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Clinical Review

EMERGENCY MEDICINE MYTHS: EPINEPHRINE IN CARDIAC ARREST

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☐ **Abstract—Background: Sudden cardiac arrest accounts for approximately 15% of deaths in developed nations, with poor survival rate. The American Heart Association states that epinephrine is reasonable for patients with cardiac arrest, though the literature behind its use is not strong. Objective: To review the evidence behind epinephrine for cardiac arrest. Discussion: Sudden cardiac arrest causes over 450,000 deaths annually in the United States. The American Heart Association recommends epinephrine may be reasonable in patients with cardiac arrest, as part of Advanced Cardiac Life Support. This recommendation is partly based on studies conducted on dogs in the 1960s. High-dose epinephrine is harmful and is not recommended. Epinephrine may improve return of spontaneous circulation, but does not improve survival to discharge or neurologic outcome. Literature suggests that three phases of resuscitation are present: electrical, circulatory, and metabolic. Epinephrine may improve outcomes in the circulatory phase prior to 10 min post arrest, though further study is needed. Basic Life Support measures including adequate chest compressions and early defibrillation provide the greatest benefit. Conclusions: Epinephrine may improve return of spontaneous circulation, but it does not improve survival to discharge or neurologic outcome. Timing of epinephrine may affect patient outcome, but Basic Life Support measures are the most important aspect of resuscitation and patient survival. Published by Elsevier Inc.**

☐ **Keywords—epinephrine; cardiac arrest; pulseless electrical activity; ventricular fibrillation; Advanced Cardiac Life Support; Basic Life Support**

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INTRODUCTION

Sudden cardiac arrest accounts for over 450,000 deaths annually in the United States. Data from death certificates suggest that sudden cardiac arrest accounts for close to 15% of mortality in industrialized nations (1–4). Approximately half are out of hospital, and the survival rate is poor, commonly 7–9% (1–5). Many conditions may cause cardiac arrest, but one of the most common causes is cardiac ischemia. The risk of cardiac arrest increases six- to 10-fold with cardiac disease, with two- to fourfold increase in risk factors for cardiac disease (5,6).

Epinephrine has been an important component of the American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Updated guidelines were released in 2015, building on a "Chain of Survival" (7). These include recognition and activation of emergency response system, immediate high-quality cardiopulmonary resuscitation (CPR), rapid defibrillation, basic and advanced emergency medical services, and advanced life support and postarrest care including Advanced Cardiac Life Support (ACLS) for out-of-hospital cardiac arrest (OHCA) (7,8). ACLS is the standard of care in cardiac

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arrest, whether in hospital or out of hospital, despite some arguing a lack of evidence.

Myth: Epinephrine is vital to improving patient survival and neurologic outcome in cardiac arrest.

Why is this Important?

One major component of ACLS is epinephrine for shockable and nonshockable rhythms. A class IIb recommendation from the AHA states "standard dose epinephrine may be reasonable for patients with cardiac arrest" in the 2015 updates, with doses of 1 mg of 1:10,000 epinephrine every 3–5 min intravenously (7). High-dose epinephrine is not recommended (class III recommendation) (7). Epinephrine has alpha- and beta-adrenergic effects, leading to supposedly improved coronary perfusion pressure through increase in alpha stimulation and aortic diastolic pressure, though the effect on cerebral perfusion is controversial (and may worsen cerebral perfusion).

The recommendation for epinephrine is largely based on resuscitation protocols and studies in the 1960s. Studies initially found that epinephrine 1 mg given to asphyxiated dogs improved survival (9). The alpha-adrenergic effects improved coronary perfusion in these dogs, with some benefit in survival. High-dose epinephrine was assumed to be better, with several studies showing increased return of spontaneous circulation (ROSC) and survival to hospital admission, but no improvement in survival to hospital discharge or neurologic recovery (10–14). Literature suggests worse outcomes in survival to hospital discharge and neurologic recovery with higher doses of epinephrine (7,15–20).

However, multiple studies have questioned the use of epinephrine. Many demonstrate increase in ROSC, but worse neurologic and survival to discharge. What is the cause of these worse outcomes? The beta agonism provided by epinephrine increases myocardial work, increases risk of tachydysrhythmia, promotes thrombogenesis and platelet activation, and reduces microvascular perfusion including the central nervous system (7,15).

DISCUSSION

The Evidence Concerning Epinephrine

What does the literature demonstrate? A summary of the studies evaluating use of epinephrine is demonstrated in Table 1. A study in 2011 included over 600 patients with OHCA (16). This is one of the few randomized controlled trials evaluating epinephrine in OHCA. Investigators find an improved likelihood of ROSC, 24% in the epinephrine group vs. 8%, with an odds ratio (OR) of 3.4 (95% confidence interval [CI] 2.0–5.6). However, patients demonstrate no improvement in survival to hospital discharge (16). A 2007 study by Ong et al. finds no difference in survival to discharge, survival to admission, or ROSC with epinephrine vs. no epinephrine (17).

Nakahara et al. conducted a retrospective cohort study comparing epinephrine vs. no epinephrine for patients with ventricular fibrillation, pulseless electrical activity, or asystole (18). This study finds higher overall survival with epinephrine (17.0% vs. 13.4%), but not neurologically intact survival (6.6% vs. 6.6%) (18). Hagihara et al. conducted a prospective nonrandomized analysis

Table 1. Summary of Studies Evaluating Epinephrine (16–19,21–24)

Study	Year	Outcome	Odds Ratio (95% CI)
Holmberg et al. (21)	2002	Survival decrease with epinephrine	Survival 0.43 (0.27–0.066) for shockable, 0.30 (0.07–0.82) for nonshockable rhythms
Stiell et al. (22)	2004	Improved ROSC, no difference in survival to discharge	Survival to discharge 1.1 (0.8–1.5)
Ong et al. (17)	2007	No difference in ROSC or survival to discharge	ROSC 0.9 (0.6–4.5), Survival to discharge 1.7 (0.6–4.5)
Olasveengen et al. (23)	2009	Improved ROSC, No difference in survival to discharge	Survival to discharge 1.15 (0.69–1.91)
Jacobs et al. (16)	2011	Improved ROSC, No difference in survival to discharge	ROSC 3.4 (2.0–5.6), Survival to discharge 2.2 (0.7–6.3)
Hagihara et al. (19)	2012	Improved ROSC, Worse survival and functional outcome	ROSC 2.35 (2.22–2.5), Survival 0.46 (0.42–0.51), Functional outcome 0.31–0.32 (0.26–0.38)
Nakahara et al. (18)	2013	No difference in neurologic outcome or total survival	Neurologic outcome 1.01 (0.78–1.30) for shockable and 1.57 (1.04–2.37) for nonshockable rhythms; Total survival 1.34 (1.12–1.60) for shockable and 1.72 (1.45–2.05) for nonshockable rhythms
Sanghavi et al. (24)	2015	No epinephrine associated with improved neurologic outcome, survival to discharge, and total survival	Improved neurologic outcome 23.0 (18.6–27.4) for no epinephrine, Survival to discharge 4.0 (2.3–5.7) for no epinephrine, Total survival 2.6 (1.2–4.0) for no epinephrine

CI = confidence interval; ROSC = return of spontaneous circulation.