard dose (unadjusted odds ratio for death with the high dose, 8.6; 97.5 percent confidence interval, 1.0 to 397.0;  $P=0.05$ ) (Table 3). After adjustment by multiple logistic-regression analysis for differences between the two treatment groups at the time of arrest (in terms of sex, race, location of the arrest, and initial cardiac rhythm), the high-dose group still tended to have a lower 24-hour survival rate and had a substantial odds ratio for death, but the difference from the standard-dose group was not significant (odds ratio, 7.9; 97.5 percent confidence interval, 0.9 to 72.5;  $P=0.08$ ). The two treatment groups did not differ significantly in terms of the rate of return of spontaneous circulation or the rate of survival to hospital discharge (Table 3). However, none of the 34 patients in the group assigned to high-dose epinephrine survived to hospital discharge, as compared with 4 of the 34 assigned to standard-dose epinephrine ( $P=0.11$ ).

Six months after discharge, two of the four children who survived to hospital discharge were alive and neurologically normal (i.e., pediatric cerebral-performance category 1).<sup>26</sup> The other two children were both neurologically impaired before their arrests, and their base-line pediatric cerebral-performance category remained unchanged six months after discharge.<sup>24</sup>

Among the patients whose cardiac arrest had been precipitated by asphyxia, none of the 12 who were assigned to high-dose rescue epinephrine survived at 24 hours. In contrast, 7 of the 18 patients who were assigned to the standard dose after asphyxia-precipitated arrest survived at 24 hours ( $P=0.02$ ) (Table 4).

Outcomes were dismal among the 38 patients whose cardiac arrest had been precipitated by some form of shock. Twenty-two were assigned to high-



dose epinephrine, and 16 to standard-dose epinephrine. Only 1 of the 38 survived at 24 hours, and none survived to hospital discharge.

We further analyzed the data after all the cases involving protocol violations had been excluded. The rate of survival at 24 hours was again lower in the high-dose epinephrine group: 1 of 27 patients survived, as compared with 6 of 23 in the standard-

**Table 1. Demographic Characteristics of the Patients at the Time of Cardiac Arrest.\***

Characteristic	High-Dose Epinephrine (N=34)	Standard-Dose Epinephrine (N=34)	P Value
Age — mo	74±62	62±64	0.45
Weight — kg	20±15	17±13	0.45
Male sex — no.	13	20	0.09
Race — no.			0.09
White	20	13	
Other	14	21	
Preexisting disease — no. (%)	32 (94)	31 (91)	0.64
Hepatic failure	11 (32)	7 (21)	0.27
Cancer	6 (18)	3 (9)	0.38
Neurologic disease	4 (12)	4 (12)	1.0
Pneumonia	1 (3)	4 (12)	0.16
Renal failure	2 (6)	2 (6)	1.0
Acquired immunodeficiency syndrome	1 (3)	2 (6)	0.56
Other	7 (21)	9 (26)	
Cause of arrest — no. (%)			
Asphyxia	12 (35)	18 (53)	0.14
Septic shock	9 (26)	11 (32)	0.59
Hypovolemic shock	4 (12)	3 (9)	0.69
Other	9 (26)	2 (6)	
Place of arrest — no. (%)			
Intensive care unit	23 (68)	21 (62)	0.61
Emergency department	5 (15)	12 (35)	0.05
Ward	6 (18)	1 (3)	0.05
Initial electrocardiographic rhythm — no. (%)			
Asystole	21 (62)	28 (82)	0.06
Pulseless electrical activity	9 (26)	6 (18)	0.38
Ventricular fibrillation or pulseless ventricular tachycardia	4 (12)	0	0.04

\* Plus-minus values are means ±SD. Because of rounding, not all percentages sum to 100.

dose group (odds ratio for death with the high dose, 9.2; 97.5 percent confidence interval, 1.3 to 63.3;  $P=0.04$ ). In addition, among the patients whose treatment involved no protocol violations and whose arrest had been precipitated by asphyxia, the 24-hour survival rate was lower with high-dose epinephrine: none of 8 such patients given the high dose survived at 24 hours, as compared with 6 of 13 patients given the standard dose ( $P=0.05$ ).

#### DISCUSSION

In this double-blind, prospective, randomized, controlled investigation in which the use of high-dose epinephrine rescue therapy was compared with con-

tinued use of standard-dose epinephrine during CPR in children, we did not find any benefit associated with the switch to high-dose epinephrine. Although the data raise the possibility that high-dose epinephrine as rescue therapy may reduce the probability of survival at 24 hours, the evidence is limited by the small sample.

The characteristics of the patients and their outcomes were similar to those previously described at the Children's Institute.<sup>24</sup> More than 90 percent of these cardiac arrests were monitored and witnessed, typically in the intensive care unit. Most of the patients were receiving mechanical ventilation before the cardiac arrest, and many were already receiving catecholamine infusions. The most com-

**Table 2. Duration of CPR and Doses of Epinephrine.\***

Variable	High-Dose Epinephrine (N=34)	Standard-Dose Epinephrine (N=34)	P Value
Duration of CPR			
Mean — min	31±22	36±21	0.32
≤15 min— no. (%)	11 (32)	10 (29)	0.79
>15 min— no. (%)	23 (68)	24 (71)	
Interval from arrest to first (standard) dose of epinephrine — min	3.1±3.8	2.6±3.4	0.57
Total doses of epinephrine — no. (%)			
2 or 3	19 (56)	11 (32)	0.05
4–6	10 (29)	11 (32)	0.79
>6	5 (15)	12 (35)	0.05

\* Plus-minus values are means ±SD. Because of rounding, not all percentages total 100. CPR denotes cardiopulmonary resuscitation.

**Table 3. Outcomes.\***

Outcome	High-Dose Epinephrine (N=34)	Standard-Dose Epinephrine (N=34)	Unadjusted Odds Ratio (95% CI)*	P Value
	<i>no. of patients (%)</i>			
Return of spontaneous circulation	20 (59)	21 (62)	1.1 (0.4–3.0)	0.80
For ≤20 min	4 (12)	6 (18)	1.6 (0.4–6.3)	0.49
For >20 min but <24 hr	15 (44)	8 (24)	0.4 (0.1–1.1)	0.07
Survival at 24 hr	1 (3)	7 (21)	8.6 (1.0–397.0)	0.05
Survival to hospital discharge	0	4 (12)		0.11

\* CI denotes confidence interval.

mon cause of arrest was asphyxia, and the initial electrocardiographic rhythm was typically asystole. The patients were critically ill children in whom aggressive critical care management was failing, and their cardiac arrests were promptly diagnosed and treated.

Of the patients whose arrests had been precipitated by shock, only one survived for 24 hours in either treatment group. The expected dismal outcomes preclude meaningful evaluation of the effects of the epinephrine dose on shock-precipitated arrests. In contrast, among the patients with asphyxia-precipitated cardiac arrests, 7 of the 18 assigned to the standard dose of epinephrine as rescue therapy were alive at 24 hours, as compared with none of the 12 assigned to the high dose.

A previous study of in-hospital cardiac arrest in children suggested that outcomes after rescue ther-

apy with high-dose epinephrine were far superior to those after rescue therapy with standard-dose epinephrine.<sup>9</sup> In that study, 14 of 20 patients given high-dose epinephrine had a return of spontaneous circulation, and 8 of those 20 survived to hospital discharge. In contrast, none of 20 historical controls who had been given standard-dose epinephrine as rescue therapy had even a transient return of spontaneous circulation. The patients in this previous study and those in our study were similar. Both investigations were in-hospital studies, and the cardiac arrests were typically precipitated by asphyxia. However, the previous study was neither randomized nor blinded, and the standard-dose group was composed of historical controls.

In another retrospective study of in-hospital cardiac arrest in children, nearly half of 51 patients were treated with high-dose epinephrine at some

**Table 4. Outcomes for Patients with Cardiac Arrest Precipitated by Asphyxia.**

Outcome	High-Dose Epinephrine (N=12)	Standard-Dose Epinephrine (N=18)	P Value
	<i>no. of patients (%)</i>		
Return of spontaneous circulation	7 (58)	13 (72)	0.43
Survival at 24 hr	0	7 (39)	0.02
Survival to hospital discharge	0	4 (22)	0.13

point during resuscitative efforts.<sup>27</sup> Although this group and a group given standard-dose epinephrine did not differ with respect to the rates of return of spontaneous circulation, 24-hour survival, or survival to hospital discharge, the 24-hour survival rate tended to be worse in the group given high-dose epinephrine: 7 of 24 patients in that group survived, as compared with 17 of 34 patients in the group given only the standard dose ( $P=0.12$ ).

In a retrospective study of out-of-hospital cardiac arrest in children, 1 of 44 patients given a high dose of epinephrine at some point during resuscitative efforts, as compared with 1 of 13 given only the standard dose, survived to hospital admission.<sup>28</sup> The high rate of death precluded assessment of the epinephrine dose in relation to outcomes.

Similarly, outcomes were poor in the only randomized, controlled trial of high-dose epinephrine versus standard-dose epinephrine as rescue therapy for out-of-hospital cardiac arrest in adults.<sup>20</sup> None of 140 patients survived to hospital discharge. Rates of survival at 24 hours were not reported. Multiple randomized, controlled trials involving adults have consistently shown that initial and subsequent administration of high-dose epinephrine during CPR does not improve the outcome as compared with the administration of standard-dose epinephrine. Most of these studies have focused on the treatment of ventricular fibrillation.<sup>1,6,14-22</sup> Although the outcomes in the two groups did not differ in any single investigation, a meta-analysis of five studies involving a total of 3199 patients suggested that survival to hospital discharge is worse with high-dose epinephrine than with standard-dose epinephrine.<sup>29</sup> In addition, a retrospective investigation in adults indicated that neurologic outcomes are worse among those who receive a higher cumulative dose of this drug.<sup>30</sup>

Epinephrine improves coronary and cerebral perfusion during CPR by directing the limited systemic blood flow to the coronary and cerebral circulations

through its peripheral vasoconstrictive effects.<sup>31,32</sup> A high dose of epinephrine increases coronary and cerebral perfusion during CPR more than does the standard dose.<sup>2-5,7</sup> However, high doses, as compared with standard doses, also increase myocardial oxygen consumption and decrease cardiac output during CPR.<sup>33,34</sup> Furthermore, high doses can result in a toxic hyperadrenergic state (manifested as severe tachycardia, severe hypertension, and ventricular arrhythmias) during the first few minutes after resuscitation.<sup>21,22,35</sup> This state may be particularly dangerous for the stunned myocardium after resuscitation.<sup>36</sup> Although we were unable to evaluate these physiological variables during the first few minutes after resuscitation in our patients, we speculate that the poor outcomes with high-dose epinephrine may be due in part to such adverse effects.

The main limitations of this investigation are related to the small sample size, use of the 24-hour survival rate as the primary outcome measure, the occurrence of protocol violations, and the extent to which the results may be generalized to other populations of children. The rate of survival at 24 hours was selected as the primary outcome measure because it is clinically important, is measurable, and is directly related to resuscitative interventions. Although long-term survival with a good neurologic outcome is the ultimate goal of resuscitation from cardiac arrest, that end point is more strongly influenced by underlying conditions that are not related to resuscitative efforts during cardiac arrest. Furthermore, attainment of an adequate sample size for assessment of that outcome would require a prolonged study period, thereby complicating the study with potentially different resuscitation strategies and protocols over time. The relevance of the effects of the epinephrine dose on survival at 24 hours is supported by similar trends in dose effects on survival to hospital discharge.

Protocol violations occurred during resuscitative efforts in 18 of the 68 cardiac arrests we studied. Ten

were inadvertent deviations in dosing from the research protocol due to the urgency of the CPR efforts, which apparently resulted in incorrect guesses at the patients' weights or doses. The other eight involved children who had been assigned to standard-dose rescue therapy received high-dose epinephrine after their experimental vials had been emptied. Subsequent doses were high because the epinephrine routinely stocked at our hospital is the 1:1000 solution. To further assure ourselves that these protocol violations did not bias our outcome analyses, we reanalyzed the data after excluding all the cases involving protocol violations. The unadjusted 24-hour survival rate was again lower with high-dose epinephrine than with standard-dose epinephrine: only 1 of 27 patients in the former group was alive at 24 hours, as compared with 6 of 23 in the latter group. In addition, among patients with asphyxia-precipitated arrests and no protocol violations, the 24-hour survival rate was also lower in the high-dose epinephrine group: none of 8 patients in that group survived, as compared with 6 of 13 in the standard-dose group.

Finally, it is possible that high-dose epinephrine may be beneficial in a different population of children. For example, the cardiac arrests in this study were witnessed, monitored, promptly recognized,

and promptly treated. Children who have more prolonged, untreated cardiac arrests, those who have undergone cardiac surgery, and those in ventricular fibrillation were underrepresented. Nevertheless, most reported cases of in-hospital cardiac arrest in children were precipitated by asphyxia or shock and were promptly diagnosed and treated.<sup>10,24,37</sup> We therefore believe that our findings are relevant to most populations of children who have in-hospital cardiac arrest.

Despite our findings, it is reasonable to speculate that some patients may benefit from high-dose epinephrine as rescue therapy. For example, the risks of high-dose epinephrine may be acceptable in the setting of inadequate coronary perfusion pressures or aortic diastolic pressures during CPR despite aggressive compression of the chest and administration of an initial standard dose of epinephrine.<sup>38-40</sup> However, our data and other published data do not support the use of high-dose epinephrine when these pressures are not monitored.

In conclusion, the results of this study suggest that high-dose epinephrine rescue therapy in children with in-hospital cardiac arrest does not improve the rate of survival at 24 hours. Among children with asphyxia-precipitated cardiac arrest, high-dose epinephrine appears to be harmful.

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