Survival Outcomes With the Introduction of Intravenous Epinephrine in the Management of Out-of-Hospital Cardiac Arrest

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Study objective: The benefit of epinephrine in cardiac arrest is controversial and has not been conclusively shown in any human clinical study. We seek to assess the effect of introducing intravenous epinephrine on the survival outcomes of out-of-hospital cardiac arrest patients in an emergency medical services (EMS) system that previously did not use intravenous medications.

Methods: This observational, prospective, before-after clinical study constitutes phase II of the Cardiac Arrest and Resuscitation Epidemiology project. Included were all patients who are older than 8 years, with nontraumatic out-of-hospital cardiac arrest conveyed by the national emergency ambulance service. The comparison between the 2 intervention groups for survival to discharge was made with logistic regression and expressed in terms of the odds ratio (OR) and the corresponding 95% confidence interval (CI).

Results: From October 1, 2002, to October 14, 2004, 1,296 patients were enrolled into the study, with 615 in the pre-epinephrine and 681 in the epinephrine phase. Demographic and EMS characteristics were similar in both groups. Forty-four percent of patients received intravenous epinephrine in the epinephrine phase. There was no significant difference in survival to discharge (pre-epinephrine 1.0%; epinephrine 1.6%; OR 1.7 [95% CI 0.6 to 4.5]; adjusted for rhythm OR 2.0 [95% CI 0.7 to 5.5]); return of circulation (pre-epinephrine 17.9%; epinephrine 15.7%; OR 0.9 [95% CI 0.6 to 1.2]), or survival to admission (pre-epinephrine 7.5%; epinephrine 7.5%; OR 1.0 [95% CI 0.7 to 1.5]). There was a minimal increase in scene time in the epinephrine phase (10.3 minutes versus 10.7 minutes; 95% CI of difference 0.02 to 0.94 minutes).

Conclusion: We were unable to establish a significant survival benefit with the introduction of intravenous epinephrine to an EMS system. More research is needed to determine the effectiveness of drugs such as epinephrine in resuscitation. [Ann Emerg Med. 2007;50:635-642.]

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Editor's Capsule Summary

What is already known on this topic

There are few human data supporting the current use of intravenous epinephrine for patients with out-of-hospital cardiac arrest.

What question this study addressed

Does the introduction of a single dose of 1 mg intravenous epinephrine improve outcomes from out-of-hospital cardiac arrest in a system that previously did not use this drug?

What this study adds to our knowledge

Only 44% of eligible subjects received epinephrine in this 1,296-patient before-after trial in Singapore. No benefit in initial survival or other common short-term resuscitation metrics occurred.

How this might change clinical practice

Given the study's limitations, the role of epinephrine remains unclear. This study highlights the difficulties in establishing the value of standard EMS resuscitative care.

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INTRODUCTION

Background and Importance

In the chain-of-survival concept,[1,2] provision of early access, early cardiopulmonary resuscitation (CPR), early defibrillation, and early advanced care, including intravenous drugs, should improve survival in sudden cardiac arrest. Survival rates for out-of-hospital cardiac arrest vary in published reports from 2% to more than 20%.[3]

Intravenous epinephrine (adrenaline) has been used since 1906 to treat cardiac arrest.[4] However, since then, there have been few formal evaluations of the value of epinephrine, and these studies are more than 10 years old.[5] Clinical trials have not been able to show any benefit with intravenous epinephrine in the field.[6,7] In fact, some suggest that harm is actually associated with its use in cardiac arrest.[8,9] Extensive clinical trials comparing high-dose epinephrine (>5-mg boluses) with standard-dose epinephrine (1 mg) have shown that there is no improvement in survival with increasing doses of epinephrine.[10-16]

The current International Liaison Committee on Resuscitation Advanced Cardiac Life Support Guidelines (2005)[17] acknowledges that there is no placebo-controlled evidence that use of any vasopressor during cardiac arrest improves survival to hospital discharge. However, acknowledging the current standard clinical practice, they state that it is reasonable to continue to use vasopressors routinely.[17] Because the use of epinephrine is ingrained in clinical practice in North America and Europe, it would probably not be possible to conduct controlled evaluations of epinephrine in these settings.

Goals of This Investigation

In this study, we aimed to evaluate the incremental benefit of introducing intravenous epinephrine in the out-of-hospital setting on the survival outcomes of cardiac arrest patients in the Singapore emergency medical services (EMS), a system that previously did not use out-of-hospital intravenous medications. Specific outcomes examined included survival to discharge, survival to hospital admission, return of spontaneous circulation, and functional status on discharge.

MATERIALS AND METHODS

Study Design

The Cardiac Arrest and Resuscitation Epidemiology Study is a prospective multiphase, before-after study of all eligible out-of-hospital cardiac arrest patients in Singapore. During phase II, intravenous epinephrine was introduced in the treatment protocols of all out-of-hospital cardiac arrest patients conveyed by the Singapore Civil Defence Force ambulance service. The Singapore Civil Defence Force operates the national 995 emergency telephone service; private ambulance operators do not convey emergency cases. The study period was October 1, 2002, to October 14, 2004.

Setting

Singapore is a city-state with a land area of 699.4 km^2 and a population of 4.35 million.[18,19] The population is multiracial, with the major ethnic groups being Chinese, Malay, and Indian. The island's EMS system is run by the Singapore Civil Defence Force, which currently operates 32 ambulances based in 15 fire stations and 14 satellite stations in a single-tier system. Emergency ambulance patients are delivered to 6 major public hospitals in the country that are equipped with modern emergency departments (ED).

Singapore EMS is activated by a universal, centralized, enhanced, 995 dispatching system run by the Singapore Civil Defence Force and using computer-aided dispatch, medical dispatch protocols, global positioning satellite automatic vehicle locating systems, and road traffic monitoring systems.

Since 1996, ambulances in Singapore have been manned by specifically trained paramedics (roughly equivalent to North American EMT-I), replacing the nurses who previously served as ambulance officers. The paramedics undergo an 18-month training, including theory and hospital and ambulance attachments. They are able to provide basic life support and defibrillation with automated external defibrillators. Before this study, cardiac arrest protocols followed basic life support guidelines and included the use of automated external defibrillators in a "shock first" protocol. Intravenous medications were previously not in use by ambulance crews. The crews are not certified to perform endotracheal intubation and do not give epinephrine by the endotracheal tube. Mechanical CPR is not used.

The Cardiac Arrest and Resuscitation Epidemiology Study Group includes representatives from the 6 major public hospitals in Singapore, the Singapore Civil Defence Force, Health Sciences Authority, and the Clinical Trials and Epidemiology Research Unit, Singapore. The Cardiac Arrest and Resuscitation Epidemiology phase I study described out-of-hospital cardiac arrest epidemiology in Singapore and served as a baseline for phase II.[20]

For this study, the investigators initiated a series of intravenous cannulation and drug administration workshops during a 9-month period for Singapore Civil Defence Force paramedics, which included didactic teaching, demonstrations and training using simulators, and an attachment to EDs in hospitals for practical training in intravenous cannulation and drug administration. Paramedics had to log 10 supervised intravenous drug administrations in the hospitals to be certified competent to give intravenous epinephrine. The Singapore Civil Defence Force maintained a register of paramedics certified to give intravenous drugs.

The Singapore Civil Defence Force ambulance service implemented intravenous epinephrine for the out-of-hospital management of cardiac arrest, with approval from the Ministry of Health and under the supervision of the Singapore Civil Defence Force Medical Advisory Committee from October 15, 2003. Treatment followed strict protocols approved by Ministry of Health and Medical Advisory Committee. Intravenous epinephrine was given after initiation of CPR and initial defibrillation (if appropriate) according to advanced cardiac life support (ACLS) guidelines. Paramedics were given 2 attempts or 2 minutes for successful intravenous placement at the scene. If intravenous placement was unsuccessful, the protocol emphasized not to delay transport any further but to transport the patient. Another 2 intravenous attempts were allowed in the ambulance en route. Only 1 dose of prediluted epinephrine 1:10,000 in 10 mL solution was given if intravenous insertion was successful according to approved protocols.

Selection of Participants

Patients older than 8 years were included. Patients older than 8 years were considered suitable for automated external defibrillator use, as well as the 1-mg dose of epinephrine used in the study. Exclusion criteria were traumatic cardiac arrest patients and those "obviously dead" as defined by the presence of decomposition, rigor mortis, or dependent lividity.

Methods of Measurement and Data Collection and Processing

Patient characteristics (age, sex, race, medical history), cardiac arrest circumstances (arrest location, witnessed, bystander CPR, defibrillation, epinephrine given), ECG rhythms, EMS response times, and outcomes were prospectively recorded in a standard report filled out by EMS and EDs according to the Utstein style.[21] ECG recordings were captured using the Lifepak 12 (Medtronic, Physio-Control, Redmond, WA) and subsequently verified by physician reviewers. EMS timings were automatically recorded by the computerized central dispatch system and ambulance automated external defibrillators. All watches and automated external defibrillators were synchronized with the central dispatch clock at the beginning of each shift. Institutional review board approval was obtained from all participating institutions.

Outcome Measures

The primary outcome measure for the study was survival to hospital discharge, which was defined as the patient leaving the hospital alive or survival to 30 days post–cardiac arrest, whichever came first. Outcomes were obtained by hospital medical record review or patient assessment by physicians in the study team. Functional assessment of survivors was performed by reviewing physicians using standardized cerebral performance category and overall performance category scores according to Utstein guidelines.

Primary Data Analysis

For sample size, it was anticipated that the introduction of epinephrine would improve the primary outcome variable "survival to discharge" from the hospital from 1% to 5%. Using a 2-sided test size of 5% and a power of 90% suggested that approximately 450 patients would be needed in each arm. It was anticipated that within the practical contingencies of the design, the 1-year trial period without and 1-year period with epinephrine would allow this number of patients to be recruited.

Data management was carried out with the Clintrial application software, version 4.2. All data analyses were performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL), presenting descriptive statistics and frequencies. The comparison between mean scene times for the 2 periods was made with a *t* test. The comparison between the 2 intervention groups for the binary variable "survival to discharge from hospital" was made with logistic regression and expressed in terms of the odds ratio (OR) and the corresponding 95% confidence interval (CI), an OR greater than 1 indicating an advantage to the epinephrine group. In view of the low prevalence of the outcome, this analysis was adjusted by a single covariate (each in turn) from 4 of those suggested by Stiell et al,[22] that is, patient age, bystander witness arrest, bystander CPR, response time, and presenting rhythm. In any event, adjustment for rhythm had the largest influence, and so this was also used for comparisons between groups according to the secondary endpoints of "survival to hospital" and "return of spontaneous circulation."

RESULTS

Characteristics of Study Subjects

From October 1, 2002, to October 14, 2004, 1,296 patients were enrolled into the study, with 615 in the pre-epinephrine and 681 in the epinephrine phase (Figure). One hundred seventeen patients in both phases had trauma arrests, and these were excluded.

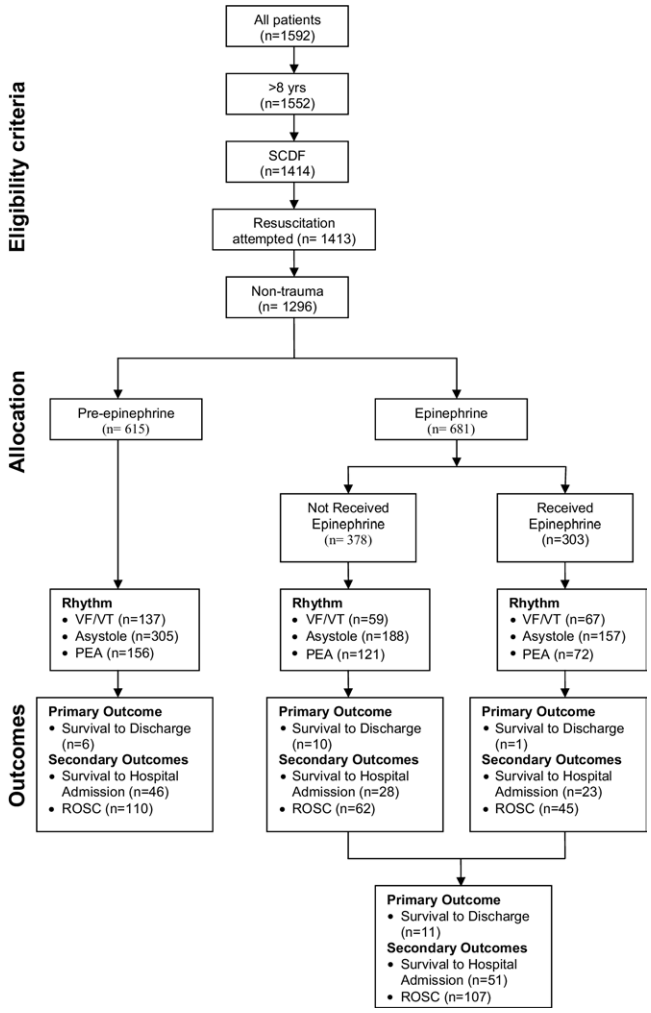

Figure. Trial profile. *SCDF*, Singapore Civil Defence Force; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia; *PEA*, pulseless electrical activity; *ROSC*, return of spontaneous circulation.

Table 1. Characteristics of patients in the pre-epinephrine and epinephrine phases.

Characteristics	Pre-epinephrine (N=615)	Epinephrine (N=681)
Mean age, y (SD)	63.3 (15.5)	63.7 (15.5)
Male (%)	435 (70.7)	456 (67.0)
Race		
Chinese	421 (68.5)	483 (70.9)
Malay	97 (15.8)	101 (14.8)
Indian	73 (11.9)	75 (11.0)
Others	24 (3.9)	22 (3.2)
Arrest location (%)		
Residence	383 (62.3)	431 (63.3)
Other	232 (37.7)	250 (36.7)
Collapse witness		
By bystander (%)	350 (57.0)	390 (57.3)
EMS witnessed (%)	59 (9.6)	72 (10.6)
Not witnessed (%)	205 (33.4)	219 (32.2)
Bystander CPR (%)	120 (21.6)	131 (21.5)
Initial rhythm		
Ventricular fibrillation (%)	134 (22.0)	120 (17.8)
Ventricular tachycardia (%)	3 (0.5)	6 (0.9)
Asystole (%)	305 (50.1)	345 (51.0)
Pulseless electrical activity (%)	156 (25.6)	193 (28.6)
Defibrillated (%)	156 (25.4)	162 (23.8)
Call receipt to vehicle stops, min (SD)	9.2 (3.5)	9.1 (4.3)
Call receipt to arrival at patient's side, min (SD)	11.6 (3.8)	11.4 (4.7)
Vehicle arrival at patient's side to leaving location, min (SD)	10.3 (4.00)	10.7 (4.4)
Vehicle leaving location to arriving at hospital, min (SD)	11.4 (7.4)	11.4 (5.9)
Medical history		
Heart disease	214 (42.1)	258 (44.8)
Diabetes	160 (31.5)	179 (31.1)
Hypertension	184 (36.2)	257 (44.6)
Stroke	38 (7.5)	46 (8.0)
Cancer	44 (8.7)	57 (9.9)
Others	73 (14.4)	125 (21.7)
% actually received IV epinephrine	0 (0)	301 (44.2)

Table 1 shows the characteristics of patients in pre-epinephrine and epinephrine phases. Characteristics such as age, race, witnessed by bystander, bystander CPR, initial rhythm, EMS response times, and out-of-hospital defibrillation were similar in both groups. There was a slightly higher incidence of hypertension and "other" medical history in the epinephrine group compared with the pre-epinephrine group. There was a minimal increase in scene time in the epinephrine phase (10.3 minutes versus 10.7 minutes; 95% CI of difference 0.02 to 0.94; $P=.04$).

Main Results

Table 2 shows the subgroup analysis for study outcomes stratified by presenting rhythm, witnessed, bystander CPR, and response time. Table 3 shows the functional status of survivors in both phases.

Table 4 shows the comparison of outcomes in the pre-epinephrine and epinephrine phases. There was no significant difference in survival to discharge (pre-epinephrine 1.0%; epinephrine 1.6%; OR 1.7 [95% CI 0.6 to 4.5], adjusted for rhythm OR 2.0 [95% CI 0.7 to 5.5]). There was no significant improvement in return of circulation (pre-epinephrine 17.9%; epinephrine 15.7%; OR 0.9 [95% CI 0.6 to 1.2]) or survival to admission (pre-epinephrine 7.5%; epinephrine 7.5%; OR 1.0 [95% CI 0.7 to 1.5]). Analysis of survival to discharge, adjusted by a single covariate (each in turn), namely, by patient age, bystander witness arrest, and response time, did not greatly change the results. The 2 covariates that had the greatest effect on the ORs (rhythm and bystander CPR) are shown in Table 4.

LIMITATIONS

Limitations of this study include that it was a before-after clinical study and not a placebo-controlled, randomized study, and thus results may be affected by secular trends. Variations in postresuscitation care can affect survival to discharge status, and variations between institutions or individual hospital providers

Table 2. Subgroup analysis for study outcomes.

		Return of Spontaneous Circulation				Hospital Admission				Hospital Discharge			
Subset	**N**	**Pre-epinephrine (%)**	**Epinephrine (%)**	**OR**	**95% CI**	**Pre-epinephrine (%)**	**Epinephrine (%)**	**OR**	**95% CI**	**Pre-epinephrine (%)**	**Epinephrine (%)**	**OR**	**95% CI**
Initial rhythm													
VF/VT	263	25 (18.2)	23 (18.3)	1.000	(0.54–1.87)	9 (6.6)	16 (12.7)	2.069	(0.88–4.87)	4 (2.9)	9 (7.1)	2.558	(0.77–8.52)
PEA	349	35 (22.4)	41 (21.2)	0.933	(0.56–1.55)	17 (10.9)	18 (9.3)	0.841	(0.42–1.69)	1 (0.6)	1 (0.5)	0.807	(0.05–13.01)
Asystole	650	49 (16.1)	35 (10.1)	0.590	(0.37–0.94)	20 (6.6)	16 (4.6)	0.693	(0.35–1.36)	1 (0.3)	1 (0.3)	0.884	(0.06–14.19)
Witness to collapse													
Bystander	740	66 (18.9)	56 (14.4)	0.721	(0.49–1.07)	25 (7.1)	32 (8.2)	1.162	(0.67–2.00)	2 (0.6)	6 (1.5)	2.719	(0.55–13.56)
EMS	131	19 (32.2)	30 (41.7)	1.504	(0.73–3.09)	11 (18.6)	13 (18.1)	0.961	(0.40–2.34)	3 (5.1)	5 (6.9)	1.393	(0.32–6.09)
None	424	25 (12.2)	21 (9.6)	0.764	(0.41–1.41)	10 (4.9)	6 (2.7)	0.549	(0.20–1.54)	1 (0.5)	0 (0.0)	—	—
Bystander CPR													
Yes	251	22 (18.3)	22 (16.8)	0.899	(0.47–1.72)	6 (5.0)	16 (12.2)	2.643	(1.00–7.00)	0 (0.0)	5 (3.8)	—	—
No	914	69 (15.8)	55 (11.5)	0.692	(0.47–1.01)	29 (6.7)	22 (4.6)	0.677	(0.38–1.20)	3 (0.7)	1 (0.2)	0.303	(0.03–2.92)
Response time													
≤8 min	590	45 (17.1)	56 (17.1)	1.001	(0.65–1.54)	24 (9.1)	24 (7.3)	0.789	(0.44–1.42)	2 (0.8)	7 (2.1)	2.855	(0.59–13.86)
>8 min	706	65 (18.5)	51 (14.4)	0.743	(0.50–1.11)	22 (6.3)	27 (7.6)	1.239	(0.69–2.22)	4 (1.1)	4 (1.1)	0.994	(0.25–4.01)

Table 3. Cerebral performance category/overall performance category of survivors at 30 days in the pre-epinephrine and epinephrine phases.

Performance Categories (%)	Pre-epinephrine (n=5)*	Epinephrine (n=11)
CPC 1	3 (60.0)	8 (72.7)
CPC 2	1 (20.0)	1 (9.1)
CPC 3	0	1 (9.1)
CPC 4	1 (20.0)	0
CPC 5	0	1 (9.1)
OPC 1	2 (40.0)	6 (54.5)
OPC 2	2 (40.0)	3 (27.3)
OPC 3	0	1 (9.1)
OPC 4	1 (20.0)	0
OPC 5	0	1 (9.1)

CPC, Cerebral performance category; *OPC,* overall performance category.
*One patient's CPC and OPC are unknown.

are difficult to account for. During this period, we were unaware of any major change in ED protocols or in ICU treatment. Nevertheless, it is possible that variations in individual and hospital practice could affect the study results in ways that are difficult to determine.

This study was performed in an EMS system that previously did not use intravenous drugs and endotracheal intubation, which differs greatly from the practice, for example, in North American EMS systems. Thus, care should be taken when the results are extrapolated to other EMS systems.

A related limitation is the relatively low rate of successful intravenous drug delivery[23] during the epinephrine phase, which may have been due to a variety of reasons. Intravenous placement may not have been successful, because of ambulance crew inexperience and our insistence on not delaying transport for more than 2 minutes or 2 attempts at intravenous insertion, after which "load and go" would be initiated. This practice was reflected in that the scene time increased by only half a minute during the 2 phases. However, nondelivery may also have been due to the patient's recovering a pulse after initial CPR and defibrillation. Our protocols would not have allowed delivery of intravenous epinephrine in those circumstances. Finally, nondelivery may have also been due to noncompliance with protocol, although we were unable to detect many instances of this.

Also, this study examined only the effect of a single dose of epinephrine. No repeated dosing of epinephrine was allowed according to protocols until after arrival at the ED. Also, no other drugs usually given in ACLS, such as atropine, amiodarone, or lidocaine, were given out-of-hospital in this study, which differs from current EMS practice, for example, in North America.

DISCUSSION

Epinephrine has been standard of ACLS care since its inception. Before this study, there were few formal evaluations, and there have not been any large-scale clinical studies that have

Table 4. Comparison of outcomes in the pre-epinephrine and epinephrine phases.

	Phase		Unadjusted		Adjusted for Rhythm		Adjusted for Bystander CPR	
Outcomes	**Pre-epinephrine (n=615)**	**Epinephrine (n=681)**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Survival to discharge/at 30 days postarrest (%)	6 (1.0)	11 (1.6)	1.666	(0.61–4.53)	1.975	(0.72–5.46)	1.843	(0.46–7.43)
Survival to hospital admission (%)	46 (7.5)	51 (7.5)	1.001	(0.66–1.52)	0.983	(0.65–1.49)	0.991	(0.62–1.59)
Return of spontaneous circulation (%)	110 (17.9)	107 (15.7)	0.856	(0.64–1.15)	0.810	(0.60–1.09)	0.739	(0.53–1.03)

been able to demonstrate a survival benefit associated with the use of epinephrine in cardiac arrest.[5] This deficit may have be due to the early, widespread adoption of intravenous epinephrine as the standard of care for cardiac arrest in EMS. Thus, it has been ethically difficult to justify any randomized controlled trials comparing epinephrine and placebo in cardiac arrest. A formal evaluation today would be impossible because it is seen as standard of care and is ingrained in practice. Our effort is notable in that it examines the effect of individual interventions in a setting untainted by customary practice.

In Singapore, ambulance crews were not previously using intravenous epinephrine in cardiac arrest, which gave us a unique opportunity to observe any effect that introduction of intravenous epinephrine in cardiac arrest protocols would have on survival outcomes. In current clinical practice, such a study would be possible only outside North America or Europe. In this study, we were unable to show a significant survival benefit with the introduction of intravenous epinephrine to an EMS system. The limitation of this study is its setting in Singapore, with relatively inexperienced rescuers.

Epinephrine is thought to aid resuscitation, mainly by its α-adrenergic effects.[24-28] However, the potential adverse effects of epinephrine include decreased total forward cardiac output, increased myocardial oxygen consumption, myocardial dysfunction postresuscitation,[28-32] and increased intrapulmonary shunting.[29,33-35] Postresuscitation, patients who received greater than 15-mg cumulative dose had significantly lower cardiac index, lower systemic oxygen consumption, lower systemic oxygen delivery, and significantly higher systemic vascular resistance index, higher lactic acid, and lower 24-hour survival.[36] Two studies, by van Walraven et al[8] and Roberts et al,[9] have suggested that use of epinephrine is a strong early predictor of mortality in cardiac arrest. However, these were both retrospective, noninterventional studies. Weaver et al[6] studied 199 patients in persistent ventricular fibrillation who were given epinephrine or lignocaine and compared them with historical controls given bicarbonate (not placebo). They found no difference in the proportion of patients resuscitated with either epinephrine or lignocaine and lower survival in both groups compared to bicarbonate. Woodhouse et al[7] compared high-dose epinephrine (10 mg), standard-dose epinephrine, and placebo in cardiac arrest. This study showed no significant difference in survival with high-dose or standard-dose epinephrine or placebo.

In our study, we believe that care should be taken when comparing outcomes according to whether epinephrine was actually given or not (see the Figure) because intravenous epinephrine may not have been given for a variety of reasons during the epinephrine phase, as elaborated previously. In the instance in which patients did not receive epinephrine because of early return of spontaneous circulation (and this group tends to have better survival), this may give a "survival bias" to the no-epinephrine group compared to the epinephrine group. Thus, we advocate an intention-to-treat approach to avoid the Van de Werf effect.[37] Perhaps the survivors who actually received intravenous epinephrine might be thought of as the additional responders to those who would not have return of spontaneous circulation after initial CPR and defibrillation (Figure).

There was also a trend in the subgroup analysis (Table 2) to suggest that the effect of epinephrine on survival might have been greater in those with response times less than or equal to 8 minutes and those presenting with ventricular fibrillation, although these were not statistically significant, because of sample size. We believe that there is some evidence to suggest that the effectiveness of any intervention in cardiac arrest is closely linked to response times and presenting rhythm.[3,22,38-44] If EMS response times are long, it is unlikely that any intervention will be able to show a difference in outcomes.

In conclusion, we were unable to establish a survival benefit with the introduction of intravenous epinephrine to an EMS system that previously did not use intravenous medications.

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