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Is Epinephrine During Cardiac Arrest Associated With Worse Outcomes in Resuscitated Patients?

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ABSTRACT

BACKGROUND Although epinephrine is essential for successful return of spontaneous circulation (ROSC), the influence of this drug on recovery during the post-cardiac arrest phase is debatable.

OBJECTIVES This study sought to investigate the relationship between pre-hospital use of epinephrine and functional survival among patients with out-of-hospital cardiac arrest (OHCA) who achieved successful ROSC.

METHODS We included all patients with OHCA who achieved successful ROSC admitted to a cardiac arrest center from January 2000 to August 2012. Use of epinephrine was coded as yes/no and by dose (none, 1 mg, 2 to 5 mg, >5 mg). A favorable discharge outcome was coded using a Cerebral Performance Category 1 or 2. Analyses incorporated multivariable logistic regression, propensity scoring, and matching methods.

RESULTS Of the 1,556 eligible patients, 1,134 (73%) received epinephrine; 194 (17%) of these patients had a good outcome versus 255 of 422 patients (63%) in the nontreated group ($p < 0.001$). This adverse association of epinephrine was observed regardless of length of resuscitation or in-hospital interventions performed. Compared with patients who did not receive epinephrine, the adjusted odds ratio of intact survival was 0.48 (95% confidence interval [CI]: 0.27 to 0.84) for 1 mg of epinephrine, 0.30 (95% CI: 0.20 to 0.47) for 2 to 5 mg of epinephrine, and 0.23 (95% CI: 0.14 to 0.37) for >5 mg of epinephrine. Delayed administration of epinephrine was associated with worse outcome.

CONCLUSIONS In this large cohort of patients who achieved ROSC, pre-hospital use of epinephrine was consistently associated with a lower chance of survival, an association that showed a dose effect and persisted despite post-resuscitation interventions. These findings suggest that additional studies to determine if and how epinephrine may provide long-term functional survival benefit are needed. (J Am Coll Cardiol 2014;64:2360–7) © 2014 by the American College of Cardiology Foundation.

International resuscitation guidelines recommend administering epinephrine every 3 to 5 min during cardiac arrest resuscitation regardless of the initial rhythm (1). The alpha-adrenergic effects of epinephrine can increase coronary and cerebral perfusion pressure during the resuscitation period (2,3) and subsequently help achieve return of spontaneous circulation (ROSC). However, epinephrine may exert adverse effects during the post-resuscitation phase and contribute to myocardial dysfunction, increased oxygen requirements, and microcirculatory abnormalities (4–8).

Although epinephrine can increase the likelihood of achieving ROSC, the balance of the effects of

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epinephrine on long-term survival remains uncertain. A randomized study found no overall survival effect of medication treatments that included epinephrine (9). In a large observational study, epinephrine was associated with a lower likelihood of long-term survival (10). In each of these studies, epinephrine was associated with a greater likelihood of ROSC, but the early potential benefit did not translate into a greater likelihood of long-term survival because outcomes among the epinephrine-treated patients were worse during the post-resuscitation phase.

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We sought to better understand the potential adverse effects of epinephrine when used during the post-resuscitation phase. We evaluated the relationship between use of epinephrine during resuscitation and survival among a cohort of patients resuscitated from out-of-hospital cardiac arrest (OHCA) and admitted to the hospital with ROSC. We also evaluated whether evidence-based post-resuscitation interventions, such as coronary reperfusion or hypothermia, may influence this epinephrine-survival relationship.

METHODS

STUDY DESIGN, PATIENTS, AND SETTING. We performed a cohort investigation of all patients who experienced nontraumatic OHCA, achieved ROSC, and were subsequently admitted to a large Parisian cardiac arrest–receiving hospital from January 2000 to August 2012. The appropriate institutional review board approved the study.

Management of OHCA involves mobile emergency units and fire departments that provide basic and advanced cardiac life support (ACLS). In suspected cases of cardiac arrest, the closest emergency unit is dispatched to the scene. Out-of-hospital resuscitation is performed by an emergency team, which includes at least 1 emergency physician trained according to international guidelines (1). When used, epinephrine is administered promptly at the beginning of ACLS or later if required. Patients in whom the resuscitation process fails are not transported to the hospital. Most patients who achieve ROSC are brought to the cardiac arrest–receiving hospital and admitted to the intensive care unit, where they are treated according to standard resuscitative guidelines including coronary angiography and mild therapeutic hypothermia. Procedures of post-cardiac arrest care have been described previously (11). Early coronary reperfusion and targeted temperature management are the most important components of these procedures.

DATA COLLECTION. The study hospital maintains an ongoing registry of all patients with OHCA who are admitted with ROSC. Information is prospectively collected according to Utstein recommendations (12). The registry includes characteristics such as age, sex, cardiovascular risk factors (hypertension, diabetes mellitus, and current smoking), location of cardiac arrest, witnessed status, bystander cardiopulmonary resuscitation (CPR), and initial cardiac rhythm as recorded by the automated defibrillator (ventricular fibrillation [VF]/ventricular tachycardia [VT] or pulseless electrical activity/asystole). The emergency medical service record is used to determine the time interval between the emergency call and successful ROSC as well as use of epinephrine, the timing of the first administration after cardiac arrest, and the total dose. Hospital data during the post-resuscitation phase include initial laboratory values, such as blood lactate levels (mmol/l), and procedures, such as therapeutic hypothermia, coronary angiography, and percutaneous coronary intervention (PCI).

Post-resuscitation shock was defined as the occurrence or persistence of arterial hypotension (mean arterial pressure <60 mm Hg or systolic blood pressure <90 mm Hg) sustained for more than 6 h after ROSC despite adequate fluid resuscitation and continuous vasopressor infusion (13). The definitive etiology of the cardiac arrest was confirmed at hospital discharge, considering all available data obtained during hospital stay. Acute coronary syndromes and/or primary ventricular arrhythmia were considered cardiac etiology. All other causes were considered to be extracardiac causes. The primary outcome was favorable neurological outcome at discharge, defined as a Cerebral Performance Category (CPC) of 1 or 2.

STATISTICAL ANALYSIS. Categorical variables were summarized with proportions and compared using Pearson chi-square test or Fisher exact test. Continuous variables were described with medians (and quartiles) or means and compared using Student *t* test or the nonparametric Wilcoxon test. Use of epinephrine was classified both dichotomously (any epinephrine vs. no epinephrine) and as a dose variable divided into 4 categories: none, 1 mg, 2 to 5 mg, and >5 mg.

We used multivariable logistic regression to evaluate the association between epinephrine and favorable neurological survival while adjusting for potential confounders. We also set up a propensity model to evaluate the relationship between epinephrine and

ABBREVIATIONS AND ACRONYMS

ACLS = advanced cardiac life support

aOR = adjusted odds ratio

CI = confidence interval

CPC = Cerebral Performance Category

CPR = cardiopulmonary resuscitation

OHCA = out-of-hospital cardiac arrest

PCI = percutaneous coronary intervention

ROSC = return of spontaneous circulation

VF = ventricular fibrillation

VT = ventricular tachycardia

TABLE 1 Baseline Characteristics According to Use of Epinephrine

	Treatment With Epinephrine (n = 1,134)	Treatment Without Epinephrine (n = 422)	p Value
Age, yrs	60.3 (16)	58.3 (16)	0.02
Male	797 (70)	315 (75)	0.09
Hypertension	408 (40)	124 (32)	0.003
Diabetes mellitus	185 (18)	47 (12)	0.004
Smoking	380 (43)	163 (45)	0.35
Witnessed status	945 (87)	371 (92)	0.006
Bystander CPR	480 (43)	201 (49)	0.05
Public location	306 (27)	185 (44)	<0.001
Initial shockable rhythm	554 (49)	291 (69)	<0.001
Resuscitation length <20 min*	373 (38)	299 (80)	<0.001
PCI	277 (24)	146 (35)	<0.001
Hypothermia	765 (67)	318 (75)	0.003
Blood lactate >5.2 mmol/l^{-1}*	652 (63)	94 (23)	<0.001
Post-cardiac arrest shock	750 (66)	191 (45)	<0.001

Values are n (%). *Summarized with its median.
CPR = cardiopulmonary resuscitation; PCI = percutaneous coronary intervention.

TABLE 2 Multivariate Models Testing the Association Between Use of Epinephrine and Good Neurological Outcome

	Odds Ratio	95% Confidence Interval	p Value
Crude association	0.14	0.10–0.17	<0.001
Standard logistic regression*	0.32	0.22–0.47	<0.001
Adjustment on PS†	0.35	0.24–0.50	<0.001
Cross-matching PS‡	0.33	0.19–0.58	<0.001
Probability of PS‡			
0.2–0.4	0.44	0.17–1.12	0.09
0.4–0.6	0.29	0.15–0.57	<0.001
0.6–0.8	0.30	0.15–0.62	0.001
0.8–1	0.31	0.16–0.60	0.001
IPTW PS‡	0.18	0.13–0.27	<0.001
SMR PS‡	0.18	0.13–0.26	<0.001
Year of inclusion			
Before or in 2005‡	0.38	0.21–0.70	0.002
After 2005‡	0.29	0.18–0.47	<0.001

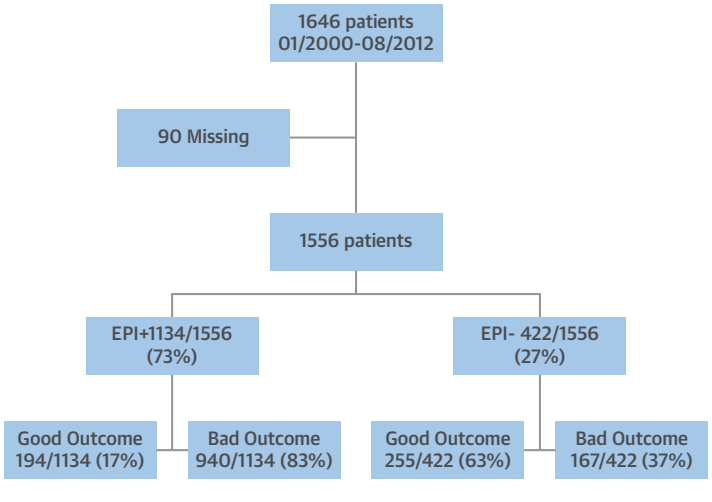
*Adjusted according to baseline characteristics (age, sex, hypertension, diabetes mellitus, smoking, witnessed status, bystander CPR, length of resuscitation) and hospital covariates (i.e., PCI, hypothermia, post-cardiac arrest shock, blood lactate level). †Adjusted on propensity score and hospital covariates. ‡Adjusted on hospital covariates.
Abbreviations as in Table 1. IPTW = inverse probability of treatment weighting; PS = propensity score; SMR = standard mortality ratio.

outcome. The propensity of receiving epinephrine was determined using pre-treatment characteristics. In an effort to control for confounding, we also used different methods (14,15) that included a logistic regression model adjusted for the propensity score, 2 conditional logistic regression analyses after matching on the propensity score in a 1:1 manner, stratification on quintiles of propensity score, and an inverse probability of treatment weighted logistic regression model. Here, we performed an additional analysis based on 1,000 bootstrap samples drawn with replacement from the study population. At this step, all models were adjusted on hospital potential confounders: PCI, therapeutic hypothermia, blood lactate level, and occurrence of post-cardiac arrest shock.

We assessed for differences in the epinephrine-outcome association among subgroups by including an interaction (cross-product) term between the use of epinephrine and the covariate of interest (initial rhythm, intervals, post-cardiac arrest shock, etiology, coronary angiography, and therapeutic hypothermia). Because the period of study was more than a decade, we performed an ancillary analysis on the period of inclusion, especially before and after 2005, the year of removed and new guidelines concerning pre-hospital care (16). Finally, an ancillary analysis was performed focusing on the intervals between cardiac arrest and ACLS (first administration of epinephrine).

All tests were 2-sided. A p value ≤0.05 was considered statistically significant. All analyses were performed using Stata 11.2/SE software (College Station, Texas).

FIGURE 1 Patient Flow



Patient outcomes are presented according to treatment with or without EPI during resuscitation. EPI = epinephrine.

RESULTS

During the study period, 1,646 patients achieved ROSC and were admitted to the hospital. Of these, 90 (5.5%) had missing epinephrine status and were excluded from the analysis.

On average, the cohort was 60 ± 16 years of age, 71% (1,112 of 1,556) were male, and 54% (845 of 1,556) presented with an initial shockable rhythm. Coronary angiography was performed in 63% (961 of 1,534) and PCI in 44% (423 of 961). Approximately 70% of patients (1,083 of 1,556) underwent therapeutic hypothermia.

Nearly three-fourths of patients received epinephrine as part of OHCA resuscitation (**Table 1**). Patient characteristics differed according to epinephrine status. Those receiving epinephrine had less favorable prognostic characteristics; for example, they were older ($p = 0.02$), less likely to have a witnessed event ($p = 0.006$), were less likely to present with a shockable rhythm ($p < 0.001$), and had a longer duration of resuscitation ($p < 0.001$).

Of the 1,556 patients included in this study, 482 (31%) had overall survival to hospital discharge and 449 (29%) had survival with good neurological outcome. Survival with good neurological outcome (CPC 1 or 2) was less likely among those who received epinephrine compared with those who did not receive epinephrine (194 of 1,134 [17%] vs. 255 of 422 [60%], respectively; $p < 0.001$) (**Figure 1**).

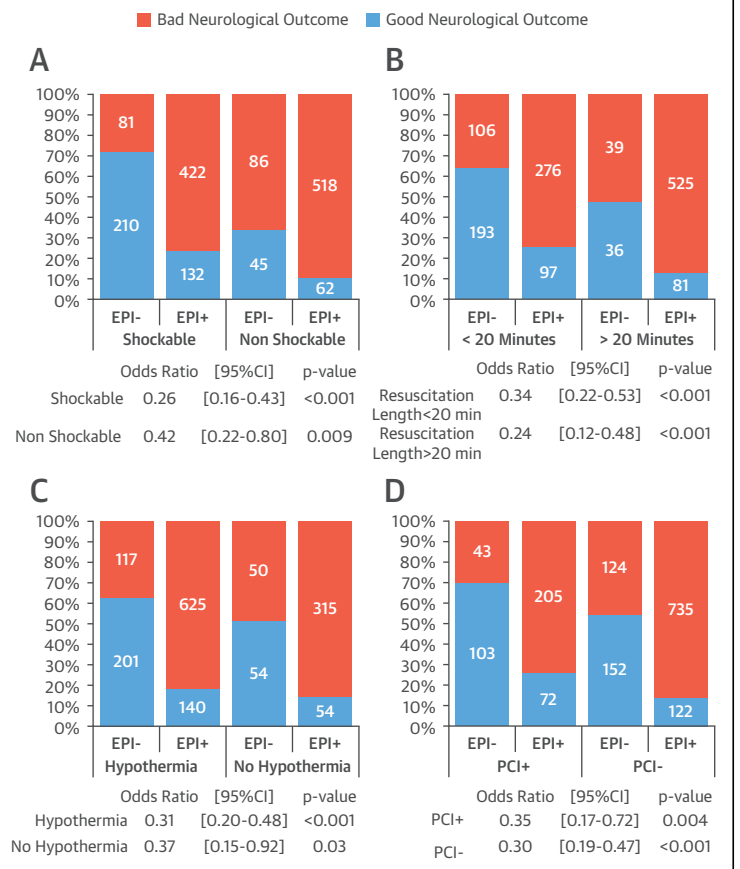
After adjusting for the different confounders, use of epinephrine was negatively associated with favorable neurological outcome (adjusted odds ratio [aOR]: 0.32; 95% confidence interval [CI]: 0.22 to 0.47), even after adjusting for hospital interventions. Furthermore, the hospital predictive factors for good outcome were PCI (aOR: 0.88; 95% CI: 1.34 to 2.65), blood lactate level >5.2 mmol/l^{-1} (aOR: 0.41; 95% CI: 0.29 to 0.58), and the occurrence of post-cardiac arrest shock (aOR: 0.66; 95% CI: 0.48 to 0.92). Therapeutic hypothermia was significantly associated with good outcome only after restricting analyses to patients with VF/VT (aOR: 1.69; 95% CI: 1.04 to 2.75) (Online Table 1).

The logistic model used to estimate the propensity score for receiving epinephrine using all available covariates yielded a C statistic of 0.80. From the propensity score, 228 pairs of treated and nontreated patients were matched, and the intervention group was similar with regard to covariates compared with the nontreated group (Online Tables 2 and 3). In this matched analysis, 68 of 228 patients (30%) in the treated group had a good outcome whereas 138 of 228 patients (61%) in the nontreated group were discharged with CPC 1 or 2 ($p < 0.001$). The negative association between the use of epinephrine and outcome persisted after stratifying on quintiles of propensity score and after use of weighted models (**Table 2**). Similarly, use of epinephrine was associated with lower odds of survival before and after the change in guidelines in 2005.

When focusing on the time intervals between collapse and first use of epinephrine, we observed that ACLS delays were similar in patients treated with or without epinephrine (13.6 ± 10.1 min vs. 13.6 ± 9.8 min; $p = 0.98$) and that the delay for first administration of treatment, if appropriate, was 16.1 ± 10.6 min after collapse. Although longer intervals for ACLS were associated with worse outcome, the influence of epinephrine remained adverse whatever the delay (Online Figure 1) (p for interaction = NS).

Moreover, the delay between cardiac arrest and first dose of epinephrine was linearly related to a bad outcome. Patients in whom epinephrine was given within the first 9 min after cardiac arrest had a better

FIGURE 2 Neurological Outcome in Treated and Nontreated Patients According to Subgroups



The adverse association between use of EPI and survival was evident according to **(A)** initial rhythm, **(B)** length of resuscitation, **(C)** performance of hypothermia, and **(D)** performance of PCI. CI = confidence interval; EPI = epinephrine; PCI = percutaneous coronary intervention.

FIGURE 3 Association Between Outcome and Early Dose of EPI and According to the Initial Rhythm

	Overall			Shockable			Non-Shockable		
	Odds Ratio	[95%CI]	p-value	Odds Ratio	[95%CI]	p-value	Odds Ratio	[95%CI]	p-value
EPI-	1			1			1		
1 mg	0.48	[0.27-0.84]	0.01	0.38	[0.18-0.78]	0.008	0.60	[0.23-1.60]	0.31
2-5 mg	0.30	[0.20-0.47]	<0.001	0.25	[0.14-0.44]	<0.001	0.40	[0.19-0.84]	0.02
>5 mg	0.23	[0.14-0.37]	<0.001	0.16	[0.08-0.30]	<0.001	0.36	[0.16-0.82]	0.01

The odds ratios were adjusted according to baseline characteristics (age, sex, hypertension, diabetes mellitus, smoking, witnessed status, bystander cardiopulmonary resuscitation, length of resuscitation), and hospital covariates (PCI, hypothermia, post-cardiac arrest shock, blood lactate level). Abbreviations as in Figures 1 and 2.

outcome (aOR: 0.54; 95% CI: 0.32 to 0.91) compared with those who received treatment between 10 and 15 min (aOR: 0.33; 95% CI: 0.20 to 0.56), between 16 and 22 min (aOR: 0.23; 95% CI: 0.12 to 0.43), and >22 min after cardiac arrest (aOR: 0.17; 95% CI: 0.09 to 0.34) (Online Figure 2).

The adverse association between use of epinephrine and survival was evident across subgroups defined by initial rhythm, length of resuscitation and post-resuscitation care (including hypothermia and PCI status), and the presence or absence of post-resuscitation shock (**Figure 2**). For example, the aOR for use of epinephrine and neurologically intact survival was 0.31 (95% CI: 0.20 to 0.48) among those who underwent therapeutic hypothermia and 0.37 (95% CI: 0.15 to 0.92) among those who did not undergo therapeutic hypothermia. In addition, we observed a stepwise dose association with decreasing odds of survival with CPC 1 or 2 associated with an increasing dose of epinephrine. Overall, compared with patients who did not receive epinephrine during resuscitation, the aOR of intact survival varied by dose of epinephrine: 0.48 (95% CI: 0.27 to 0.84) for 1 mg, 0.30 (95% CI: 0.20 to 0.47) for 2 to 5 mg, and 0.23 (95% CI: 0.14 to 0.37) for >5 mg (**Figure 3**). A similar dose relationship was observed across the a priori subgroups (Online Figures 3A to 3C).

DISCUSSION

In this large cohort, use of epinephrine during resuscitation of OHCA was associated with a worse neurological outcome during the post-resuscitation period after adjustment for confounding factors. This relationship was robust to a variety of different methodological approaches designed to limit confounding. The adverse association of epinephrine was not modified by post-resuscitation interventions such as PCI or therapeutic hypothermia. Importantly, the timing of first administration and epinephrine dose response became critical in terms of the potential benefit of this drug (**Central Illustration**).

Even if it is impossible to circumvent in many cases, use of epinephrine was independently associated with a decreased likelihood of neurologically intact survival among patients who successfully achieved ROSC. Although epinephrine is known to increase ROSC after arrest (17,18), its effects during the post-resuscitation phase on later outcome are not clear, with potential for relative harm (9,10,19). The benefit of this drug when used during the resuscitation period relies on the implied vasostress, which in turn may also promote secondary detrimental effects during the post-cardiac arrest phase, combining myocardial dysfunction, ischemia-reperfusion, and post-anoxic injury (20). Several animal studies support these mechanisms (6,8,21,22). Furthermore, use of epinephrine was associated with post-resuscitation shock and increased blood lactate levels. Previous clinical studies (both randomized and observational) suggested that epinephrine might worsen survival at hospital discharge and later outcome (9,10,19,23-25). These studies converged, suggesting a potential risk of use of epinephrine, especially in VF/VT groups; however, the investigations were not statistically definitive or did not focus on the role of post-resuscitation care.

One hypothesis is that the potential adverse post-resuscitation effects of epinephrine could be attenuated by in-hospital interventions such as PCI or hypothermia; these relationships have not been fully investigated (23). By focusing on patients with successful ROSC and by integrating post-cardiac arrest care into our analysis, we assessed the specific influence of the drug on the post-cardiac arrest period and confirmed that this period is the time frame during which epinephrine may reveal adverse effects. Importantly, we observed a negative association of epinephrine across all subgroups, even in patients treated with hospital interventions such as PCI and hypothermia.

It could be contended that epinephrine should be considered a surrogate marker of severity rather than

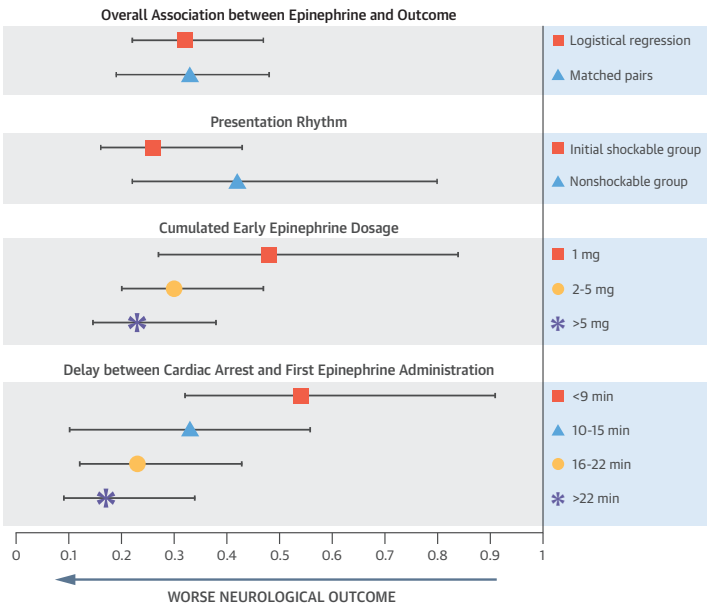
an independent predictive factor, complicating the current debate on the benefit of this agent (26). However, this relationship has been already described when looking at observational data and the few randomized studies that were recently performed (5,27). We made multiple methodological efforts (using propensity score, cross-matching, and different sensitivity analysis) to discriminate the specific role of the intervention. The results were robust regardless of the methodological approach. To our knowledge, this is the first study depicting such a linear relationship between the dose and outcome, which is consistent with an increasing effect of the ascendant dose of the drug. Some studies have previously shown that repeated and increased doses of epinephrine could worsen the chances of survival (28,29).

Before incriminating the drug itself, our findings probably should provoke further discussion on the most appropriate scheme of treatment and its interaction regarding the resuscitation phases. Our sensitivity analyses showed that the role of epinephrine did not change according to ACLS delay or length of resuscitation but was clearly dependent on the timing of first administration. These last findings are consistent with other studies, emphasizing the potential benefit of an early dose of epinephrine (30–32).

Moreover, these observations concur with what Weisfeldt and Becker (33) previously described as the 3 phases of resuscitation in VF arrest: "the electrical phase" within the first few minutes after arrest, in which epinephrine should not be required; "the circulatory phase," during which time chest compressions and epinephrine could help reperfusion; and finally "the metabolic phase," when the drug may be detrimental in regard to the peripheral ischemia release of massively cytotoxic proteins. As supported by our results, it is highly probable that patients receiving late or repeated doses of epinephrine have little or low chance of survival. Currently, no existing alternative can bring these patients back from near-death except mechanical circulatory assistance in very select cases. Altogether, the scheme and timing of administration may be crucial to provide the appropriate effect of epinephrine.

This study highlights the need to assess the quality of resuscitation, such as the quality of CPR and ACLS response (34–36), to improve clinical practice (37,38). We may be able to better understand the role of epinephrine with careful investigation of its timing and dose in the context of intermediate outcomes such as the electrocardiographic waveform and rhythm transition, end-tidal carbon dioxide, and brain perfusion (31,39). Finally, our results highlight the need for additional studies with different schemes of treatment, such as the combination of epinephrine with other drugs such as vasopressin or beta-blockers (40).

CENTRAL ILLUSTRATION Neurological Outcomes of Resuscitated Patients



Dumas, F. et al. J Am Coll Cardiol. 2014; 64(22):2360–7.

Administration of epinephrine during cardiac arrest is associated with worse neurological outcomes in resuscitated patients. This effect is consistent in all subgroups of patients and increased with the cumulated dosage and delay of the first administration (association between epinephrine and worse neurological outcome at discharge, expressed as odds ratios with 95% confidence intervals, adjusted on confounders).

STUDY LIMITATIONS. This study is limited by its observational design; consequently, it precludes any causal relationship between use of epinephrine and outcome. However, we used a variety of analytical approaches to rigorously address confounding. Despite our efforts, some potential confounders may not have been included; for instance, we do not have reliable time points for establishment of an intravenous or intraosseous line. Our findings are drawn from a single center and may not be generalizable to all communities.

Guidelines have supported the use of additional outcome endpoints such as 90-day survival in evaluating treatment effects. However, using the CPC score at discharge appears to be a good indicator of long-term survival (41). These limitations should be considered in the context of the strengths of this study: a large cohort with detailed

information ascertained using a standard approach to data abstraction regarding care and outcome.

CONCLUSIONS

In this large cohort of patients who achieved ROSC after OHCA, we observed an adverse association between epinephrine and neurologically intact survival despite rigorous efforts to address confounding; this relationship was not modified by specific post-resuscitation care such as hypothermia or PCI. As a result, these findings suggest the need for additional investigations to determine if and how epinephrine may provide long-term functional survival benefit.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: During resuscitation of patients with out-of-hospital cardiac arrest, administration of epinephrine may enhance the likelihood of return of spontaneous circulation but is associated with worse neurological outcomes and the impact on long-term survival is uncertain.

TRANSLATIONAL OUTLOOK: Additional studies are needed to assess the impact of other treatment strategies for patients with out-of-hospital cardiac arrest, such as combinations of epinephrine and other drugs, on time to return of spontaneous circulation, neurological outcomes, and long-term survival.

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APPENDIX For supplemental tables and figures, please see the online version of this article.