Epinephrine in Resuscitation: Curse or Cure?
Robert R Attaran, Gordon A Ewy
Future Cardiol. 2010;6(4):473-482.

Abstract and Introduction

Abstract

The use of epinephrine during cardiac arrest has been advocated for decades and forms an integral part of the published guidelines. Its efficacy is supported by animal data, but human trial evidence is lacking. This is partly attributable to disparities in trial methodology. Epinephrine’s pharmacologic and physiologic effects include an increase in coronary perfusion pressure that is key to successful resuscitation. One possible explanation for the lack of epinephrine's demonstrated efficacy in human trials of out-of-hospital cardiac arrest is the delay in its administration. A potential solution may be intraosseus epinephrine, which can be administered quicker. More importantly, it is the quality of the basic life support, early and uninterrupted chest compressions, early defibrillation and postresuscitation care that will provide the best chance of neurologically intact survival.

Introduction

Epinephrine administration has been advocated during resuscitation of cardiac arrest for decades. The 2005 guidelines by both the American Heart Association and the European Resuscitation Council recommend its use. Surprisingly, definitive evidence for epinephrine's efficacy in humans is lacking. As with many components of the Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiac Care, its recommendation is largely based on tradition and its success in animal models. Conflicting results between animal and human research are due to the disparate methodology and populations studied, as well as the duration of untreated and treated cardiac arrest prior to epinephrine administration. The purpose of this article is to review the pertinent literature and to provide our perspective on the present role of epinephrine in resuscitation of out-of-hospital cardiac arrest (OHCA), with emphasis on primary cardiac arrests owing to ventricular fibrillation (VF). This perspective is influenced by the senior author's extensive experience with epinephrine use during experimental and clinical resuscitation studies of subjects with primary cardiac arrest.

Historical Considerations

In 1874, Pellacani became perhaps the first to administer adrenal extract to animals. The extract was found to increase arterial tone, ventricular contractions and blood pressure. In 1896, after inducing profound hypotension, Gottlieb restored circulation by administering adrenal extract.

As early as 1906, Crile and Dolley noted the importance of an adequate aortic diastolic pressure during attempted cardiac resuscitation. They stated that it often was not possible to achieve an adequate aortic diastolic pressure without the addition of epinephrine.

Since epinephrine has both inotropic and chronotropic effects on the beating heart and also produces peripheral vasoconstriction, there was confusion regarding which of these effects was the most important. Epinephrine increases the peripheral vascular resistance, transiently decreasing perfusion to most of the body, but in the process increases the aortic diastolic pressure and perfusion to the heart.

The classic studies of Pearson and Redding performed in the 1960s merit emphasis. After induction of asphyxial cardiac arrest, chest compressions and ventilations resulted in survival of none of the ten animals that received isoproterenol, all of the animals that received epinephrine and nine of the ten animals that received the α-agonist methoxamine. In a similar study following VF induction, survival was one out of ten without drugs, nine out of ten with epinephrine and ten out of ten with the α-agonist phenylephrine. In the 1970s, a re-examination of this phenomenon found that α-adrenergic blockade administered with epinephrine prevented resuscitation in animals with cardiac arrest. However, resuscitation of animals with β-adrenergic blockade administered with epinephrine, however, was uniformly successful.
Early on it was concluded that drugs that have their principal effect by cardiac stimulation, such as isoproterenol or dobutamine, did not help during cardiac arrest. Drugs that were potent peripheral vasoconstrictors, such as phentolamine, methoxamine or dopamine, were as effective as epinephrine during cardiopulmonary resuscitation (CPR).

Pharmacologic & Physiologic Considerations: The Importance of Coronary Perfusion Pressure

It is now known that there are subtypes of both the α- and β-adrenergic receptors and that epinephrine's effects are mediated through α₁, α₂, β₁ and β₂-receptors.[16–23] Its nonselective agonist profile results in a host of effects.[24] The α₁-receptors mediate arteriolar vasoconstriction and are also positively inotropes, chronotropes and may induce coronary vasoconstriction. The α₂-receptors mediate venoconstriction, among other effects. The β₁ and β₂-receptors induce positive inotropy and chronotropy and can also vasodilate the coronaries.

To paraphrase what Crile and Dolley stated over a century ago: the secret of resuscitation seems to be to increase the aortic diastolic pressure. It turns out that they were correct.[11] During resuscitation efforts, coronary perfusion pressures (aortic diastolic minus right atrial diastolic pressure) above 15 mmHg during resuscitation are associated with improved return of spontaneous circulation (ROSC) in both humans and animals[25,26] and increased survival in animals.[26] During resuscitation from cardiac arrest, epinephrine improves coronary and cerebral perfusion.[27–30]

Wegria et al. induced VF in experiments and observed that epinephrine could alter the ECG VF character from coarse and slow (the variant observed in late-stage VF) to fine and rapid.[31]

However, epinephrine also has adverse effects. It increases myocardial oxygen consumption,[32] postresuscitation myocardial dysfunction[33] and ventricular arrhythmias.[34] Ristagno et al. suggest that microcirculation to the superficial areas of the brain is decreased with epinephrine.[35] Lindberg et al. propose that epinephrine may reduce overall cardiac output since blood flow to nonvital organs falls to almost zero owing to vasoconstriction.[36] This may induce ischemia in underperfused organs (e.g., bowel) and lead to an inflammatory response following successful resuscitation.[37,38] There is also some evidence that epinephrine may induce hypokalemia,[39] platelet aggregation[40] and oxidative damage.[41,42]

During resuscitation efforts, end-tidal CO₂ has been shown to reflect pulmonary blood flow,[43,44] coronary perfusion pressure[36] and improved outcomes in OHCA.[45] Lindberg et al., using a swine model, administered epinephrine or norepinephrine during CPR and defibrillated 4 min later.[36] These vasopressors improved coronary perfusion pressure but reduced end-tidal CO₂ and pulmonary flow. Thrush et al. demonstrated increased intrapulmonary shunting and hypoxia with epinephrine during CPR.[46] They proposed β-mediated pulmonary vasoconstriction as a possible factor. In a rat asphyxial cardiac arrest model, epinephrine use was associated with increased mortality.[47]

Epinephrine Dosing

In animal studies, higher doses of epinephrine have been found to cause myocardial necrosis[48] and to be harmful in resuscitation.[49,50] Several human studies have evaluated higher doses of epinephrine in human cardiac arrest. Among children with in-hospital cardiac arrest, once standard-dose epinephrine had failed, rescue high doses of epinephrine did not alter ROSC or survival compared with a standard dose.[51]

Woodhouse et al. evaluated 194 patients with cardiac arrest.[52] A total of 94 patients were randomized to receive two ampoules of 10 mg intravenous epinephrine 5–10 min apart versus 100 patients who received placebo. Both groups could subsequently be administered 1-mg doses of epinephrine, as per American Heart Association guidelines. In addition, 145 patients who met the inclusion criteria were not randomized, as the supervising medical staff chose to administer open-label 1 mg epinephrine ampoules rather than risk using placebo. Data from this group was retrospectively included in the analysis (as a registry). There was no significant difference in the rate of survival or hospital discharge between initial high-dose epinephrine versus placebo. The authors also found no difference in survival or hospital discharge in the open-label standard epinephrine (registry) group compared with the early high-dose epinephrine and early placebo groups. Despite the several limitations of this study, high-dose epinephrine is not recommended.
Epinephrine versus other Vasopressors: Animal & Human Studies

Is epinephrine the ideal drug? There is a sizeable body of research on alternative or adjunctive drug therapies for cardiac arrest. As noted previously, it has been shown in our laboratory and elsewhere that it is the $\alpha$-adrenergic and not $\beta$-adrenergic effects of epinephrine that are beneficial during resuscitation.\[^{[53]}\] In other experimental studies of VF arrest from our laboratory, we found no difference in either the 24-h survival or the neurological outcome between epinephrine and phenylephrine.\[^{[54]}\] Huang et al. compared epinephrine, phenylephrine and the combination of epinephrine and esmolol in rats, before attempting defibrillation.\[^{[55]}\] The epinephrine-treated rats required more countershocks for ROSC to occur than the other two groups. Furthermore, the epinephrine-treated group demonstrated greater postresuscitation ventricular dysfunction and worse survival. The addition of esmolol to epinephrine appeared to attenuate left ventricular dysfunction and the lower survival associated with epinephrine administration.\[^{[55]}\] In another study, pretreatment of rats with the $\beta$- and $\alpha_1$-blocker carvedilol before VF, followed by CPR combined with epinephrine, has resulted in improved survival and reduced myocardial dysfunction postresuscitation.\[^{[56]}\]

In our laboratory, Hilwig et al. used a swine VF model to compare several groups according to drug therapy during advanced cardiac life support (ACLS): epinephrine (0.02 mg/kg), epinephrine with propranolol (0.04 mg/kg), high-dose epinephrine (0.2 mg/kg) with propranolol and phenylephrine (0.4 mg/kg) with propranolol.\[^{[57]}\] The 24-h epinephrine survival was significantly less in the high-dose group even when given with the $\beta$-blocker propranolol. There was no difference in ROSC or 24-h survival among the groups. The combination of epinephrine and vasopressin in a swine VF arrest model resulted in improved coronary and cerebral perfusion pressure compared with epinephrine alone.\[^{[58]}\]

In VF arrest, comparisons of epinephrine to vasopressin have yielded discordant results. Compared with epinephrine, vasopressin has resulted in improved coronary perfusion pressure,\[^{[59]}\] higher coronary venous pH,\[^{[60]}\] and higher coronary and cerebral flow.\[^{[61]}\] In the swine VF model, higher coronary perfusion pressures were observed with vasopressin, but there was no statistically significant difference in ROSC or 24-h neurologically normal survival.\[^{[62]}\]

In a large multicenter prospective randomized human trial, patients with OHCA were randomized to receive either epinephrine 1 mg and 40 IU of vasopressin ($n = 1442$) versus epinephrine alone ($n = 1452$).\[^{[63]}\] There was no significant difference in survival to hospital admission, ROSC, survival to hospital discharge, neurologic recovery or 1-year survival. Notably, the mean down-time in each arm was 16.3 min. As with other human studies of vasopressors, this may be related to the late administration of these vasoactive drugs. Down-times exceeding 10 min are known to confer low ROSC rates.\[^{[64]}\]

In a small single-center, double-blind trial of in-hospital cardiac arrest,\[^{[65]}\] patients receiving intravenous epinephrine, vasopressin and methylprednisolone during CPR showed improved ROSC ($p = 0.003$) and survival to discharge rates ($p = 0.02$) over those receiving epinephrine alone ($n = 48$).

Endothelin-1 is a potent vasoconstrictor without $\beta$-adrenergic effects.\[^{[66]}\] It is believed to also possess positive inotropic and chronotropic properties.\[^{[67,68]}\] In our laboratory, following prolonged VF, endothelin-1 administration was associated with dramatically higher coronary perfusion pressures during CPR, as well as higher mean arterial pressures postresuscitation.\[^{[69]}\] However, in this study, the resulting vasoconstriction was so marked that end-tidal CO$_2$ (a measure of forward blood flow) dropped dramatically and was associated with much lower survival rates compared with epinephrine. More recently, elevated endogenous endothelin-1 levels have been found to predict resuscitation failure in VF.\[^{[70]}\]

Human Studies of Epinephrine in Cardiac Arrest

To date, no randomized controlled human trial has specifically evaluated early epinephrine administration in cardiac arrest and CPR. While several observational studies have reported on epinephrine usage for OHCA, their design features and limitations have resulted in findings that cannot be applied to modern approaches to OHCA.\[^{[71–73]}\]

The most recent randomized controlled trial of the use of epinephrine together with other drugs in OHCA was conducted by Olasveengen et al. in Norway.\[^{[74]}\] Adults with confirmed nontraumatic cardiac arrest were randomized to ACLS with – versus without – intravenous drug administration during the resuscitation effort. The ‘no intravenous’ group did not have an intravenous access established until an average of 5 min after ROSC. After exclusions, 433 patients were randomized to the
In the intravenous arm versus 418 in the no intravenous arm. In approximately 62% of cases, the arrests were witnessed and bystander basic life support was reported to be initiated in almost all patients with witnessed arrest. Approximately a third of the patients had an initial rhythm that was shockable (VF or pulseless ventricular tachycardia). There were equivalent hands-off ratios and compression and ventilation rates between the two groups. However, there were some dissimilarities. The intravenous group demonstrated longer CPR duration (p < 0.001) and more shocks delivered (p = 0.008). There was a tendency towards less asystole but more pulseless electrical activity in the intravenous group (p = 0.06).

There was better short-term survival in the intravenous group.\textsuperscript{[74]} A total of 40% achieved ROSC versus only 25% in the no intravenous group (p < 0.001). More intravenous group patients survived to hospital admission (43 vs 29%, p < 0.001). In the subgroup with asystole or pulseless electrical activity, the ROSC rate was improved by threefold better in the intravenous group (p < 0.001), although this advantage did not carry over to hospital discharge. In the subgroup with shockable rhythms (VF or pulseless ventricular tachycardia), no differences in ROSC, hospital admission or discharge rates were found between the intravenous versus no intravenous groups. The study found no difference in survival to hospital discharge or survival with good neurological outcome between the two approaches. Furthermore, there was no postarrest difference in survival at 1 month or 1 year. The authors note that this study may have been too underpowered to prove a difference. In summary, this prospective, single-center study demonstrated that early intravenous administration of epinephrine, atropine and/or amiodarone during OHCA was associated with improved ROSC, but not longer-term survival. Notably, the authors did not find epinephrine usage to be an independent predictor of poor outcome.\textsuperscript{[74]}

This study found that the late administration of epinephrine during OHCA did not result in improved hospital discharge.\textsuperscript{[74]} The mean ambulance response time was 10 min. The time between ambulance arrival and intravenous administration was not provided. What one can conclude from this report is that the late administration of epinephrine did not appear to be helpful. However, since individuals with nonshockable rhythms (the group known to have worse outcomes) had a higher ROSC, and the fact that patients with OHCA and ROSC are significantly more likely to survive to hospital discharge, one could argue that this study supported the use of epinephrine in OHCA. The most powerful predictor by far of survival to hospital discharge is ROSC in the field.\textsuperscript{[75]} This finding is evidence that the battle to save victims of OHCA is won or lost at the scene.

### Intraosseous Administration of Epinephrine

Animal studies clearly show that the early administration of vasopressor drugs in prolonged VF cardiac arrest may be crucial to achieving adequate perfusion pressures to vital organs, thereby improving the likelihood for successful defibrillation and good neurological outcome. However, placing an intravenous line in patients during cardiac arrest while CPR is being performed is difficult and sometimes not possible. A systematic review of studies between 1990 and 2005 found that in humans the time to first drug administration from the time of dispatch ranged from 10 to 25 min (mean: 17.7 min).\textsuperscript{[76]} This is significantly longer than administration times in animal studies where drugs are frequently given in under 10 min.\textsuperscript{[77–79]} Reynolds et al. found a mean time of 9.5 min to first drug administration in animal CPR models compared with the 19.4 min reported in human clinical trials.\textsuperscript{[80]}

One approach to earlier administration of epinephrine during OHCA is via the intraosseous route, as this can be performed quickly in the field. In our laboratory, Zuercher et al. recently found that the time from injection to peak coronary perfusion pressure attainment was only slightly slower in the intraosseous group compared with the intravenous group, but the hemodynamic effects were similar [Ewy GA, Personal Communication]. In this study, where intraosseous epinephrine was administered 6 min earlier than intravenous epinephrine, Zuercher et al. found a reduced number of required shocks, less time to ROSC and a favorable neurological outcome with early intraosseous compared with later intravenous epinephrine. For these reasons, intraosseous epinephrine is recommended.

### Deleterious Effects of Multiple-dose Epinephrine

Having recommended epinephrine, a caveat must be added. As noted previously, epinephrine may not be the ideal vasopressor to use during resuscitation of cardiac arrest, as it is the α- or vasoconstrictive effects of epinephrine that are beneficial, while its β-effects may be detrimental. Clinical experience with more effective approaches to resuscitation of OHCA has resulted in better survival,\textsuperscript{[81]} but also a higher incidence of recurrent VF during resuscitation efforts. This may be
due to the excessive β-adrenergic effects of epinephrine. For example, it is known, that the preferred treatment of 'electrical storm' is β-adrenergic blockade.\[62\] Future studies in humans should evaluate alternatives such as epinephrine plus β-blockers or a single dose of epinephrine followed by a single dose of vasopressin to decrease the number of subsequent doses of epinephrine required. The use of pure α-adrenergic drugs such as vasopressors has been shown to be effective in animals and needs to be studied in humans. However, the use of epinephrine is so engrained in the current guidelines that it would take compelling evidence to remove it, evidence that to this day does not exist.

**Quality of Resuscitation is Critically Important**

The message regarding optimal care in cardiac arrest and in particular OHCA should not be lost in the debate over the use of epinephrine. It is the quality of the basic and advanced resuscitation efforts that determines survival. While there is no compelling controlled trial evidence to demonstrate harm or benefit from epinephrine use in human cardiac arrest, we think the lack of demonstrated effects in humans is partly due to the prolonged delay in epinephrine administration and partly due to suboptimal guideline approaches to advanced cardiac life support.

A cogent argument can be made that during the early minutes of resuscitation efforts, there are other interventions that have been shown to improve survival, such as the use of continuous chest compression CPR by bystanders,\[83\] delaying or eliminating endotracheal intubation,\[81,84–88\] early and continuous chest compressions and early defibrillation.\[84,86,89–91\]

The requirement for the establishment of intravenous access and intravenous drug therapy (often with its resultant interruptions to chest compressions) is difficult to meet efficiently and may be counterproductive.

Mader et al. recently conducted a study of the emergency medical services (EMS) component of cardiocerebral resuscitation with intraosseous epinephrine versus CPR with intravenous epinephrine using a swine model of OHCA.\[89\] Following prolonged (10 min of untreated) VF, intraosseous epinephrine was given 11 min after VF arrest and intravenous epinephrine 16.5 min after arrest. Survival was significantly better with the EMS portion of CCR with intraosseous epinephrine than with the CPR with intravenous epinephrine (2005 EMS guidelines). The proportions of VF termination, ROSC and 20-min survival all strongly favored the CCR with intraosseous group. This and other studies suggest that the quality of advanced life support is important and augments the desired hemodynamic effects of epinephrine.\[92\]

It has now been shown in several clinical studies that CCR (a new ACLS approach that prohibits early endotracheal intubation, advocates 200 chest compressions before and immediately after a single shock and advocates the early administration of epinephrine) significantly improves survival of patients with OHCA who have a witnessed arrest and a shockable rhythm on arrival of the paramedics.\[81,84,86,87,93\]

**Postresuscitation Care**

The fact that early intravenous drug use showed improved ROSC and survival to hospital admission but no difference in survival to discharge could provide an impetus for better postresuscitation care of the so-called 'post-cardiac arrest syndrome'.\[74\] Improved postresuscitation care, strategies for neuro- and cardio-protection, including therapeutic hypothermia, early cardiac catheterization and attention to glucose and other metabolic abnormalities, could result in improved longer-term survival.\[94–101\]

**Conclusion**

Epinephrine can be either a curse or a cure when used as an adjunct to resuscitation of cardiac arrest. Its value depends on the dosage given, the timing of administration and the initiating factor of the cardiac arrest. Epinephrine can be a curse in excessive doses or if used too late in resuscitation efforts, resulting in ROSC without improved (and neurologically intact) survival.

Epinephrine's use is based on decades of efficacy in animal models, despite a lack of definitive evidence in clinical trials. There are two major reasons for the disparity between models. The first relates to the timing of its administration. On average, epinephrine has been administered nearly 10 min earlier in the experimental laboratory. The second reason may be that in animal studies, the cause of the VF is often different. If the initiating factor (i.e., the electrical current that initiated the VF in the animal model) is no longer present, epinephrine given early clearly improves survival. In humans, the cause of
the VF arrest may be coronary occlusion, thus even after defibrillation the initiating factor is still present, resulting in recurrent VF. In this situation, repeated doses of epinephrine contribute to the electrical storm. Accordingly, the concomitant use of vasopressin and the addition of β-adrenergic blockers to epinephrine may well be needed to improved survival.

But even if epinephrine can be administered earlier in patients with OHCA via intraosseous administration, this by itself is not a cure. Epinephrine is but one of many interventions that need to be appropriately integrated into the series of essential steps of advanced cardiac life support for optimal resuscitation of patients with OHCA. Many of these features have been integrated into CCR.

Future Perspective

In the future, we can look forward to the use of different and perhaps newer ‘vasopressive’ agents with more specific α-adrenergic or direct vasoconstricting properties without β-adrenergic effects. Equally important is the earlier administration of drugs, so the use of intraosseus drug and fluid administration will be routine.

Vasopressor drugs will be more effective with wider adoption of strategies that delay the inevitable deterioration that accompanies untreated or suboptimally treated cardiac arrest. The future will bring acceptance of CCR, a new approach to resuscitation of primary cardiac arrest that has been shown to significantly improve survival.

It has been shown that bystander resuscitation prolongs the so-called ‘electrical phase’ of VF arrest. The future will witness a paradigm shift in bystander CPR from mouth-to-mouth plus chest compressions to chest compressions only, thus resulting in more frequent and more effective perfusion prolonging the electrical phase of VF arrest, making defibrillation more effective.

The future will bring more effective methods of defibrillation; that is, defibrillation with minimal interruption of chest compressions. Here, perhaps, we will ‘go back to the future’ and return to the 1960s approach, with less reliance on automated external defibrillators and returning to the ‘quick look’ handheld defibrillator electrodes, where the diagnosis of VF and delivery of a shock can be executed in seconds.

Finally, the future will see the emergence of cardiac arrest centers, where patients with ROSC will be treated with early mild hypothermia therapy, early cardiac catheterization, appropriate percutaneous coronary intervention and other more effective therapies of postresuscitation syndrome.

Sidebar

Executive Summary

Introduction

- Epinephrine administration has been advocated in resuscitation for decades and forms a key component of published guidelines. Its usage is based chiefly on animal studies, and human trial evidence is scant.

Pharmacologic & physiologic considerations: the importance of coronary perfusion pressure

- There are subtypes of both the α- and β-adrenergic receptors, and that epinephrine’s effects are mediated through α₁, α₂, β₁, and β₂ receptors.

- The key to successful resuscitation is to achieve a high aortic diastolic pressure and, by extension, coronary perfusion pressure.

- High coronary perfusion pressures have been associated with improved return of spontaneous circulation (ROSC) in human and animal studies and with improved survival in animal studies.

- Epinephrine can also have adverse effects including increased myocardial oxygen consumption and necrosis, postresuscitation myocardial dysfunction and ventricular arrhythmias.
**Epinephrine dosing**

- Higher-dose epinephrine has been found to be harmful in animal studies.
- Limited human trial data show no benefit to higher-dose epinephrine over standard dosing.

**Human studies of epinephrine in cardiac arrest**

- To date, no randomized controlled human trial has specifically evaluated early epinephrine administration in cardiac arrest.
- One recent randomized controlled trial (RCT) from Norway evaluated early administration of epinephrine and other intravenous drugs (atropine and amiodarone) in out-of-hospital cardiac arrest (OHCA). The group treated with early intravenous drugs had higher ROSC and survival to hospital admission, but there was no difference in survival to discharge, survival with good neurological function or longer-term survival. This RCT did not find epinephrine use to be an independent predictor of poor outcome.

**Intraosseous administration of epinephrine**

- Animal studies support early administration of vasopressors for improving neurologically intact survival.
- Vasopressor administration times in animal studies are often less than 10 min.
- By contrast, in human studies, the first drugs are administered at 10–25 min (mean: 17.7 min) post-emergency medical services dispatch. This can explain the lack of observed benefit of epinephrine usage in human OHCA.
- One way to administer epinephrine quicker is with intraosseus access.

**Deleterious effects of multiple-dose epinephrine**

- Epinephrine is not always the ideal vasopressor and this may be attributable to its β-adrenergic effects.
- Epinephrine usage may result in increased recurrent VF and in electrical storm, β-blockade is the preferred treatment.
- Future human RCTs should evaluate epinephrine combined with β-blockers and pure α-adrenergic drugs.
- Epinephrine usage is so engrained in the current guidelines that it would take compelling evidence to remove it, evidence that to this day does not exist.

**Quality of resuscitation is critically important**

- The message regarding optimal care in cardiac arrest, in particular OHCA, should not be lost in the debate over the use of epinephrine. It is the quality of the basic and advanced resuscitation efforts that determines survival.
- During early cardiac arrest, interventions that have been shown to improve survival must be emphasized: early and continuous chest compressions, early defibrillation and delaying endotracheal intubation.
- Interruptions to chest compressions to obtain intravenous access may be counterproductive. Intraosseus administration of epinephrine can minimize the interruption and allow for quicker drug delivery.
- Cardiocerebral resuscitation, a system that prohibits early endotracheal intubation, advocates 200 chest compressions before and immediately after a single shock and advocates the early administration of epinephrine, significantly improves survival of patients with OHCA who have a witnessed arrest and a shockable rhythm on arrival of the paramedics.

**Conclusion**
• Epinephrine can be either a curse or a cure in cardiac arrest.

• Its value depends on the dosage given, the timing of administration, and the initiating factor of the cardiac arrest.

• Epinephrine can be a curse in excessive doses or if used too late in resuscitation efforts, resulting in ROSC without improved (and neurologically intact) survival.

• Despite the demonstrated benefit of epinephrine in animal studies, human trials have failed to show a benefit. The two major explanations for this disparity are: epinephrine in animal trials is given approximately 10 min sooner; and the initiating factor of the VF arrest in animal studies is often different.

• Nevertheless, earlier administration of epinephrine (e.g., via the intraosseous route) is not the cure by itself. Its usage should be integrated into a series of essential steps including cardiocerebral resuscitation and postresuscitation care.

References


2. Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA 244(5), 453–509 (1980).


• Notes the importance of an adequate aortic diastolic pressure during attempted cardiac resuscitation. The authors state that it was often not possible to achieve an adequate aortic diastolic pressure without the addition of epinephrine.

• After induction of cardiac arrest, chest compressions, ventilations and epinephrine administration resulted in optimal animal survival rates. In a similar study following ventricular fibrillation induction, survival was one out of ten without drugs, nine out of ten with epinephrine, and ten out of ten with the α-agonist phenylephrine.


• Demonstrates the resuscitation of animals with β-adrenergic blockade administered with epinephrine.


• Demonstrates that during resuscitation efforts, higher coronary perfusion pressures are associated with improved return of spontaneous circulation in humans.


• Demonstrates that during resuscitation efforts, coronary perfusion pressures above 15 mmHg are associated with improved return of spontaneous circulation and increased survival in animals.


• Demonstrates improved cerebral and myocardial blood flow with epinephrine during resuscitation.


   • Demonstrates improved cerebral and myocardial blood flow with epinephrine during resuscitation.


- Demonstrates that high-dose epinephrine is no better than standard-dose epinephrine in cardiac arrest.


- Demonstrates that the α-adrenergic and not the β-adrenergic effects of epinephrine are beneficial during resuscitation.


61. Lindner KH, Prengel AW, Pfenninger EG et al.: Vasopressin improves vital organ blood flow during closed-chest


• Only human randomized controlled trial demonstrating the use of epinephrine together with other drugs in out-of-hospital cardiac arrest. There was better short-term survival in the early intravenous treatment group, although this advantage did not translate to improved hospital discharge rates or neurological recovery. The study may have been underpowered. Epinephrine usage was not found to be an independent predictor of poor outcome.


• Meta-analysis demonstrating that the most powerful predictor of survival to hospital discharge is return of spontaneous circulation in the field.

76. Rittenberger JC, Bost JE, Menegazzi JJ: Time to give the first medication during resuscitation in out-of-hospital

- Systematic review of studies between 1990 and 2005 finding that in humans the time to first drug administration from the time of dispatch ranged from 10 to 25 min (mean: 17.7 min), significantly higher than in animal studies.


- Landmark study supporting the superiority of cardiocerebral resuscitation over the traditional cardiopulmonary resuscitation.


- Landmark study supporting the superiority of cardiocerebral resuscitation to the traditional cardiopulmonary resuscitation.


- Landmark study supporting the superiority of cardiocerebral resuscitation to the traditional cardiopulmonary resuscitation.


- Landmark study supporting the idea that delaying intubation to allow for uninterrupted chest compressions is superior.


• Demonstrates that earlier administration of epinephrine by gaining intraosseous access is associated with improved survival in a swine model.


• Demonstrates the hemodynamic benefits of epinephrine are assisted by good quality chest compressions.


• Demonstrates that early coronary reperfusion and hypothermia are emerging paradigms in postresuscitation care.

• Demonstrates that early coronary reperfusion and hypothermia are emerging paradigms in postresuscitation care.

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.