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The Role of Epinephrine in Cardiac Arrest

Introduction

1. There are greater than 350,000 out-of-hospital cardiac arrests annually, and nearly 90% of them are fatal.
2. The effects of epinephrine on animal hemodynamics have been studied since the late 1800s.
3. While the first advanced cardiac life support (ACLS) guidelines were first published in 1974, the role of epinephrine remains controversial.

Epinephrine [Adrenalin®]			
Dose	**Cardiac arrest:** 1 mg IV/IO every 3 to 5 minutes		
Mechanism of Action	Receptor Activity	Pharmacological Action	Effect
	α agonist	Peripheral vasoconstriction	↑ myocardial and cerebral blood flow
	β agonist	↑ heart rate and contractility	↑ myocardial oxygen demand
Indications	Asystole/pulseless electrical activity (PEA) Pulseless ventricular tachycardia/fibrillation		
Pharmacokinetics	**Onset**: immediate **Distribution:** 1-2 minutes to reach central circulation during CPR **Metabolism:** rapid hepatic degradation **Elimination**: urine (inactive metabolites) **Half-life:** <5 minutes		
Adverse Effects	Tachyarrhythmias, myocardial ischemia, may decrease cerebral perfusion, mesenteric ischemia, extravasation leading to necrosis, lactic acidosis		
Dosage Forms	Vial: 1 mg/mL (1 mL & 30 mL) Pre-filled syringe: 1 mg/10 mL (10 mL)		
Compatibility	**Compatible with:** NS, D5W, and LR **Incompatible with** sodium bicarbonate		

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Overview of Evidence

Author (Year)	Study Design/Patient Population	Intervention	Results
Pearson, 1963	Animal study (n=80) Asphyxiated dogs with asystole and ventricular fibrillation	• Epinephrine 1 mg • Positive-pressure breathing • Chest compressions • Defibrillation	↑ **ROSC in dogs that received epinephrine** 5 min and 10 min after asystole ↑ **ROSC in dogs that received epinephrine** 1 min after ventricular fibrillation Ventricular fibrillation occurred only in the epinephrine group
Stiell, 1992	RCT (650) Out-of-hospital cardiac arrest	• Epinephrine 7 mg every 5 min • Epinephrine 1 mg every 5 min	**No difference in survival to hospital admission or discharge and neurologic outcomes** between low- and high-dose epinephrine
Brown, 1992	RCT (n=1280) Out-of-hospital cardiac arrest	• Epinephrine 0.2 mg/kg • Epinephrine 0.02 mg/kg	**No difference in ROSC, survival to hospital admission and discharge, or neurological outcomes** between low- and high-dose epinephrine
Choux, 1995	RCT (n=536) Out-of-hospital cardiac arrest	• Epinephrine 5 mg every 5 min • Epinephrine 1 mg every 5 min	**No difference in ROSC at any time, admission to hospital, or neurological outcomes** between low- and high-dose epinephrine
Sherman, 1997	RCT (n =140) Out-of-hospital cardiac arrest	• Epinephrine 0.1 mg/kg • Epinephrine 0.01 mg/kg	**No difference in rhythm improvement, ROSC, neurologic outcomes, or discharge from hospital** between low- and high-dose epinephrine
Gueugniaud, 1998	RCT (n= 3327) Out-of-hospital cardiac arrest	• Epinephrine 5 mg every 3 min • Epinephrine 1 mg Every 3 min	↑ **ROSC** in high-dose epinephrine group **No difference in admission to hospital, 24-hour survival, discharge from hospital, or neurological outcomes** between low- and high-dose epinephrine
Fisk, 2018	Pre-post study (n= 2255) Out-of-hospital cardiac arrest	• Epinephrine 1 mg at 4 min, then 1 mg every 8 min (2 min for non-shockable rhythms) • Epinephrine 0.5 mg at 4 min and 8 min, then 0.5 mg every 8 min (2 min for non-shockable rhythms)	**No difference in any ROSC, sustained ROSC, survival to discharge, or favorable neurological outcomes** between low- and high-dose epinephrine
Stiell, 2004 **(OPALS)**	Pre-Post study (n=5638) Out-of-hospital cardiac arrest	• Rapid defibrillation ACLS (endotracheal intubation & IV medications)	98.5% of ACLS group received epinephrine ↑ **ROSC and survival to hospital admission** in group receiving epinephrine **No difference in survival to hospital discharge and neurological outcomes**
Olasveengen, 2009	RCT (n=851) Out-of-hospital cardiac arrest	• ACLS with IV medications • ACLS without IV medications	79% of IV medication group received epinephrine ↑ **ROSC at any time and survival to hospital admission** in group receiving epinephrine **No difference in survival to hospital discharge and neurological outcomes**

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Author (Year)	Study Design/Patient Population	Intervention	Results
Jacobs, 2011	RCT (n=534) Out-of-hospital cardiac arrest	• Epinephrine • Placebo	↑ **ROSC and survival to hospital admission** in group receiving epinephrine **No difference in survival to hospital discharge or neurological outcomes**
Hagihara, 2012	Observational study (n=417,188) Out-of-hospital cardiac arrest	• Epinephrine • No epinephrine	↑ **ROSC** in group receiving epinephrine ↓ **1-month survival and neurological outcomes** in epinephrine group
Perkins, 2018 **(PARAMEDIC-2)**	RCT (n=8007) Out-of-hospital cardiac arrest	• Epinephrine 1 mg every 3-5 min • Placebo	↑ **ROSC, survival to hospital admission, and 30-day survival** in epinephrine group **No difference in favorable neurologic outcome** at hospital discharge ↑ **severe neurologic impairment** in group receiving epinephrine

Conclusions

1. The dose of epinephrine is based on animal studies from the 1960s, in which epinephrine was administered immediately after the induction of cardiac arrest.
2. There have been no differences found between standard and high-dose epinephrine.
3. Epinephrine may lead to increased ROSC and survival to hospital admission but has not been found to consistently improve long-term outcomes.
4. **Bottom Line: Quality chest compressions and early defibrillation continue to be the standard of care in ACLS and should not be delayed for administration of epinephrine.**

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