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Impact of epinephrine administration frequency in out-of-hospital cardiac arrest patients: a retrospective analysis in a tertiary hospital setting

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Abstract

Introduction: Epinephrine is recommended for patients with out-of-hospital cardiac arrest (OHCA). However, whether epinephrine improves or adversely affects OHCA outcomes is controversial.

Objectives: This study aims to determine whether the frequency of epinephrine administration impacts OHCA patient survival.

Methods: We conducted a retrospective analysis of OHCA cases registered in the Emergency Department at King Fahd University Hospital, Saudi Arabia between 2005 and 2015. The primary outcomes were mortality and survival rates until discharge. The impact of epinephrine administration timing and frequency on patient survival was analyzed.

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Results: Data from 300 OHCA cases were analyzed. Among them, 66.3% were men, and the overall mean age of 50.4 ± 20.6 years. The overall survival rate until hospital discharge was 12%. There was no statistically significant difference between in gender, age, or time interval to the first epinephrine dose in the survival and non-survival groups. Only the number of epinephrine doses was related to the survival outcome.
Conclusion: Non-survivors received significantly more epinephrine doses compared with survivors. However, a causal relationship between OHCA patient survival and epinephrine dose and time cannot be confirmed. Further studies are needed to investigate whether the long-term outcomes in OHCA patients are influenced by the timing and frequency of epinephrine administration.

Keywords
Epinephrine, cardiac arrest, out-of-hospital cardiac arrest, survival rate, emergency department, dosing frequency

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Introduction

Out-of-hospital cardiac arrest (OHCA) remains a significant cause of death worldwide. There is an estimated annual rate of 300,000 OHCA cases in the USA.[1] Despite the advances in medical treatment, OHCA survival rates remain low; the average survival rate of OHCA patients treated by emergency medicine services ranges from 8 to 11%.[2]

For the management of cardiac arrest patients, epinephrine administration remains a substantial component in advanced cardiac life support, based on the American Heart Association (AHA) 2015 guidelines. However, the same guidelines recommended against the use of high epinephrine doses because it might not improve patient survival compared with the standard 1-mg dose.[3,4]

The recommendation for epinephrine use in cardiopulmonary resuscitation (CPR) is primarily based on its ability to increase blood pressure and coronary artery perfusion through systemic vasoconstriction. However, epinephrine also stimulates adrenal cardiac receptors and consequently may have detrimental effects on the heart during ischemia and upon reperfusion after the return of spontaneous circulation (ROSC).[5,6]

There are inconsistent results for epinephrine use and OHCA patient neurological outcome. A large observational study indicated that epinephrine administration led to a worse neurological outcome.[1] However, another recent study showed favorable neurological outcomes for OHCA patients who receive epinephrine administration.[7]

Although several studies have demonstrated that epinephrine is one of the most extensively used resuscitation drugs worldwide,[8–10] the outcomes for epinephrine injection in OHCA patients regarding neurological functions, reperfusion after the ROSC, and survival rate have been challenged by some recent reports.[11–13] Thus, the impact of dosage and timing of epinephrine administration on patient outcomes remains controversial.[13–16]

An observational study showed that increasing the dose of epinephrine was an independent predictor of mortality and poor functional outcomes in patients with ventricular fibrillation cardiac arrest.[17] This controversy is crucial because current guidelines recommend epinephrine administration every 3 to 5 minutes based on expert opinions.[18]

Thus, we sought to determine the impact of the timing and frequency of epinephrine administration on OHCA patient outcomes.

Methods

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for this manuscript.[19] This study was approved by the ethics committee of the King Fahd University Hospital, Saudi Arabia (N2016059). The ethics committee waived the requirement for informed consent because this was a retrospective chart review study and it involved no risk to the patients.

Study design, study setting, and study participants

We conducted a retrospective analysis of 300 records for OHCA patients who were registered in the Emergency Department of King Fahd University Hospital, Saudi Arabia between 2005 and 2015.

We included patients who met the following criteria: adult patients >18 years old; OHCA patients who were either traumatic or non-traumatic; and patients who received CPR either before arriving at the hospital or in the Emergency Department (ED) for at least 5 minutes.

We excluded patients with the following conditions: OHCA patients with "Do not resuscitate" orders; cases with incomplete data; and patients who were transferred to another facility after the initial resuscitation, and therefore, their follow up data could not be obtained.

Epinephrine administration frequency

We defined epinephrine administration as the bolus dose given to the patient via the intravenous route. We calculated the number and frequency of epinephrine dosing as the time interval from the start of CPR to the time of the first epinephrine administration. All CPR was performed by the ED physicians, nurses, paramedics, or emergency medical technicians who were all advanced cardiac life support (ACLS)-certified based on the university hospital Joint Commission International Accreditation (JCIA) standards.

Study variables

From the hospital records, we retrieved the following data: 1) demographic data including age and gender; 2) patient history including co-morbidities, time of arrest, and time to CPR; 3) blood test results including hemoglobin, renal function, and cardiac panel; 4) treatment details during resuscitation including epinephrine doses, frequency, and electrical therapy; and 5) outcomes of cardiac arrest including ROSC, ED, hospital mortality, and duration of hospital stay. The primary outcomes of this study were the rates of mortality and survival until discharge from the hospital.

Statistical analysis method

Statistical Packages for Social Sciences (SPSS) version 20 (IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses. Descriptive and inferential statistics tables were generated where numbers and percentages were used to present all categorical variables while mean ± standard deviation (SD) were used to summarize all

continuous variables. A P value less than 0.05 was considered to be statistically significant. The analyses measured the relationship between socio-demographic and clinical characteristics among survival and non-survival rates using the chi-squared test. Binary logistics regression analysis was also conducted where the odds ratio and 95% confidence interval (CI) were also reported.

Results

Characteristics of the study population

There were 300 patients included in the study. Among them, 199 (66.3%) were men and 101 (33.7%) were women. The overall age was 50.4 ± 20.6 years (range, 14 to 98 years); 195 (65%) of them were in the age group of 60 years or less, and 105 (35.0%) were in the age group of over 60 years old. Most of the participants were Saudis (59.3%) while 122 (40.7%) were non-Saudis. One hundred seventy-eight (59.3%) received the epinephrine dose more than 15 minutes after ED arrival, 24 (8.0%) received the dose within 11 to 15 minutes of arrival, 35 (11.7%) receive the dose within 6 to 10 minutes of arrival, and 63 (21.0%) received the dose within 0 to 5 minutes of arrival. More than half of the patients (56.7%) received fewer than five epinephrine doses during the treatment while 130 patients (43.3%) received five or more doses. There were 24 patients (8%) with a shockable rhythm, and 223 patients (74.3%) classified as having bystander CPR. The etiology of cardiac arrest was cardiac in 64 patients (21.3%), trauma in 56 patients (18.7%), submersion in six patients (2.0%), and respiratory in three patients (1%), and most ($n = 171$; 57%) of them were of an unknown cause. The patient outcomes in ED revealed that 160 patients (53.3%) were in the non-survival group and 140 patients (46.7%) were in the survival group. Two hundred twenty-six (75.3%) stayed in the hospital fewer than 5 days while 74 patients remained in hospital for 5 days or more with (24.7%). After ROSC, 153 patients (51.0%) arrested in the ER, 116 patients (38.7%) were admitted, 16 patients (5.3%) went to the cath lab, seven patients (2.3%) were admitted to the OR, and one patient was transferred to another hospital. Additionally, 79 patients (26.3%) had abnormal echocardiogram results, five (1.7%) patients showed normal results, and 167 (55.7%) other patients were classified as having unknown results (Table 1). Details of the patients' laboratory test results are presented in Table 2. Comorbidities of the patients were identified as follows: cardiac (41.7%), hypertension (38.7%), diabetes mellitus (37.7%), pulmonary (18.7%), kidney (11.3%), neurologic (6.3%), malignancy (5%), and hepatic (2.7%) (Figure 1).

Overall survival rate

The overall survival rate until hospital discharge was 12.3% (37 of 300). Additionally, 92 patients (30.7%) died in hospital, four patients were transferred to another hospital, and 55.7% were classified as unknown cases (Figure 2).

Comparison between survivors vs. non-survivors

There was no statistically significant difference between the survival and non-survival groups in terms of gender, age, time interval until the first epinephrine dose. Non-survivors had a significantly shorter hospital stay compared with survivors (1 vs. 5 days), but non-survivors received significantly more epinephrine ($P < 0.0005$ for both). The comparison between the two groups is shown in Table 3.

Table 1. Participants' baseline characteristics.

Characteristics	N (%) (n = 300)
Gender	
• Male	199 (66.3%)
• Female	101 (33.7%)
Age group in years	
• ≤60 years	195 (65.0%)
• >60 years	105 (35.0%)
Duration of first epinephrine dose	
• 0–5 minutes	63 (21.0%)
• 6–10 minutes	35 (11.7%)
• 11–15 minutes	24 (8.0%)
• More than 15 minutes	178 (59.3%)
Number of epinephrine doses given	
• <5	170 (56.7%)
• ≥5	130 (43.3%)
Initial rhythm	
• Shockable	24 (8.0%)
• Unknown	276 (92.0%)
Bystander CPR	
• Yes	223 (74.3%)
• No	12 (4.0%)
• Undocumented/Unknown	65 (21.7%)
Etiology of Cardiac Arrest	
• Cardiac	64 (21.3%)
• Trauma	56 (18.7%)
• Submersion	6 (2.0%)
• Respiratory	3 (1.0%)
• Unknown	171 (57.0%)
Outcome in ED	
• Survivor	140 (46.7%)
• Non-survivor	160 (53.3%)
Length of hospital stay	
• <5 days	226 (75.3%)
• ≥5 days	74 (24.7%)
Post-ROSC	
• Cath lab	16 (5.3%)
• OR	7 (2.3%)
• Arrested in ED	153 (51.0%)
• Admitted	116 (38.7%)
• Transferred to other hospital	1 (0.3%)
• Missing	7 (2.3%)
Echo results	
• Normal	5 (1.7%)
• Abnormal	79 (26.3%)
• Not done	49 (16.3%)
• Unknown	167 (55.7%)

ED, emergency department; ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation; OR, operating room

Table 2. Participants' laboratory test results.

Characteristics	Mean ± SD
Heart rate (bpm)	78.2 ± 50.8
SBP (mmHg)	118.1 ± 36.9
DBP (mmHg)	69.3 ± 26.1
MBP (mmHg)	86.5 ± 28.6
Respiratory Rate (/min)	25.6 ± 08.7
Temperature (°C)	36.4 ± 01.2
GCS	08.8 ± 05.8
Hgb (g/dL)	12.4 ± 08.7
Hct (%)	35.9 ± 09.5
WBC ($\times 10^9$/L)	14.0 ± 10.8
Platelet ($\times 10^9$/L)	252.8 ± 133.5
LDH (U/L)	478.2 ± 660.1
CK-MB (IU/L)	57.5 ± 134.3
PTT (s)	38.4 ± 28.8
INR	2.1 ± 05.9
Creatinine (mg/dL)	2.2 ± 02.5
Na (mmol/L)	138.1 ± 09.4
Potassium (mmol/L)	4.7 ± 03.5
Lactate (mmol/L)	6.9 ± 05.0
pH	6.9 ± 0.5
PCO2 (Pa)	108.8 ± 104.8
Apache	31.8 ± 08.4

SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; bpm, beats per minute; GCS, Glasgow coma scale; Hgb, hemoglobin; Hct, hematocrit; WBC, white blood cell; LDH, lactate dehydrogenase; CK-MB, creatine kinase-muscle/brain; PTT, partial thromboplastin time; INR, international normalized ratio; Na, sodium; PCO2, partial pressure of carbon dioxide.

Factors associated with survival among OHCA patients

A binary logistics regression analysis was conducted to determine the effect of socio-demographic and clinical characteristics of patients among the survival group. Items included in the logistics regression model were as follows: gender, age (in years), duration of first epinephrine dose, and the number of epinephrine doses. Binary logistic regression analysis showed that only the number of epinephrine doses was related to the survival outcome (OR 0.773, 95% CI [0.678 to 0.882]) while other variables

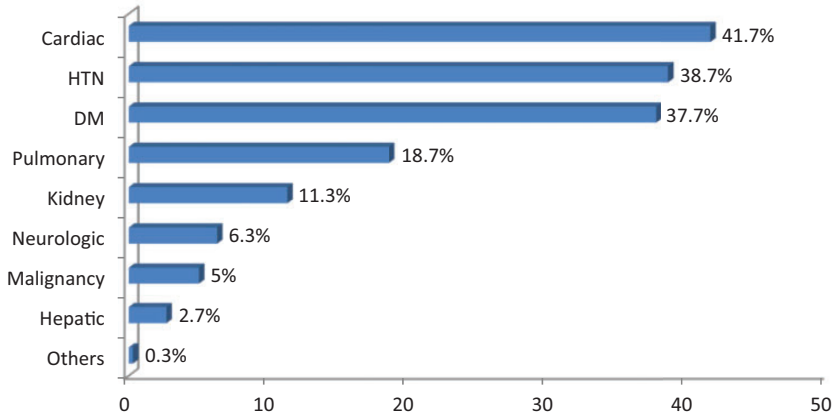

Figure 1. Percentage of comorbidities in the study population.

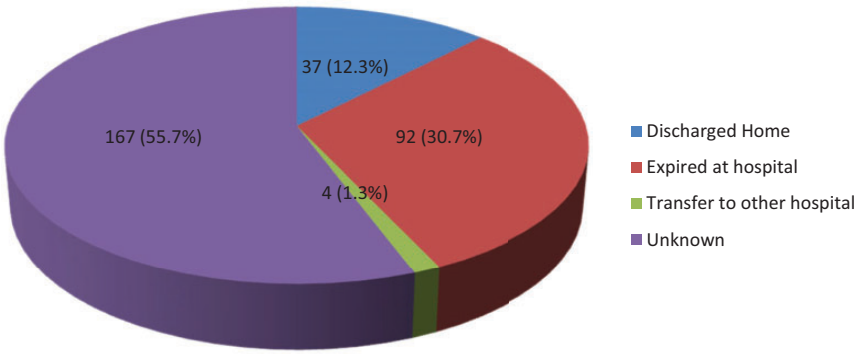

Figure 2. Overall outcome on hospital discharge.

Table 3. Relationship between sociodemographic and clinical characteristics among mortality rates.

Characteristics	Survival N (%) (n = 140)	Non-survival N (%) (n = 160)	P-value[§]
Gender			
Male	88 (62.9%)	111 (69.4%)	0.233
Female	52 (37.1%)	49 (30.6%)	
Age (years)	53.3 (33.3–70)	48 (34–64)	0.446
Duration of first epinephrine dose (min)	5 (3–10)	5 (2.25–24.75)	0.697
Number of epinephrine doses given	3 (2–5.75)	5 (3–6)	<0.0005*
Length of hospital stay (days)	5 (2–11)	1	<0.0005*

[§]P-value has been calculated using chi squared test for gender and Mann–Whitney *U* test for other variables.
*statistically significant.

Table 4. Binary logistic regression analysis to predict survival rates based on the sociodemographic and clinical characteristics of patients.

Variable	OR	95% CI	
		Lower	Upper
Age	1.007	0.990	1.025
Sex (male)	0.849	0.430	1.674
Time interval from arrival in ED to arrest	1.000	1.000	1.000
Time interval from arrest to first epinephrine dose	1.000	1.000	1.000
Number of doses given	0.773	0.678	0.882

OR, Odds ratio; CI, confidence interval; ED, emergency department.

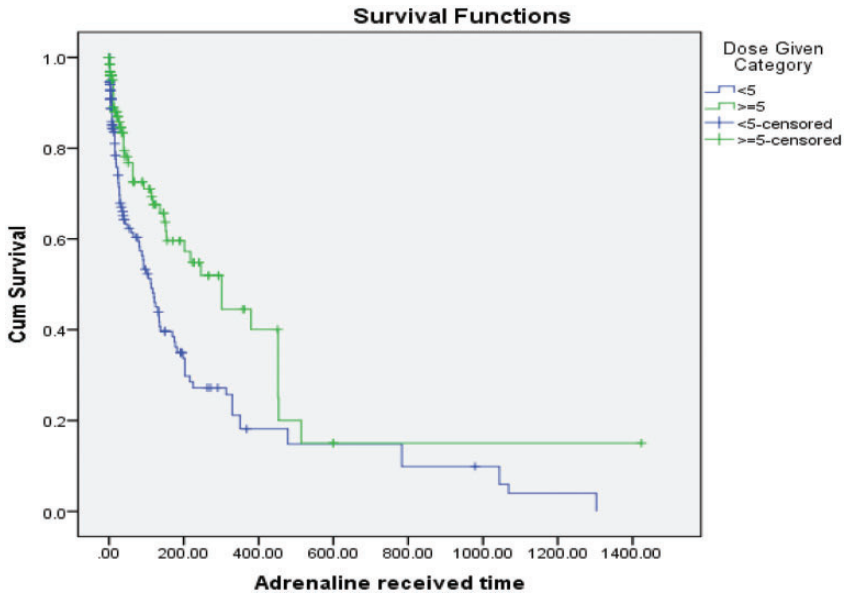

Figure 3. Survival plot between doses administered and the duration of the initial epinephrine administration time (minutes).

showed no significant influence in the survival (Table 4).

Impact of the timing of the first dose on patient survival

The overall median survival time in the study population was 148 minutes. For the group of patients who received fewer than five doses, the mean survival time was 113 minutes while in the group that received more than five doses, the mean survival time was 301 minutes. Our analysis revealed that there was a significant difference between the two groups based on the log-rank (Mantel–Cox) test ($P = 0.001$). The Kaplan–Meier survival plot is shown in Figure 3.

Discussion

The results of this retrospective analysis showed that epinephrine doses were

administered significantly more frequently in OHCA non-survivors compared with survivors. The survival benefit in our study is consistent with the findings of a recent randomized, double-blind trial of 8014 OHCA patients in the United Kingdom; Perkins et al.[20] found that epinephrine administration was associated with higher 30-day survival rate compared with the placebo group. However, there was no benefit in the neurological outcome (OR 1.39, 95% CI [1.06 to 1.82]).[20]

Kosnik et al.[21] and Bar-Joseph et al.[22] conducted animal experiments where they examined the effect of repeated epinephrine doses on hemodynamic outcomes. These studies showed that a single high dose of epinephrine resulted in more favorable cardiovascular outcomes compared with repeated epinephrine administration.[21,22] Another study by Cairns et al.[23] showed no significant increase in coronary perfusion time after repeated epinephrine doses. These results from animal experiments are contradictory to the recent AHA guidelines that recommend 1 mg of epinephrine every 3 to 5 minutes.[18]

Cantrell et al.[24] found no significant differences in the frequency of epinephrine administration between patients who did and did not achieve ROSC. Warren et al.[25] showed that survival until hospital discharge was associated with less frequent epinephrine administration compared with the AHA guidelines.[18] These results might be because of repeated epinephrine injections, which lead to desensitization of the epinephrine receptors.[26]

There is no consensus about the optimal time for epinephrine administration. Our study showed that early epinephrine administration within 5 minutes was associated with a lower survival rate until hospital discharge. Two large population-based studies examined the relationship between the timing of epinephrine administration and the outcomes in OHCA patients.[7,27] They concluded that epinephrine administration within 10 minutes was associated with a favorable neurological outcome.[7,27] In patients with non-shockable cardiac arrest, Donnino et al.[28] concluded that early administration of epinephrine within 3 minutes was associated with increased survival and proper neurological functions. Andersen et al.[29] showed that epinephrine administration within 2 minutes after the first defibrillation was associated with decreased odds of survival until hospital discharge as well as decreased odds of ROSC and survival until hospital discharge with a good functional outcome. Hansen[30] showed that the mean time of epinephrine administration in OHCA patients was less than 10 minutes, and they concluded that every minute of delay in epinephrine administration was associated with a worse neurologic outcome. However, a limitation of these studies is that they did not compare the outcomes before and after 5 minutes. Our study expands upon the previous results by categorizing the survival rate based on the timing of epinephrine administration (within 5 minutes vs. after 5 minutes).

Weisfeldt and Becker[31] suggested a three-phase model to represent the progression of cardiac arrest physiology over time. The first phase extends to 4 minutes after cardiac arrest, and ventricular fibrillation responds better to counter-shock measures. The second phase extends between 4 to 10 minutes and supports the use of epinephrine and CPR measures.[32] The third phase exceeds 10 minutes and supports the use of advanced life support measures with little evidence to support their use in this phase.[32] The practical limitation for this model is that clinicians need to know the time of cardiac arrest, which might not be feasible in unwitnessed cases.

The impact of epinephrine administration in OHCA is controversial. A meta-analysis of 655,853 patients investigated

the impact of epinephrine administration in prehospital settings on patient survival until hospital discharge.[33] In this meta-analysis, epinephrine administration was associated with increased ROSC, but with decreased survival rates until hospital discharge. Moreover, those who survived until hospital discharge had poor neurological outcomes. A posthoc analysis of the Olasveengen trial[34] showed that epinephrine administration was associated with poor survival until hospital discharge and poor neurological outcomes. However, these studies did not report the time of epinephrine administration.[33,34] The results from the Consortium Registry of Cardiac Arrest[35] showed an inverse relationship between the time of epinephrine administration and the survival until hospital discharge.

Reynolds[32] observed that there is a time difference between epinephrine administration in animal studies and human studies; epinephrine administration is often late in OHCA, with a mean of 19.4 minutes, while in animal studies, the mean time of epinephrine administration is 9.5 minutes. This might explain the controversial results of epinephrine administration in OHCA.

However, it is suggested that early epinephrine administration was associated with rapid delivery of hospital care including antiarrhythmic medications and better management of post-cardiac arrest syndrome.[36] Epinephrine increases blood flow to macroscopic brain vessels and impairs microscopic brain circulation, which worsens the neurologic outcome.[37] Unlike other organs, the brain is sensitive to ischemic events, which reduces the possibility of restoring its normal function.[38] This might be why epinephrine was associated with poor neurologic outcomes in some reports.

Limitations of our study are as follows: (1) this is an observational study that lacks randomization and therefore, these data can establish an association between epinephrine frequency and patient outcomes but it cannot establish causation; (2) time and frequency of epinephrine administration were obtained from the hospital records that were completed during an emergency and therefore, they might not be very accurate because of the emergency situation; (3) CPR was not standardized across all cases and the quality of the maneuver might be a confounding variable because it affects cardiac arrest outcomes; and (4) we could not analyze the long-term follow up in the patients who survived and were discharged.

Conclusion

Our findings showed that non-survivors had received significantly more epinephrine doses compared with survivors. However, because of the methodological limitations in our study a causal relationship between OHCA patient survival and epinephrine dose and time cannot be confirmed. Further studies are needed to investigate whether the long-term outcomes of OHCA patients are influenced by the timing and frequency of epinephrine administration.

Authors' Note

Ahmad Abdulhady is also affiliated with faculty of medicine, Alexandria University as lecturer of critical care.

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Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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References

1. Hagihara A, Hasegawa M, Abe T, et al. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. *JAMA* 2012; 307: 1161. doi: 10.1001/jama.2012.294
2. Lin S, Callaway CW, Shah PS, et al. Adrenaline for out-of-hospital cardiac arrest resuscitation: a systematic review and meta-analysis of randomized controlled trials. *Resuscitation* 2014; 85: 732–740. doi: 10.1016/j.resuscitation.2014.03.008
3. Finn J, Jacobs I, Williams TA, et al. Adrenaline and vasopressin for cardiac arrest. *Cochrane Database Syst Rev* 2019; 1: CD003179. doi: 10.1002/14651858.CD003179
4. Vandycke C and Martens P. High dose versus standard dose epinephrine in cardiac arrest — a meta-analysis. *Resuscitation* 2000; 45: 161–166. doi: 10.1016/S0300-9572(00)00188-X
5. Cummins RO and Hazinski MF. The next chapter in the high-dose epinephrine story: unfavorable neurologic outcomes? *Ann Intern Med* 1998; 129: 501. doi: 10.7326/0003-4819-129-6-199809150-00014
6. Paradis NA. *Cardiac arrest: The science and practice of resuscitation medicine*. Cambridge: Cambridge University Press, 2007.
7. Hayashi Y, Iwami T, Kitamura T, et al. Impact of early intravenous epinephrine administration on outcomes following out-of-hospital cardiac arrest. *Circ J* 2012; 76: 1639–1645. doi: 10.1253/circj.CJ-11-1433
8. Nolan JP, Deakin CD, Soar J, et al. European resuscitation council guidelines for resuscitation 2005. *Resuscitation* 2005; 67: S39–S86. doi: 10.1016/j.resuscitation.2005.10.009
9. Ohshige K, Shimazaki S, Hirasawa H, et al. Evaluation of out-of-hospital cardiopulmonary resuscitation with resuscitative drugs: a prospective comparative study in Japan. *Resuscitation* 2005; 66: 53–61. doi: 10.1016/j.resuscitation.2004.10.019
10. Ong MEH, Tan EH, Ng FSP, et al. Survival outcomes with the introduction of intravenous epinephrine in the management of out-of-hospital cardiac arrest. *Ann Emerg Med* 2007; 50: 635–642. doi: 10.1016/j.annemergmed.2007.03.028
11. Sigal AP, Sandel KM, Buckler DG, et al. Impact of adrenaline dose and timing on out-of-hospital cardiac arrest survival and neurological outcomes. *Resuscitation* 2019; 139: 182–188. doi: 10.1016/j.resuscitation.2019.04.018
12. Fothergill RT, Emmerson AC, Iyer R, et al. Repeated adrenaline doses and survival from an out-of-hospital cardiac arrest. *Resuscitation* 2019; 138: 316–321. doi: 10.1016/j.resuscitation.2019.01.022
13. Lin YR, Wu MH, Chen TY, et al. Time to epinephrine treatment is associated with the risk of mortality in children who achieve sustained ROSC after traumatic out-of-hospital cardiac arrest. *Crit Care* 2019; 23: 101. doi: 10.1186/s13054-019-2391-z
14. Nawrocki PS, Poremba M and Lawner BJ. Push dose epinephrine use in the management of hypotension during critical care transport. *Prehosp Emerg Care* 2019; 1–8. doi: 10.1080/10903127.2019.1588443
15. Fisk CA, Olsufka M, Yin L, et al. Lower-dose epinephrine administration and out-of-hospital cardiac arrest outcomes. *Resuscitation* 2018; 124: 43–48. doi: 10.1016/j.resuscitation.2018.01.004
16. Woodhouse SP, Cox S, Boyd P, et al. High dose and standard dose adrenaline do not alter survival, compared with placebo, in cardiac arrest. *Resuscitation* 1995; 30: 243–249.
17. Behringer W, Kittler H, Sterz F, et al. Cumulative epinephrine dose during cardiopulmonary resuscitation and neurologic outcome. *Ann Intern Med* 1998; 129: 450. doi: 10.7326/0003-4819-129-6-199809150-00004
18. Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*

2010; 122: S729–S767. doi: 10.1161/CIRCULATIONAHA.110.970988
19. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; 61: 344–349. doi: 10.1016/j.jclinepi.2007.11.008
20. Perkins GD, Ji C, Deakin CD, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med* 2018; 379: 711–721. doi: 10.1056/NEJMoa1806842
21. Kosnik JW, Jackson RE, Keats S, et al. Dose-related response of centrally administered epinephrine on the change in aortic diastolic pressure during closed-chest massage in dogs. *Ann Emerg Med* 1985; 14: 204–208.
22. Bar-Joseph G, Weinberger T and Ben-Haim S. Response to repeated equal doses of epinephrine during cardiopulmonary resuscitation in dogs. *Ann Emerg Med* 2000; 35: 3–10. doi: 10.1016/S0196-0644(00)70098-9
23. Cairns CB and Niemann JT. Hemodynamic effects of repeated doses of epinephrine after prolonged cardiac arrest and CPR: preliminary observations in an animal model. *Resuscitation* 1998; 36: 181–185. doi: 10.1016/S0300-9572(98)00018-5
24. Cantrell CL, Hubble MW and Richards ME. Impact of delayed and infrequent administration of vasopressors on return of spontaneous circulation during out-of-hospital cardiac arrest. *Prehospital Emerg Care* 2013; 17: 15–22. doi: 10.3109/10903127.2012.702193
25. Warren SA, Huszti E, Bradley SM, et al. Adrenaline (epinephrine) dosing period and survival after in-hospital cardiac arrest: a retrospective review of prospectively collected data. *Resuscitation* 2014; 85: 350–358. doi: 10.1016/j.resuscitation.2013.10.004
26. Insel PA. Adrenergic receptors — evolving concepts and clinical implications. *N Engl J Med* 1996; 334: 580–585. doi: 10.1056/NEJM199602293340907
27. Nakahara S, Tomio J, Nishida M, et al. Association between timing of epinephrine administration and intact neurologic survival following out-of-hospital cardiac arrest in Japan: a population-based prospective observational study. *Acad Emerg Med* 2012; 19: 782–792. doi: 10.1111/j.1553-2712.2012.01387.x
28. Donnino MW, Salciccioli JD, Howell MD, et al. Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: retrospective analysis of large in-hospital data registry. *BMJ* 2014; 348: g3028. doi: 10.1136/BMJ.G3028
29. Andersen LW, Kurth T, Chase M, et al. Early administration of epinephrine (adrenaline) in patients with cardiac arrest with initial shockable rhythm in hospital: propensity score matched analysis. *BMJ* 2016; 353: i1577. doi: 10.1136/bmj.i1577
30. Hansen M, Schmicker RH, Newgard CD, et al. Time to epinephrine administration and survival from nonshockable out-of-hospital cardiac arrest among children and adults. *Circulation* 2018; 137: 2032–2040. doi: 10.1161/CIRCULATIONAHA.117.033067
31. Weisfeldt ML and Becker LB. Resuscitation after cardiac arrest. *JAMA* 2002; 288: 3035. doi: 10.1001/jama.288.23.3035
32. Reynolds JC, Rittenberger JC and Menegazzi JJ. Drug administration in animal studies of cardiac arrest does not reflect human clinical experience. *Resuscitation* 2007; 74: 13–26. doi: 10.1016/j.resuscitation.2006.10.032
33. Loomba RS, Nijhawan K, Aggarwal S, et al. Increased return of spontaneous circulation at the expense of neurologic outcomes: is prehospital epinephrine for out-of-hospital cardiac arrest really worth it? *J Crit Care* 2015; 30: 1376–1381. doi: 10.1016/J.JCRC.2015.08.016
34. Olasveengen TM, Wik L, Sunde K, et al. Outcome when adrenaline (epinephrine) was actually given vs. not given – post hoc analysis of a randomized clinical trial. *Resuscitation* 2012; 83: 327–332. doi: 10.1016/J.RESUSCITATION.2011.11.011
35. Glover BM, Brown SP, Morrison L, et al. Wide variability in drug use in out-of-hospital cardiac arrest: a report from the

resuscitation outcomes consortium. *Resuscitation* 2012; 83: 1324–1330. doi: 10.1016/J.RESUSCITATION.2012.07.008
36. Homma Y, Shiga T, Funakoshi H, et al. Association of the time to first epinephrine administration and outcomes in out-of-hospital cardiac arrest: SOS-KANTO 2012 study. *Am J Emerg Med* 2019; 37: 241–248. doi: 10.1016/j.ajem.2018.05.037
37. Deakin CD, Yang J, Nguyen R, et al. Effects of epinephrine on cerebral oxygenation during cardiopulmonary resuscitation: a prospective cohort study. *Resuscitation* 2016; 109: 138–144. doi: 10.1016/j.resuscitation.2016.08.027
38. Busl KM and Greer DM. Hypoxic-ischemic brain injury: pathophysiology, neuropathology and mechanisms. *NeuroRehabilitation* 2010; 26: 5–13. doi: 10.3233/NRE-2010-0531