

Epinephrine for Cardiac Arrest

Are We Doing More Harm Than Good?

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WHAT is the first drug we give the pulseless patient? On this, most Hollywood scriptwriters agree: adrenaline! Unfortunately, it does not generally work as well in real life as portrayed in the movies. The predictable inotropic, chronotropic, and pressor effects of adrenergic receptor activation are offset by widespread vasoconstriction and tissue hypoperfusion, metabolic derangements, and oxidative stress. In fact, well-designed clinical trials have repeatedly failed to demonstrate a durable survival benefit, and some observational studies show that epinephrine might even be detrimental.^{1,2} We believe that it is time to reconsider the reflexive, repeated use of adrenaline when treating the pulseless patient.

Although our current rationale for using repeated doses of epinephrine (1 mg) is based on limited animal data and clinical experience, the phenomenon of epinephrine-induced cardiovascular collapse has been recognized for nearly a century. Bainbridge and Trevan³ first showed and Erlanger and Gasser⁴ confirmed that administering adrenaline reliably produces shock in anesthetized dogs: “When the injection of adrenalin was stopped, the arterial pressure fell rapidly to a low level...and the animal passed into a condition of shock with feeble pulse and shallow respiration” (fig. 1). Similarly, Freeman *et al.*⁵ showed that prolonged epinephrine infusion in dogs resulted in hypotension and death. Berk *et al.*^{6–8} later found that prolonged epinephrine infusion also produces arteriovenous mismatch and pulmonary shunting in the dog, leading to hypoxia, pulmonary edema, and histologic evidence of alveolar injury. Our interest in this phenomenon derives from the observation that arterial oxygen tension and pulmonary gas exchange decline very rapidly (within a minute) after bolus epinephrine administration in intact, anesthetized rats.⁹ Blood pressure also substantially declined after the initial, predictable, increase



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(fig. 1). If animal studies suggest that epinephrine is injurious to the intact animal, it causes us to ask, “How does epinephrine rate in models of resuscitation?”

Early studies sought to define epinephrine’s role among other proposed treatments in animal models of cardiac arrest. Crile and Dolley¹⁰ reported that adding epinephrine to cardiac massage and artificial respiration improved recovery after asphyxia but not chloroform-induced arrest in dogs. Their rationale for using 1–2 mg intraarterial epinephrine was the recent recognition that successful resuscitation required achieving an aortic root pressure of 30–40 mmHg, which was not obtainable with chest compressions alone. Interestingly, they found that many animals died shortly after return of circulation: “In a number of instances after a temporary resuscita-

tion, the circulation and the respiration failed after which a second attempt at resuscitation was useless.”¹⁰ Similarly, Wegria *et al.*¹¹ showed that administering epinephrine to dogs in ventricular fibrillation improved circulation following defibrillation but that its use also led to re-occurrence of ventricular fibrillation, and “...necessitates the repeated use of the electrical counter-shock.” However, studies by Pearson and Redding¹² set the tone for the future clinical use of epinephrine in cardiac arrest. They found that intracardiac injection of 1 mg epinephrine given to pentobarbital-anesthetized dogs after asphyxial arrest improved survival when added to chest compressions, mechanical ventilation, and (alternating current) external cardio-version. Return of spontaneous circulation (ROSC) occurred in 1 of 10 animals without and 9 of 10 animals with epinephrine. These observations, along with their *anecdotal* clinical experience using 1 mg epinephrine, led the authors to state, “Epinephrine is of great benefit

Image: J. P. Rathmell.

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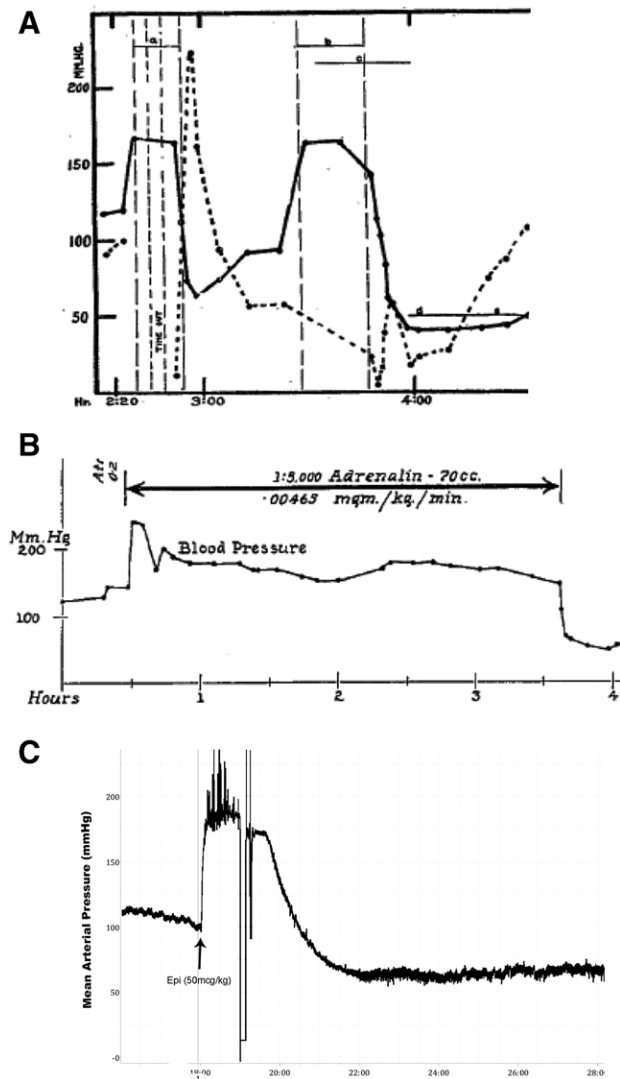


Fig. 1. Three plots from different laboratories and eras (circa, 1919, 1941, and 2012) showing arterial pressure versus time during infusion of epinephrine. (A) (1919) Two 20-min infusions of 6 mg epinephrine in anesthetized dogs, each showing biphasic blood pressure response.⁴ (B) (1941) Infusion of epinephrine, $7.9 \mu\text{g kg}^{-1} \text{min}^{-1}$, in an unanesthetized dog for 2 h leads to progressive shock and death.⁵ (C) (2012) Bolus infusion of $50 \mu\text{g/kg}$ epinephrine (arrow) in an anesthetized rat provokes a biphasic blood pressure response with hypotension (mean arterial pressure approximately 55 mmHg) occurring by 4 min (bar, 2 min).⁹ We were impressed that the early studies produced plots (although for longer infusions) that were nearly identical to ours. Apparently, each generation discovers anew that epinephrine infusion can be harmful.

in restoring spontaneous circulation.” This was also the basis of the current practice of repeating doses of 1 mg for adults in cardiac arrest.

Later studies, many from the laboratory of HM Weil, showed that epinephrine administration exerts severe, deleterious effects in animal models of cardiac arrest, including postresuscitation myocardial dysfunction,¹³ decreased cerebral perfusion,¹⁴ impaired microcirculatory blood flow,¹⁵

and worsened survival.¹⁶ More recent models of resuscitation have shown similar effects of epinephrine. For instance, McCaul *et al.*¹⁷ found in a rodent model of asphyxia arrest that epinephrine was associated with increased mortality and dose-related decrease in left ventricular function. So, how does epinephrine fare clinically in treatment of cardiac arrest?

Recent reviews and meta-analyses of clinical trials have questioned the efficacy of standard-dose epinephrine (1 mg, repeated as necessary) for cardiac arrest.^{1,2} In a national survey examining cardiac arrest in 10,966 patients, no beneficial effect of the administration of epinephrine was found.¹⁸ In addition, in a recent prospective observational analysis of 417,188 patients, intravenous epinephrine given before hospital arrival in out-of-hospital cardiac arrest resulted in worsened overall 1-month mortality.¹⁹

Although compelling and interesting, the observational design of the above studies has several limitations. A recent prospective trial randomized 851 patients during out-of-hospital cardiac arrest to receive advanced cardiac life support with or without drug administration. The patients receiving *any* intravenous drug had higher rates of short-term survival with no improvement in in-hospital or long-term mortality.²⁰ Furthermore, the only randomized, double-blind, placebo-controlled trial of this problem was underpowered, examined 534 patients receiving either epinephrine or placebo in out-of-hospital cardiac arrest, and showed that epinephrine improved ROSC but not survival to hospital discharge.²¹ These results are consistent with an observational, multicenter study on 5,638 patients.²² In the aggregate, *there is strong agreement across a large number of clinical studies, that epinephrine use improves the chances of ROSC but does not benefit survival.* Notably, some studies suggest that epinephrine might actually worsen neurologic outcome and cardiac function.^{23,24} This comports with results from the animal models demonstrating that epinephrine offers initial improvement in physiologic parameters but leads to postresuscitation cardiopulmonary and, potentially, neurologic dysfunction.¹⁶ It appears the transient benefit of epinephrine is purchased at the price of more lasting organ damage.

Despite decades of compelling animal and clinical data speaking to its downsides why do many still regard epinephrine as a mainstay for treating the patient *in extremis*? Maybe it is our persistent, abiding need to do *something*. The American Heart Association guidelines for Advanced Cardiac Life Support acknowledge that both safety and efficacy of epinephrine are controversial but describe its use as “reasonable to consider...during adult cardiac arrest.” This tepid endorsement tacitly acknowledges the conflict between time-honored practice and our intellectual preference for evidence-based medicine. The brief return of circulation that often follows epinephrine administration provides misleading positive feedback that tricks us into giving more. It is very hard to say, “Stop!” in that key moment when someone calls for another round of epinephrine, especially because the patient might have seemed to respond to earlier doses and the negative outcome for failed resuscitation is immediate death of the patient. This slants our

clinical-equipose very much in favor of treatment. The problem with this rationale is that the treatment apparently does not improve the likelihood of meaningful survival. Giving epinephrine at current doses is unwarranted if recovery is transient and achieving ROSC means doing more harm than good.

We believe that the current knowledge base dictates questioning the dose, timing, and overall role of epinephrine in the pulseless patient. Epinephrine might still have a role in resuscitation, possibly by infusion rather than bolus, or in doses smaller than 1 mg, or when delivered very early,^{25,26} or when combined with other therapies.²⁷ We also need better clinical markers than ROSC to predict long-term outcomes and system improvements to accelerate delivery of treatment in the field. Such advances could increase the likelihood of meaningful survival after cardiac arrest. Large, prospective clinical trials are needed to identify rational alternatives to epinephrine or modification of dosage and timing. Until then, the next time the team calls for “another round of epi!” in the midst of cardiac resuscitation, perhaps we should stop and think twice: too much of a good thing can have unintended consequences.

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