Epinephrine in Out-of-Hospital Cardiac Arrest: What Is the Role of the Timing Interval?

Nicholas M. Mohr, MD, MS*; Brett Faine, PharmD, MS

*Corresponding Author. E-mail: nicholas-mohr@uiowa.edu.

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2019.05.038

A **podcast** for this article is available at www.annemergmed.com.

SEE RELATED ARTICLE, P. 797.

[Ann Emerg Med. 2019;74:807-808.]

Almost since its early use, epinephrine has been a controversial therapy for cardiac arrest resuscitation.[1] Epinephrine dose, timeliness, efficacy, and safety in cardiac arrest have all been questioned, fundamentally probing the mechanisms of a drug that has been challenging to study clinically. In this issue of *Annals,* Grunau et al[2] seek to add perspective to this debate with a secondary analysis of data from a Resuscitation Outcomes Consortium trial to assess the association between the average epinephrine dosing interval and patient outcomes.

The authors used an elegant approach to test an important hypothesis using a high-quality prospectively collected data source. In addition to a very carefully constructed regression analysis, they conducted 8 sensitivity analyses, and their results are robust. The authors' findings suggest that the administration of epinephrine with a shorter mean dosing interval is associated with improved neurologically intact survival (5% with epinephrine dosing interval <3 minutes versus 1.4% with the dosing interval >5 minutes). The authors should be commended for using a large and robust data set; considering multiple outcomes independently is a powerful strategy to uncover the actual association between epinephrine frequency and outcome.

Many previous studies have tried to answer the question of how epinephrine affects neurologically intact survival. Epinephrine has been shown in multiple animal models to improve coronary perfusion and increase return of spontaneous circulation,[3-5] but it also may compromise cerebral microvascular perfusion.[6,7] A post hoc analysis of a Norwegian cardiac arrest trial showed that epinephrine use was associated with improved short-term survival, but worse long-term neurologically intact survival.[8] Similarly, in a registry study of out-of-hospital cardiac arrest in Japan, epinephrine was associated with worse overall 1-month survival and cerebral performance.[9] A systematic review and meta-analysis published in 2014 concluded that epinephrine did not improve survival to hospital discharge or neurologic outcomes.[10]

These studies set the stage for the Prehospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug Administration in Cardiac Arrest (PARAMEDIC-2) trial, one of the largest trials conducted in out-of-hospital cardiac arrest. Published in 2018, this trial randomized 8,014 patients to epinephrine versus placebo, with a primary outcome of 30-day survival. Although survival was higher in the epinephrine group (3.2% versus 2.4%; P=.02), the incidence of severe neurologic impairment was higher as well (31.0% versus 17.8%; P=.04). Favorable neurologic outcome at 3 months was not significantly different (2.1% versus 1.6%; adjusted odds ratio 1.39; 95% confidence interval 0.97 to 2.01), perhaps supporting the notion that any early improvements in coronary perfusion are not matched with a cerebral perfusion profile conducive to long-term neurologic recovery.[11]

Against the backdrop of previous data on epinephrine use, the report by Grunau et al raises an interesting hypothesis about epinephrine dosing and timeliness. Nevertheless, the main limitation of this article arises from its observational methods and the prospect of confounding by indication. Why did some patients receive epinephrine more frequently than others? Does more frequent epinephrine administration occur when out-of-hospital personnel are able to off-load other patient management tasks, and could that be a marker for better care in other unmeasured ways? Do some paramedics routinely administer epinephrine more frequently than others, and do they provide otherwise faster care? Imagining these patient-oriented, provider-oriented, and systems factors that contribute to variability in epinephrine dosing frequency is important to interpreting to what degree residual confounding may exist.

So how should we interpret these results? There are 2 possibilities for the findings of Grunau et al: either we don't yet fully understand the dose and timing of epinephrine in

cardiac arrest or the results of this article arise principally from bias. Recent attention has questioned whether epinephrine can change neurologically intact survival,[10,11] and previous analyses testing the dosing frequency hypothesis for inhospital cardiac arrest have suggested that *less* frequent dosing is associated with improved survival.[12-14] This report that frequent epinephrine is associated with a 3.5-fold *higher* survival is a surprising finding, and one that should be tested rigorously in other environments.

Science needs a marketplace of ideas to challenge our understanding and to inspire others to subject our hypotheses to rigorous verification. This well-done comparative effectiveness analysis accomplishes that aim. Although the findings of Grunau et al may not lead to rewriting our out-of-hospital protocols yet, they can add another observation to the ongoing debate about the role of epinephrine in cardiac arrest.

Supervising editor: Henry E. Wang, MD, MS. Specific detailed information about possible conflict of interest for individual editors is available at https://www.annemergmed.com/editors.

Author affiliations: From the Department of Emergency Medicine (Mohr, Faine) and Department of Anesthesia (Mohr), University of Iowa Carver College of Medicine; and the Department of Pharmacy Practice and Science, University of Iowa College of Pharmacy, Iowa City, IA (Faine).

Authorship: All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

REFERENCES

1. Redding JS, Pearson JW. Resuscitation from ventricular fibrillation. Drug therapy. *JAMA*. 1968;203:255-260.
2. Grunau BE, Kawano T, Scheuermeyer FX, et al. The association of average epinephrine dosing interval and neurological outcomes at hospital discharge in out-of-hospital cardiac arrest. *Ann Emerg Med*. 2019;74:797-806.
3. Paradis NA, Martin GB, Rosenberg J, et al. The effect of standard- and high-dose epinephrine on coronary perfusion pressure during prolonged cardiopulmonary resuscitation. *JAMA*. 1991;265:1139-1144.
4. Hardin RA, Scott JB, Haddy FJ. Effect of epinephrine and norepinephrine on coronary vascular resistance in dogs. *Am J Physiol*. 1961;201:276-280.
5. Brown CG, Werman HA, Davis EA, et al. The effect of high-dose phenylephrine versus epinephrine on regional cerebral blood flow during CPR. *Ann Emerg Med*. 1987;16:743-748.
6. Ristagno G, Tang W, Sun S, et al. Cerebral cortical microvascular flow during and following cardiopulmonary resuscitation after short duration of cardiac arrest. *Resuscitation*. 2008;77:229-234.
7. Ristagno G, Tang W, Huang L, et al. Epinephrine reduces cerebral perfusion during cardiopulmonary resuscitation. *Crit Care Med*. 2009;37:1408-1415.
8. 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.
9. Hagihara A, Hasegawa M, Abe T, et al. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. *JAMA*. 2012;307:1161-1168.
10. 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.
11. 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.
12. 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.
13. Wang CH, Huang CH, Chang WT, et al. The influences of adrenaline dosing frequency and dosage on outcomes of adult in-hospital cardiac arrest: a retrospective cohort study. *Resuscitation*. 2016;103:125-130.
14. Hoyme DB, Patel SS, Samson RA, et al. Epinephrine dosing interval and survival outcomes during pediatric in-hospital cardiac arrest. *Resuscitation*. 2017;117:18-23.