Epinephrine use in cardiac arrest

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Epinephrine

Most commonly used drug
during cardiopulmonary resuscitation

Epinephrine (Adrenaline)

- Hormone, Neurotransmitter, Medicine
- Produce : Adrenal gland, Neurons, synthesized
  - Function : Fight-or-flight response & hyperarousal, acute stress response
- Receptors : **α & β adrenergic receptors**
- Adrenal gland extract
  - ***Pellacani***, 1874
    - first administration of adrenal gland extract to animals
  - ***Napoleon Cybulski***, 1875
    - first isolation of adrenal gland extract
  - ***Abel*** (US) named epinephrine (1899) / ***Takamine*** (Europe) named adrenaline (1901)

Historical considerations of epinephrine in cardiac resuscitation

- ***George Crile & David H. Dolley***, 1906, J Exp Med
  - asphyxial cardiac arrest of dogs
    - Adrenaline : markedly more successful in resuscitation
    - noted the importance of an adequate aortic diastolic pressure
      - ***coronary pressure*** : 30-40mmHg

- **Cardiovascular effect of epinephrine (adrenaline)**

Heart (β1 receptors)	↑ heart rate	↑ contractility	↑ heart work & O2 consumption
Blood vessels (α & β2 receptors)	Vasoconstriction of blood vessels of skin and mucous membrane (α-stimulation)	vasodilation of the skeletal muscles and coronary blood vessels (β2-stimulation)	

- **Effect of epinephrine during CPR**

Inotropic and chronotropic effects

VS.

Peripheral vasoconstriction

↑ Diastolic aortic pressure → ↑ perfusion to the heart

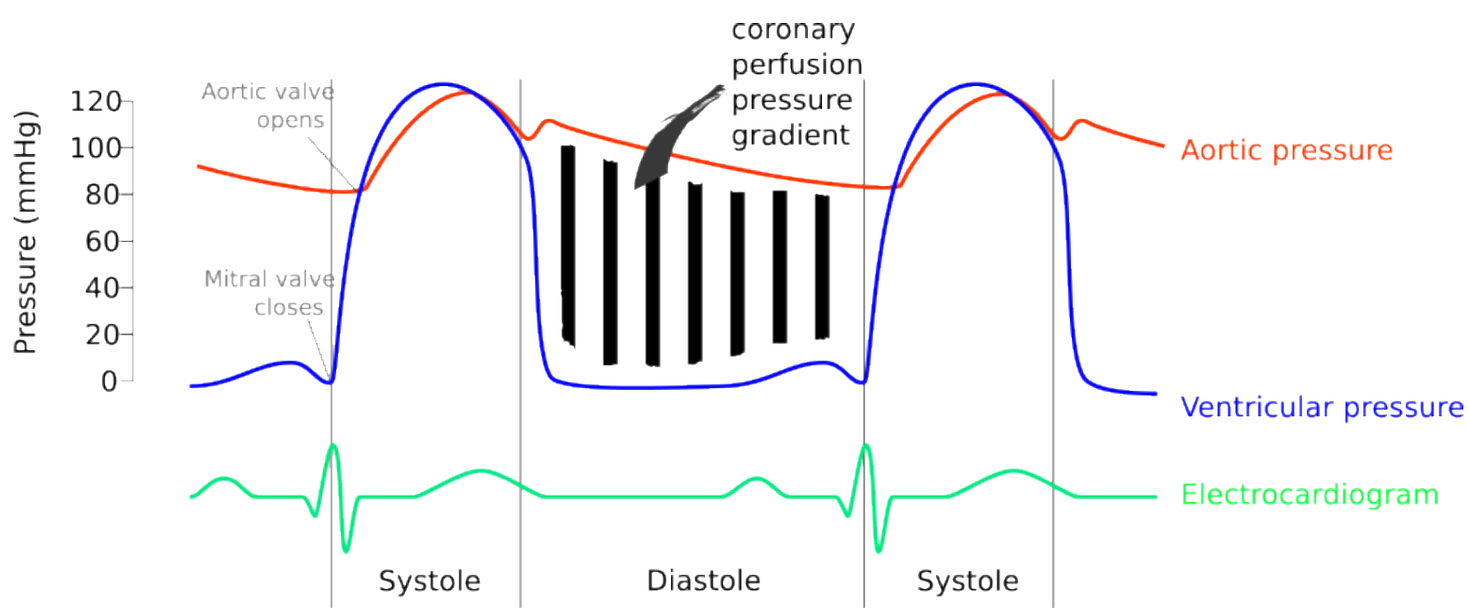
- ***Redding & Pearson***, 1963, Anesthesiology
  - Asphyxia cardiac arrest in dogs

Drugs	ROSC rate
Epinephrine (non-selective)	**10/10**
Phenylephrine (α1 selective)	9/10
Isoproterenol (β1, β2, β3)	0/10
metaraminol (α1>β)	9/10
Methoxamine (α1 selective)	9/10
Mephentermine (α1, α2, β1)	3/10
Calcium chloride	6/10

- ***Yakaitis RW et al***. 1979, Crit Care Med

	Group A	Group B	Group C
Drug treatment	Phenoxybenzamine (α blocker) + isoproterenol (β agonist)	Propranolol (β blocker) + Phenylephrine (α1 agonist)	Epinephrine
ROSC	ROSC 3/11	ROSC 10/10	ROSC 10/10
Mean diastolic pressure	10mmHg	38mmHg	40mmHg

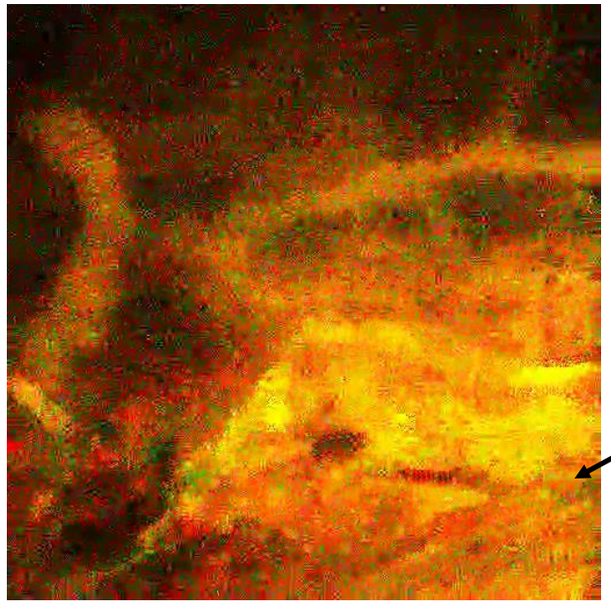
- **Return of spontaneous circulation**
  - Depends on adequate coronary perfusion pressure
  - CPP = diastolic aortic pressure - LVEDP



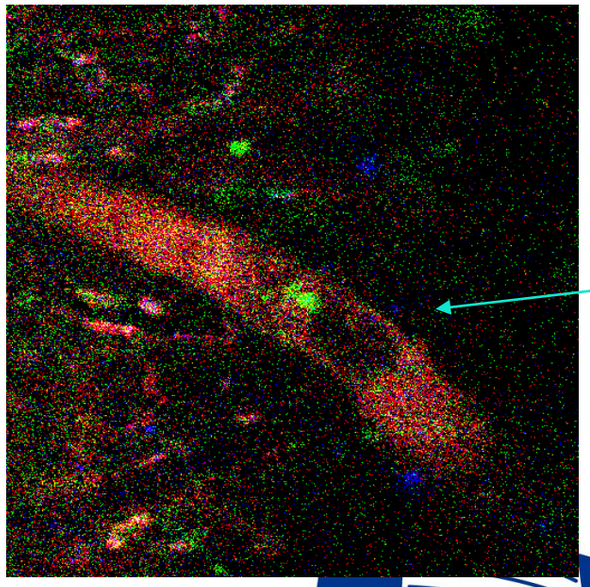
Epinephrine (Adrenaline)

- **Effect during cardiac arrest**

	α-adrenergic effect	β-adrenergic effect
Beneficial	↑ Coronary perfusion pressure	Vasodilation of coronary blood vessels → increase coronary blood flow
Harmful	Platelet activation → thrombosis → impairs microvascular blood flow	↑ myocardial work & O2 consumption ↓ subebdocardial perfusion



- C57BL/6 Mouse
- Post-cardiac arrest
- Brain capillary



- LysM $^{GFP/+}$ Mouse
- Post-cardiac arrest
- Brain capillary

Recommendation of epinephrine in cardiopulmonary resuscitation

- **2015 AHA guidelines**
  - Standard-dose epinephrine (1mg every 3 to 5 minutes) may be reasonable for patients in cardiac arrest (Class IIb, LOE B-R)
    - **For VF/pVT : after 2 defibrillation attempts**
    - For non-VF/pVT : as soon as IV/IO access is achieved
- **2015 ERC guidelines**
  - 1mg every 3-5 minutes
    - **For VF/pVT : after 3 defibrillation attempts**
    - For non-VF/pVT : as soon as IV/IO access is achieved

Efficacy of epinephrine in cardiac arrest

Administration of epinephrine during CPR is beneficial ?

Epinephrine : as a pressor to increase coronary perfusion pressure

during chest compression

Survival Outcomes With the Introduction of Intravenous Epinephrine in the Management of Out-of-Hospital Cardiac Arrest

Ann Emerg Med, 2007

- **Singapore**
- **Before and After study**
  - **Introduction of IV epinephrine in prehospital phase**
- **1,296 OHCA patients**
  - **Pre-epinephrine (n=615) vs. Epinephrine (n=681)**

	Pre-epinephrine (n=615)	Epinephrine (n=681)
ROSC	110 (17.9%)	107 (15.7%)
Survival to hospital admission	46 (7.5%)	51 (7.5%)
Survival to discharge	6 (1.0%)	11 (1.6%)

Epinephrine use : no survival benefit

Intravenous Drug Administration During Out-of-Hospital Cardiac Arrest

- A Randomized Trial

JAMA, 2009

- Norway
- adults (>18years), non traumatic OHCA
- evaluate IV access and drug administration during Prehospital ACLS
- 851 patients randomized

	No IV group (n=433)	IV group (n=418)
IV drug during CPR	42 (10%)	343 (82%)
Epinephrine	37 (9%)	330 (79%)
Atropine	20 (5%)	194 (46%)
Amiodarone	17 (4%)	69 (17%)
Outcomes		
Any ROSC	107 (25%)	165 (40%)
Hospital admission	126 (29%)	178 (43%)
Survival to discharge	40 (9.2%)	44 (10.5%)
Good neurological outcome at discharge	35 (8.1%)	41 (9.8%)
1-yr survival	36 (8%)	41 (10%)

Intravenous drug during ACLS: ↑ short-term survival, but not survival to discharge

PACA (Prehospital Adrenaline in Cardiac Arrest) trial

Resuscitation, 2011

- **Western Australia, Perth**
- **Randomized double blind placebo-controlled trial**
  - **Adrenaline vs. placebo**
- **Sample size = 2,213 per group**
  - **601 victims randomized**

First RCT !

	Placebo, n=262	Adrenaline, n=272
pre-hospital ROSC	22 (8.4%)	64 (23.5%)
Hospital admission	34 (13.0%)	69 (25.4%)
Survival to discharge	5 (1.9%)	11 (4.0%)
Good neurological outcome	5 (100%)	9 (81.8%)

use of adrenaline in cardiac arrest : ↑ prehospital ROSC

Study ended prematurely (enrolled 10 % of the intended)

Prehospital epinephrine Use and Survival Among Patients With Out-of-Hospital Cardiac arrest

JAMA, 2012

- **Japan**
- **Prospective observational Propensity analysis using national registry**
- **Adult OHCA patients**
- **Study period: 2005.1 ~ 2008.12**
  - **IV access by EMT since 2004**
  - **IV epinephrine by EMT since 2006**
- **417,188 cases**
- **Propensity score matching**
  - **Epinephrine vs. No epinephrine (n=13,401 per group)**

	Epinephrine (n=13,401)	No epinephrine (n=13,401)
prehospital ROSC	2446 (18.3%)	1400 (10.5%)
1-month survival	687 (5.1%)	944 (7.0%)
Good neurological outcome	173 (1.3%)	413 (3.1%)

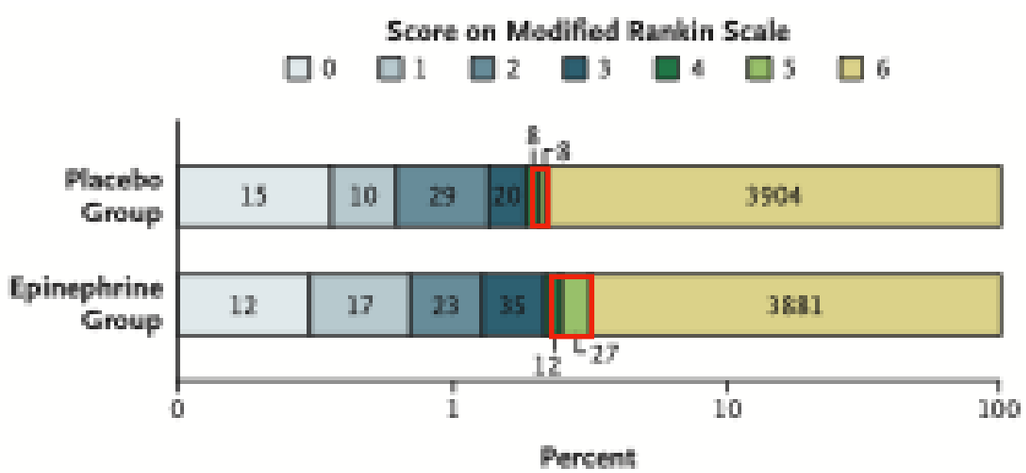
Epinephrine use : improved ROSC, but not 1-month survival & resulted in poor neurological outcome

PARAMEDIC2 trial

N Engl J Med, 2018

- **UK**
- **multi center randomized double-blind placebo controlled trial**
- **prehospital ACLS**
  - **epinephrine vs. placebo**
- **Study period : 2014.12~2017.10**
- **8,016 patients randomized**

	Epinephrine (n=4,015)	Placebo (n=3,999)
Prehospital ROSC	1457/4015 (36.3%)	468/3999 (11.7%)
30-day survival	130/4012 (3.2%)	94/3995 (2.4%)
hospital admission	947/3973 (23.8%)	319/3982 (8.0%)
survival to discharge	128/4009 (3.2%)	91/3995 (2.3%)
Good neurological outcome at discharge	87/4007 (2.2%)	74/3994 (1.9%)
3-month survival	121/4009 (3.0%)	86/3991 (2.2%)
Good neurological outcome at 3mo	82/3986 (2.1%)	63/3979 (1.6%)



Survival with a favorable neurological outcome at hospital discharge

Epinephrine: ↑ survival, but not favorable neurological outcome

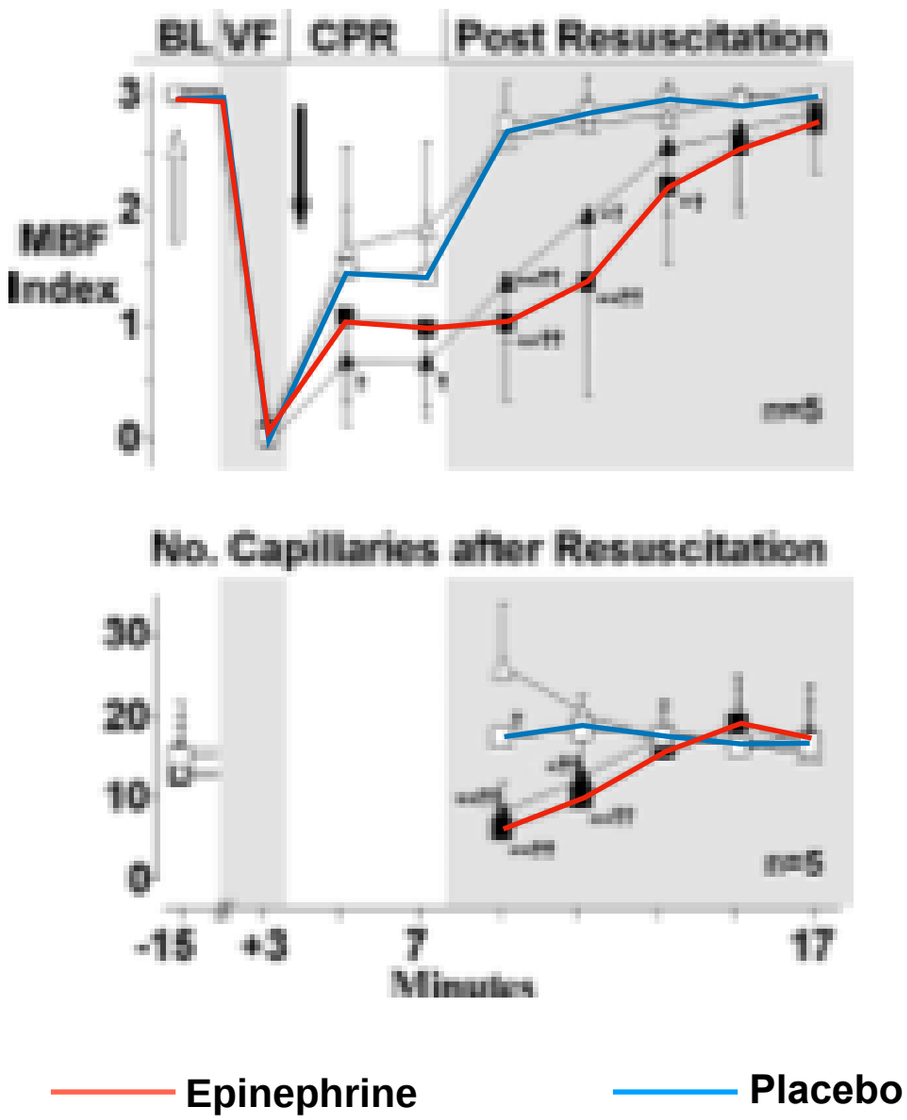
Epinephrine during CPR

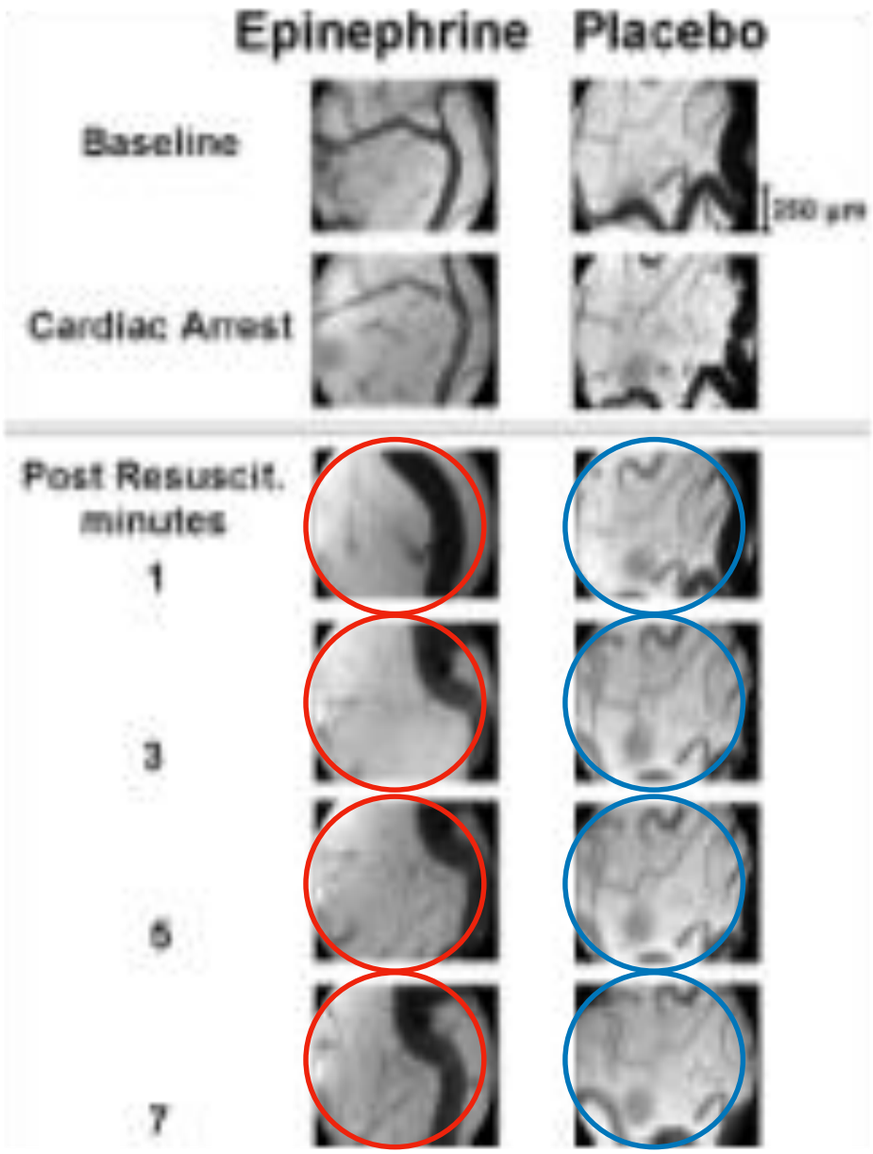
Increase coronary perfusion pressure → increase chance of ROSC

Increase cerebral blood flow during CPR ?

Epinephrine reduces cerebral perfusion during CPR

Crit Care Med, 2009



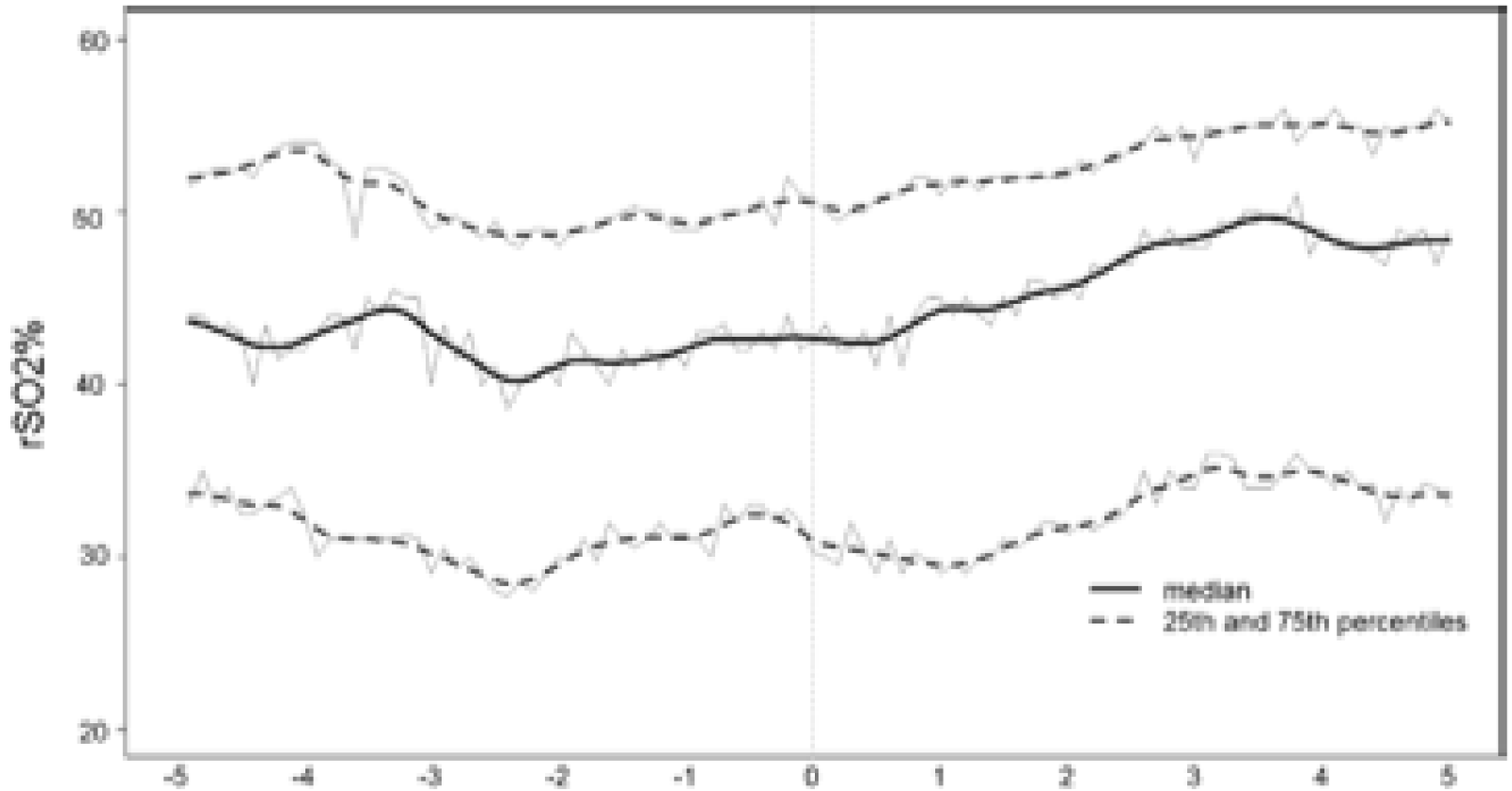


Epinephrine decreased cerebral microcirculation during post-resuscitation phase

Effects of epinephrine on cerebral oxygenation during cardiopulmonary resuscitation: A prospective cohort study

Resuscitation, 2016

- **Study period : 2011.8~2014.9**
- **adult IHCA (n=36)**
- **Using Cerebral oximetry (Equanox 7600, Nonin Medical, USA)**



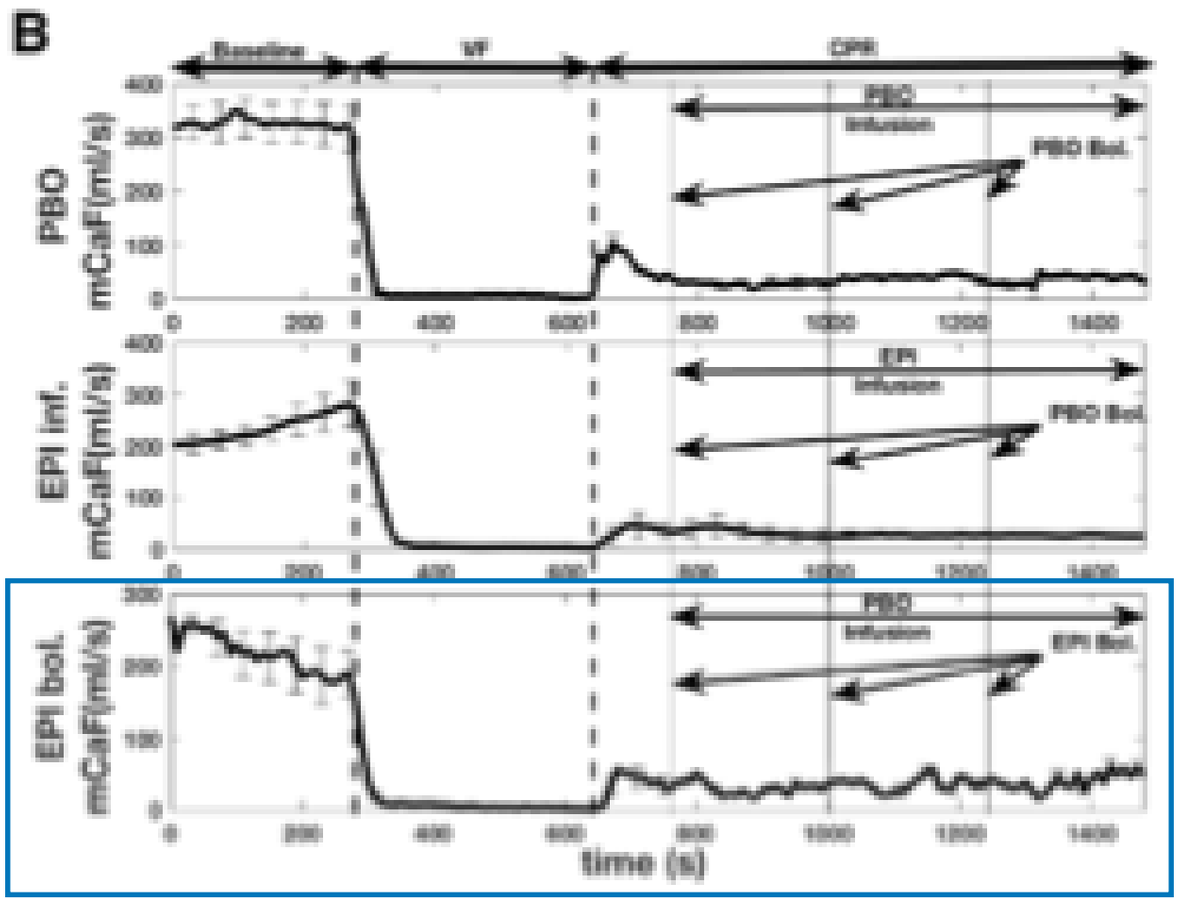
Time before and after adrenaline injection

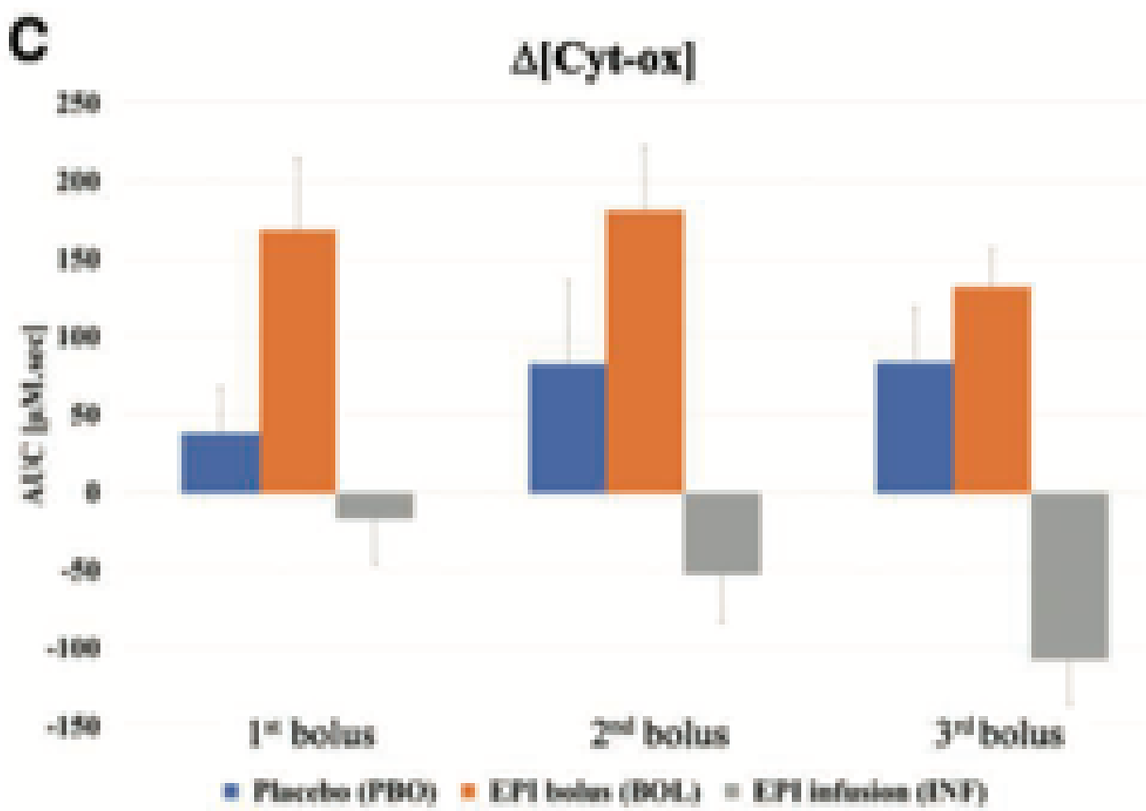
1mg epinephrine : small, but insignificant increase in rSO_2

Study of the Effects of Epinephrine on Cerebral Oxygenation and Metabolism During Cardiac Arrest and Resuscitation by Hyperspectral Near-Infrared Spectroscopy

Crit Care Med, 2018

- **Swine cardiac arrest model**
- **Placebo vs. Epi bolus (0.015mg/kg every 4 min) vs. Epi continuous (0.045mg/kg over 12min)**





Carotid blood flow

Epinephrine bolus : no significant change in carotid blood flow, but transient improvement of cerebral metabolism

Adequate dose of epinephrine

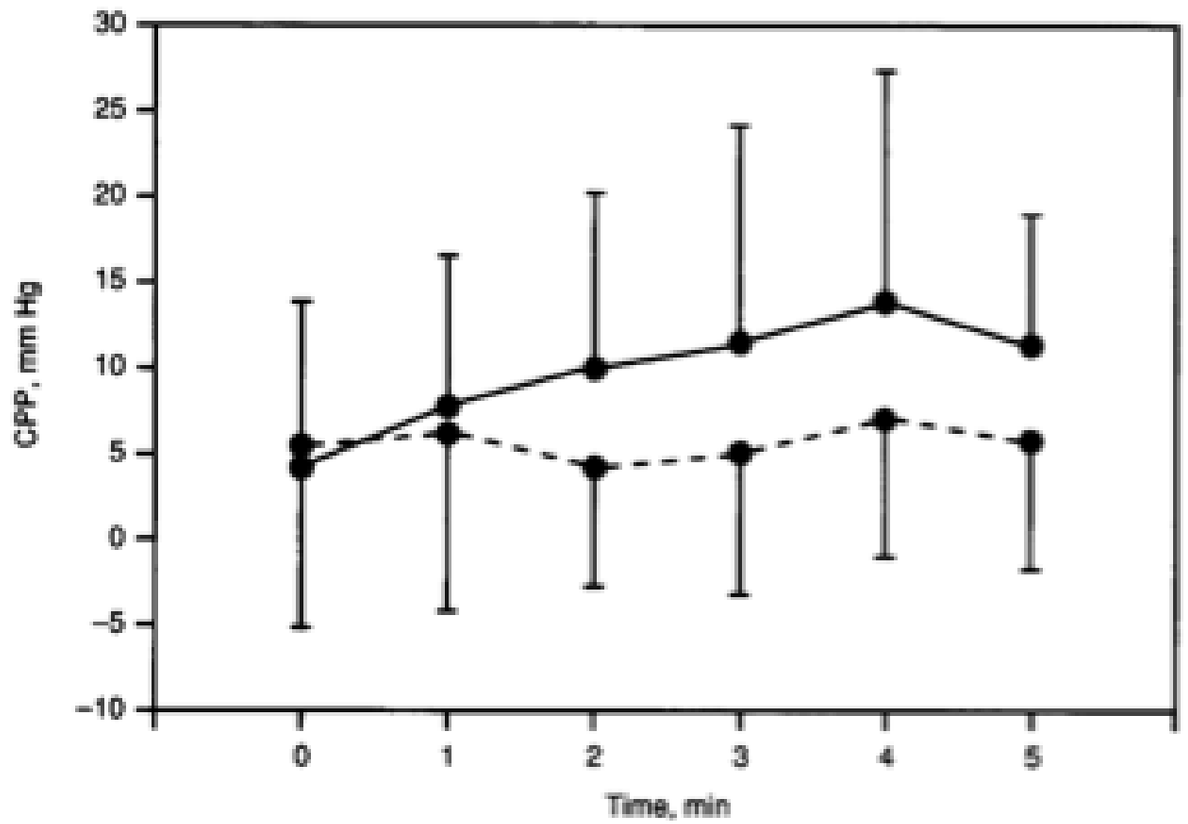
Standard dose (1mg) vs. High dose (0.1~0.2mg/kg) vs. Low dose (0.5mg)

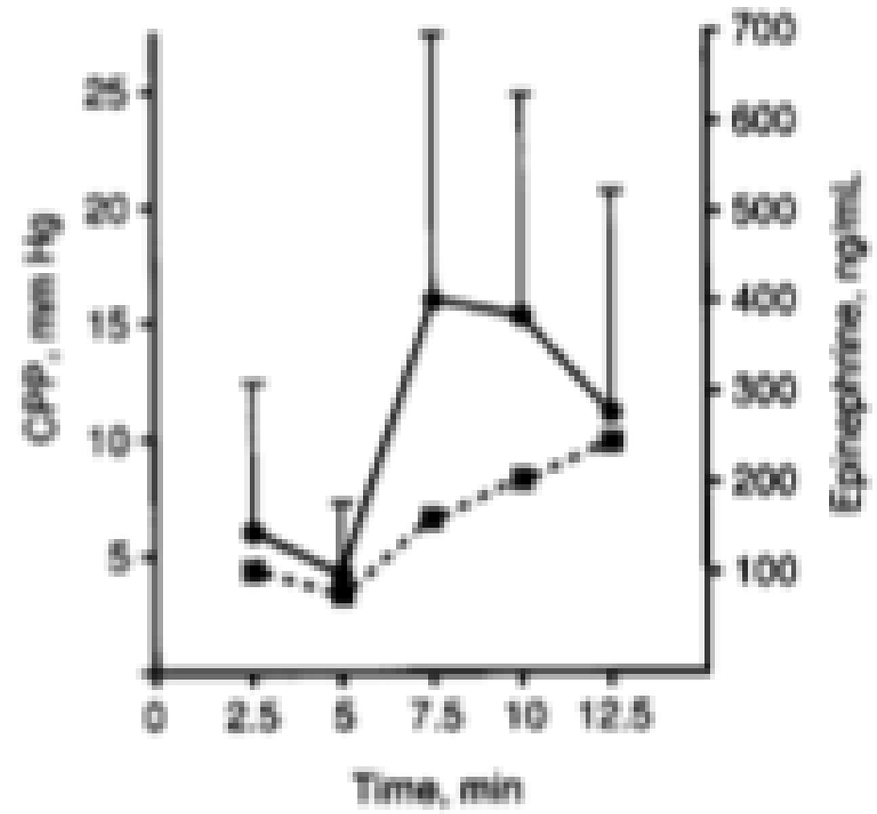
Standard vs. High dose

The Effect of Standard- and High-Dose Epinephrine on Coronary Perfusion Pressure During Prolonged Cardiopulmonary Resuscitation

JAMA, 1991

- Prospective cross-over design
- 32 patients who were in prolonged cardiac arrest
- Epinephrine 1mg vs. 0.2mg/kg





High dose epinephrine increased CPP in prolonged CPR, but standard dose did not

Standard vs. High dose

A Randomized Clinical Trial of High-Dose Epinephrine and Norepinephrine vs Standard-Dose Epinephrine in Prehospital Cardiac Arrest

JAMA, 1992

- **US**
- **Prehospital cardiac arrest**
- **816 patients**
- **High dose epinephrine (15mg) vs. Norepinephrine (11mg) vs. Standard-dose epinephrine (1mg)**

	High dose epinephrine (n=286)	Standard dose epinephrine (n=270)	Norepinephrine (n=260)
Prehospital ROSC	37 (13%)	22 (8%)	35 (13%)
Hospital admission	30 (10%)	21 (8%)	27 (10%)
Survival to discharge	5 (1.7%)	3 (1.2%)	7 (2.6%)
Good neurological outcome	0 (0%)	2 (67%)	0 (0%)

High dose epinephrine : increased ROSC & hospital admission , but not hospital discharge and good neurological outcome

High dose epinephrine in adult cardiac arrest

N Engl J Med, 1992

- **Canada**
- **Randomized controlled trial**
- **IHCA and OHCA (n=650)**
- **High dose (7mg) vs Standard dose (1mg) every 5 minutes**
- **Study period : 1989.12~1992.1**

	High dose (n=317)	Standard dose (n=333)
Resuscitated	56 (18%)	76 (23%)
Discharged	10 (3%)	16 (5%)
Good CPC	9 (90%)	15 (94%)

High dose epinephrine : no benefit on the survival and neurological outcome

A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital

N Engl J Med, 1992

- **US**
- **Randomized controlled trial**
- **OHCA (n=1280)**
- **Prehospital ACLS**
- **epinephrine 0.2mg/kg vs. 0.02mg/kg**

	High dose (n=648)	Standard dose (n=632)
ROSC	217 (33%)	190 (30%)
Hospital admission	145 (22%)	136 (22%)
Survival to discharge	31 (5%)	26 (4%)
Conscious at discharge	29 (94%)	24 (92%)

No difference in outcomes

Standard doses versus repeated high doses of epinephrine in cardiac arrest outside the hospital

Resuscitation, 1995

- **France**
- **Study period : 1991.1~1992.7**
- **OHCA (n=536)**
- **Randomized controlled trial**
- **Epinephrine 1mg vs 5mg every 5 minutes**

	High dose	Standard dose
ROSC	96 (35.5%)	85 (32%)
Hospital admission	65 (24%)	54 (20.4%)
Neurological outcome	no difference	

No difference in outcomes

A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital

N Engl J Med, 1998

- **France and Belgium**
- **Multicenter Randomized trial**
- **OHCA (n=3327)**
- **Epinephrine 1mg vs 5mg every 5 minutes**

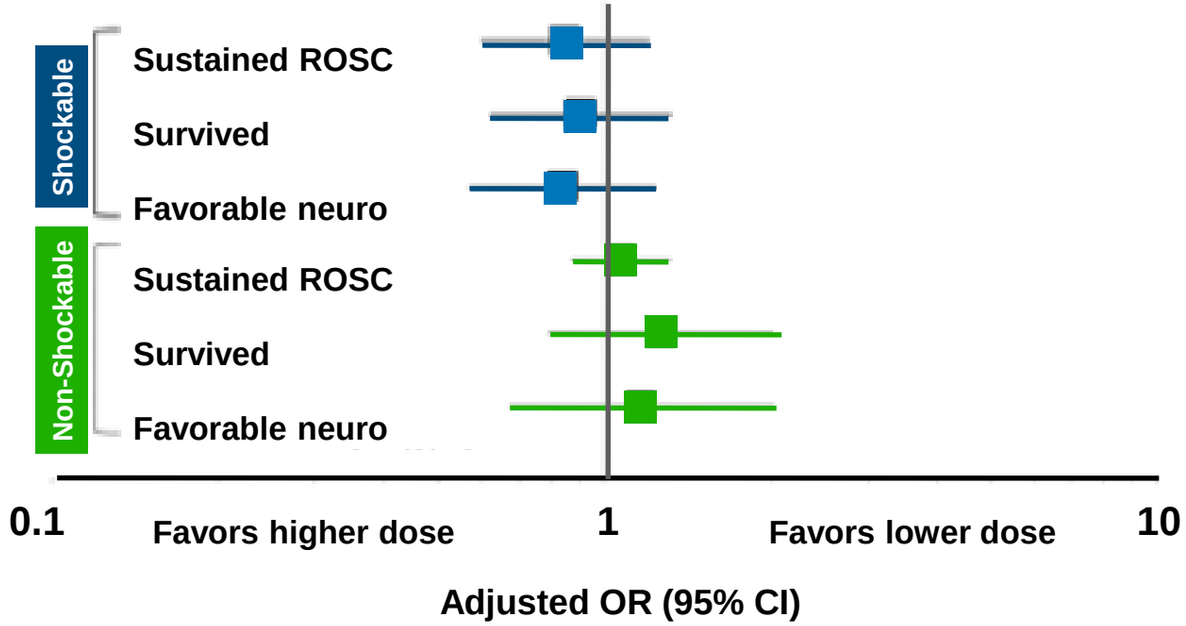
	High dose (n=1677)	Standard dose (n=1650)
ROSC	678 (40.4%)	601 (36.4%)
Hospital admission	444 (26.5%)	389 (23.6%)
Survival to discharge	38 (2.3%)	46 (2.8%)
Neurological outcome	no difference	

high dose epinephrine : improved ROSC and hospital admission, but not long-term survival and neurological outcome

Lower-dose epinephrine administration and out-of-hospital cardiac arrest outcomes

Resuscitation, 2018

- US
- OHCA
- Before and After study
  - Before period : 2008.1~2012.9
    - Shockable 1mg at 4 min then 1mg every 8min
    - Non-shockable 1mg every 2min
  - After period : 2012.10~2016.6
    - Shockable 0.5mg at 4 min and 8 min, then 0.5mg every 8 min
    - Non-shockable 0.5mg every 2 min



Lower dose epinephrine : not associated with a change in survival and neurological outcome

Optimal dosing interval ? Not known yet

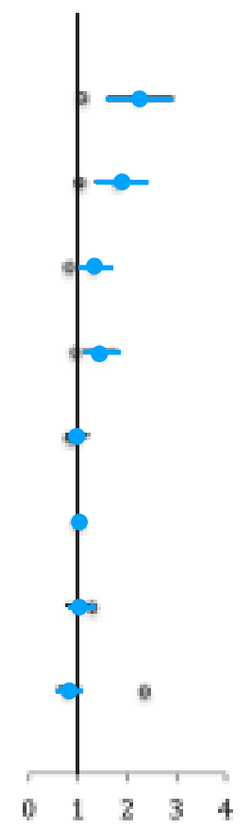
Adrenaline (epinephrine) dosing period and survival after in-hospital cardiac arrest: A retrospective review of prospectively collected data

Resuscitation, 2014

- US
- GWTG-Resuscitation registry (National Registry of CPR)
- Study period : 2000.1~2009.11
- 20,909 patients

Epinephrine average dosing period	No. of patients	Unadjusted survival to discharge No. (%)	Unadjusted Odds Ratio for Survival (95%CI)	Adjusted Odds Ratio for Survival (95%CI)
9-10 min/dose	1522	112(7.4)	1.08 (0.85, 1.37)	2.17 (1.62, 2.92)
8-9 min/dose	1961	138(7.0)	1.03 (0.82, 1.29)	1.79 (1.38, 2.32)
7-8 min/dose	2676	151(5.6)	0.82 (0.67, 1.01)	1.30 (1.02, 1.65)
6-7 min/dose	3373	216(6.4)	0.94 (0.77, 1.14)	1.41 (1.12, 1.78)
5-6 min/dose	4184	240(5.7)	0.84 (0.70, 0.99)	0.96 (0.78, 1.19)
4-5 min/dose	3712	251(6.8)	1(ref.)	1(ref.)
3-4 min/dose	2381	203(8.5)	1.28 (1.06, 1.55)	0.96 (0.76, 1.21)
1-3 min/dose	1100	159(14.5)	2.31 (1.85, 2.86)	0.78 (0.59, 1.03)

Adjusted Odds Ratio for Survival (95%CI) Plotted (● = unadjusted odds ratio)

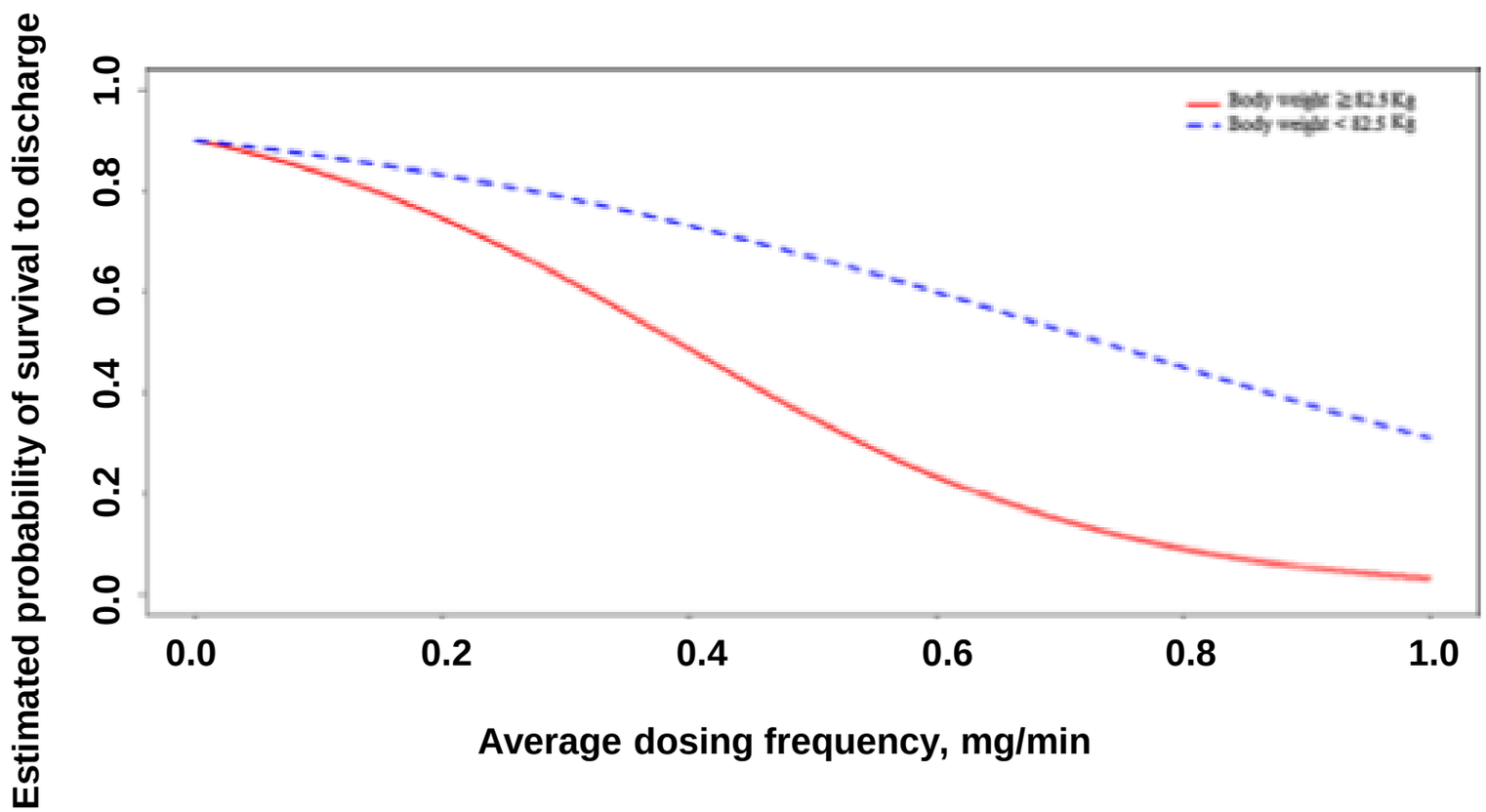


Less frequent dosing of epinephrine was associated with improved survival

The influences of adrenaline dosing frequency and dosage on outcomes of adult in-hospital cardiac arrest: A retrospective cohort study

Resuscitation, 2016

- **Taiwan**
- **National Taiwan University Hospital**
- **IHCA (n=896)**
- **Study period: 2006~2012**



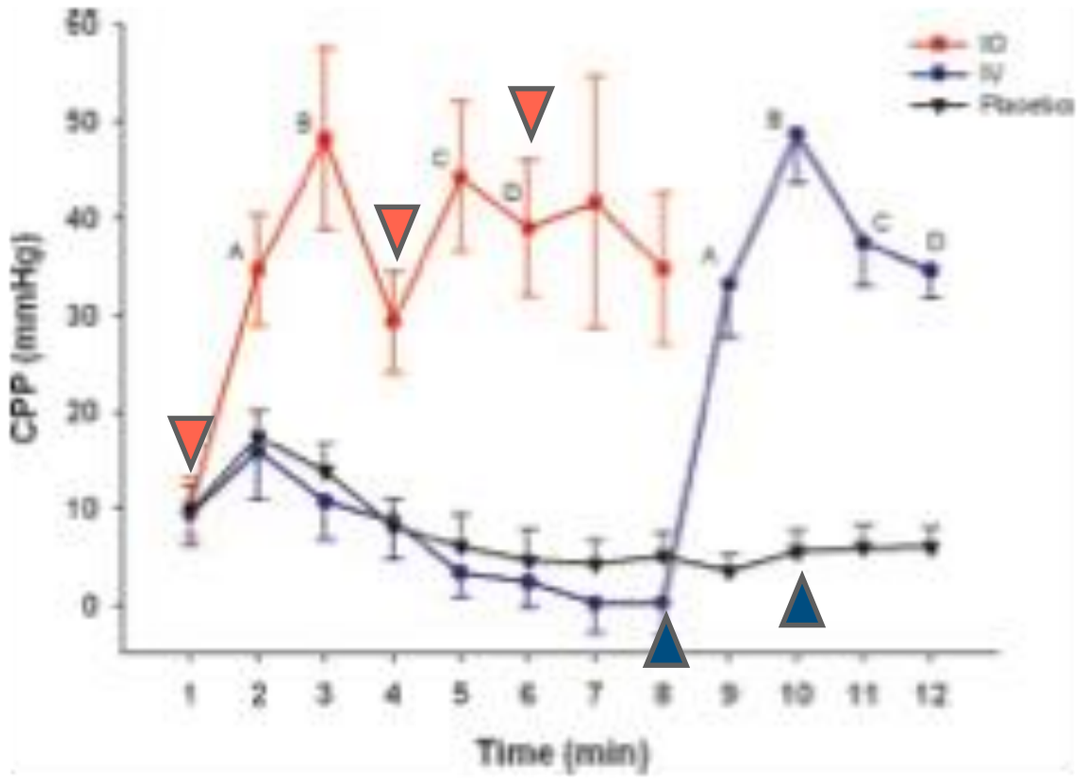
Higher dosing frequency : lower rates of survival and favorable neurological outcomes

Time to first epinephrine

OHCA vs. IHCA
Shockable vs. Non-shockable

Epinephrine Improves 24-Hour Survival in a Swine Model of Prolonged Ventricular Fibrillation Demonstrating that Early Intraosseous Is Superior to Delayed Intravenous Administration

Anesth Analg, 2011



	ROSC	24 hour survival	24 hour neurologically intact survival
IO epinephrine	100%	100%	60%
IV epinephrine	90%	40%	30%

Effectiveness of epinephrine decreased over time

Association between timing of epinephrine administration and intact neurologic survival following out-of-hospital cardiac arrest in Japan: A population-based prospective observational study

Acad Emerg Med, 2012

- **Japan**
- **Retrospective analysis**
- **adult, witnessed OHCA, Prehospital setting**
- **49,165 patients**
  - **Cardiac cause (n=33,163)**
  - **Non-cardiac cause (n=16,002)**
- **Early epinephrine (<10min) vs. Delayed epinephrine (>10min)**

	Cardiac cause		Non-cardiac cause	
	Early epi (n=1762)	Delayed epi (n=31401)	Early epi (n=639)	Delayed epi (n=15363)
Survival	199 (11.3%)	1877 (6.0%)	44 (6.9%)	561 (3.7%)
Intact neurologic survival (CPC 1-2)	80 (4.5%)	812 (2.6%)	8 (1.3%)	93 (0.6%)

Early epinephrine : associated with intact neurologic survival

Rapid epinephrine administration improves early outcomes in out-of-hospital cardiac arrest

Resuscitation, 2013

- **US**
- **Retrospective analysis**
- **Adult OHCA**
- **Study period : 2005.11~2011.4**
- **686 patients analyzed**
  - **Epinephrine < 10 min vs. >10min**

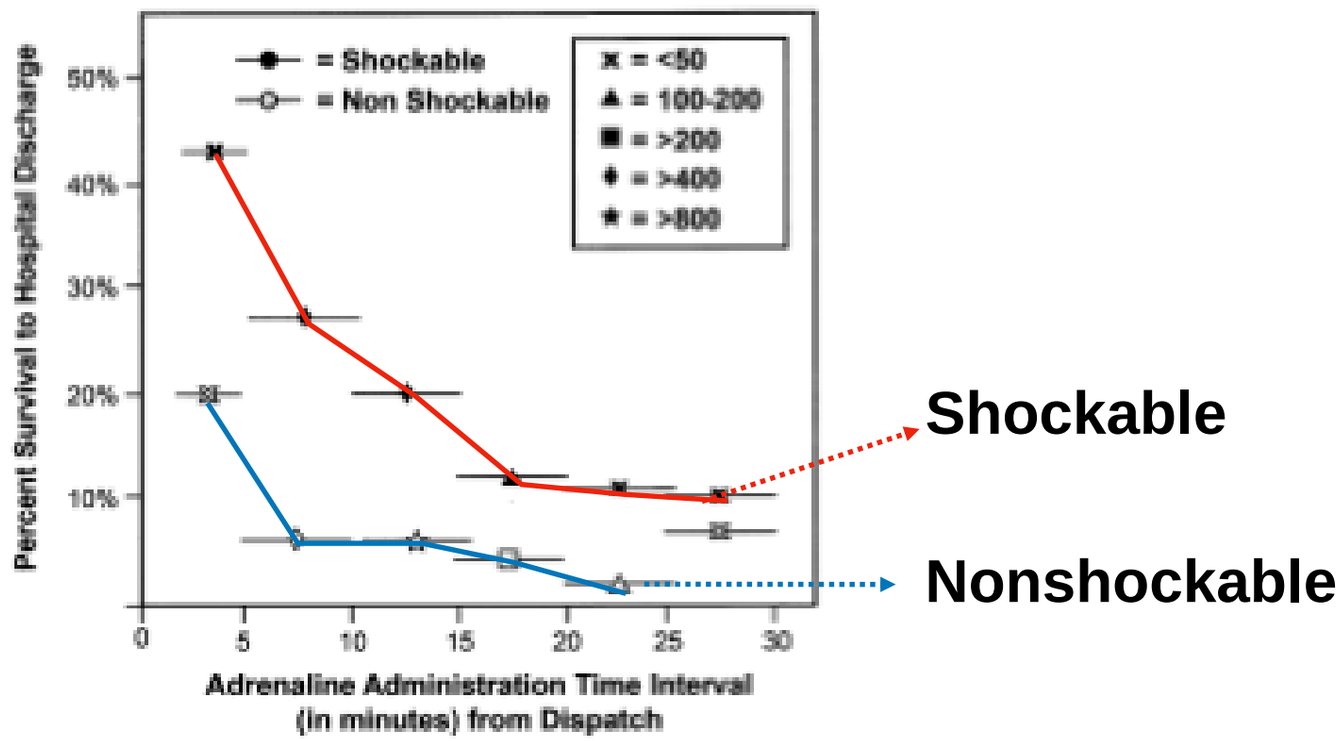
	Epi < 10min	Epi > 10min
All patients	n=155	n=531
prehospital ROSC	51 (33%)	124 (23%)
Survival to discharge	8/150 (5.3%)	19/514 (3.7%)
Shockable	n=47	n=123
prehospital ROSC	20 (43%)	38 (31%)
Survival to discharge	6 (13%)	11 (9.2%)
Non-shockable	n=107	n=406
prehospital ROSC	31 (29.0%)	85 (20.9%)
Survival to discharge	2 (1.9%)	8 (2.0%)

Early administration of epinephrine improved rates of ROSC, but not survival to discharge

The time dependent association of adrenaline administration and survival from out-of-hospital cardiac arrest

Resuscitation, 2015

- US
- Retrospective analysis of Save Hearts in Arizona Registry and Education (SHARE) database
- Study period : 2005.1~2013.11
- Witnessed arrest (n=3,469)
  - Shockable (n=1,451), Non-shockable (n=2,018)



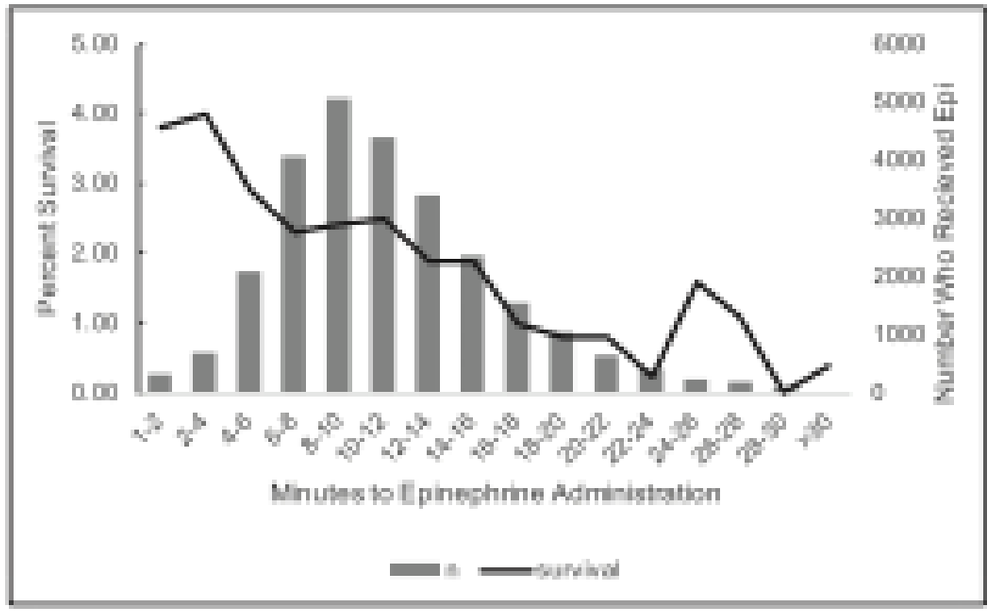
Early administration of epinephrine : associated with survival to discharge, but not with good neurological outcome

Time to Epinephrine Administration and Survival From Nonshockable Out-of-Hospital Cardiac Arrest Among Children and Adults

Circulation, 2018

- **North America**
- **Retrospective analysis of Resuscitation Outcome Consortium database**
- **Study period : 2011.6~2015.6**
- **Non-shockable OHCA (n=32,101)**
  - **epinephrine < 10min (n=12,238) vs. >10min (n=14,517) vs. no epinephrine (n=5,346)**

	Epi < 10min	Epi > 10min
Survival to discharge	2.6%	1.7%

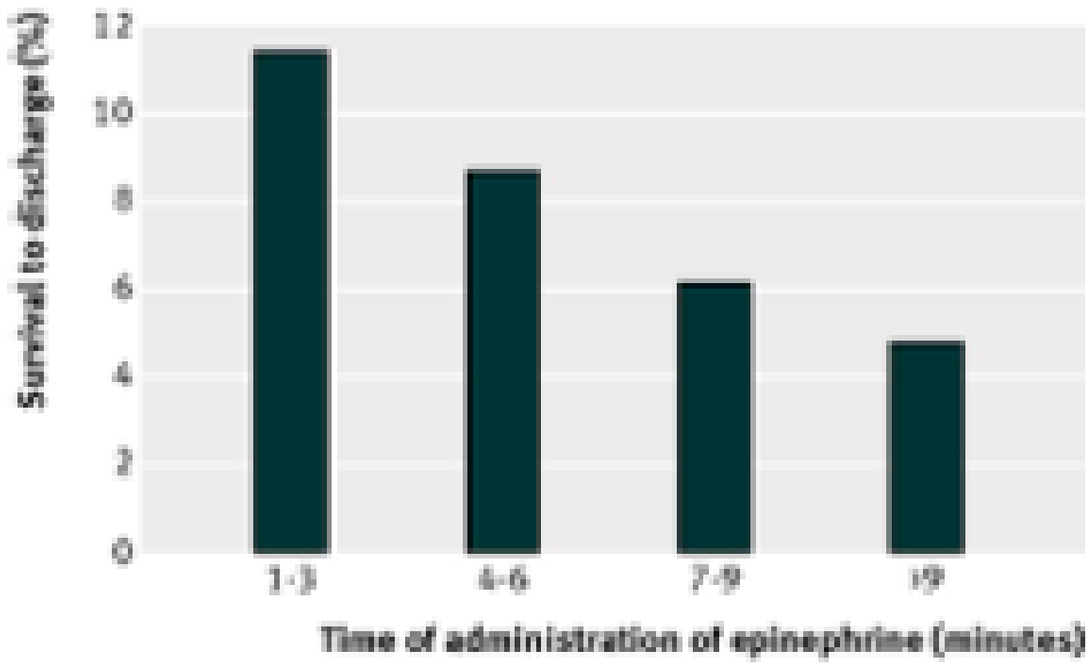


Delay in administration of epinephrine decreased survival to discharge in non-shockable OHCA patients

Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: retrospective analysis of large in-hospital data registry

BMJ, 2014

- **US**
- **Retrospective analysis of GWTG-R registry**
- **Study period : 2000.1~2009.11**
- **Non-shockable IHCA (n=25,095)**

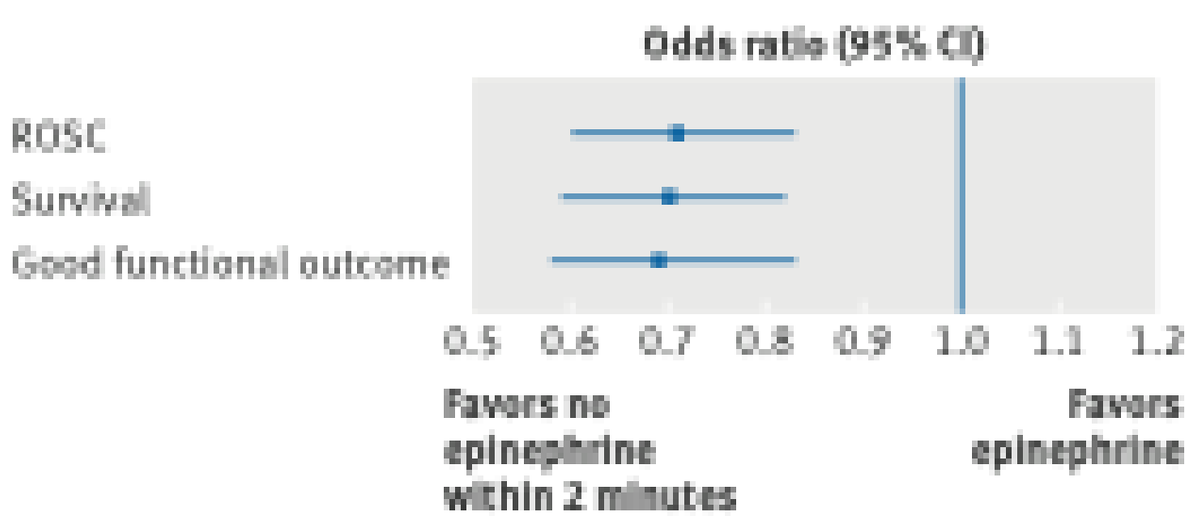


Earlier administration of epinephrine associated with better survival to discharge

Early administration of epinephrine in patients with cardiac arrest with initial shockable rhythm in hospital: propensity score matched analysis

BMJ, 2016

- US
- Retrospective analysis of GWTG-R registry
- Study period : 2006.1~2012.9
- shockable IHCA (n=2,974)
  - Epinephrine (n=1,510) vs No epinephrine (n=1,464) within 2 min after first defib.



Early administration of epinephrine : associated with decreased chance of good outcomes

Hospital Variation in Time to Epinephrine for Nonshockable In-Hospital Cardiac Arrest

Circulation, 2016

- US
- Retrospective analysis of GWTG-R registry
- Non-shockable IHCA
  - n=103,932 patients at 548 hospitals
- Epinephrine < 5min vs. >5 min (delayed)
  - Hospitals Stratified by rates of delayed administration of epinephrine

Table 3. Outcomes, by Quartiles of Delayed Epinephrine Use

Hospital Characteristics	Q1	Q2	Q3	Q4	*P* Value (trend)
Unadjusted hospital-level survival, median (%)					
To discharge (interquartile range)	12.0 (8.7–15.6)	11.3 (7.8–15.9)	11.6 (7.4–15.2)	8.1 (5.6–12.8)	<0.0001
With CPC 1 or 2	6.6 (3.0–10.0)	6.4 (3.2–8.9)	6.2 (3.2–9.7)	5.3 (0–7.8)	0.0026
Hospital risk-standardized survival, median (%)					
To discharge	12.9 (11.1–15.4)	12.3 (10.4–15.7)	12.4 (10.5–14.7)	10.8 (9.7–12.7)	<0.0001
With CPC 1 or 2	8.3 (5.1–12.0)	8.0 (5.2–11.0)	7.4 (4.9–11.1)	6.6 (5.0–8.6)	0.0032

CPC indicates cerebral performance category score; Q1–Q4, hospital quartiles for proportion of patients with delayed epinephrine use: Q1 (0%–9.5%), Q2 (9.5%–13.5%), Q3 (13.5%–19.0%), and Q4 (19.0%–53.8%).

Hospitals of high rates of delayed epinephrine administration had worse survival outcomes

Summary

Epinephrine

- ***Efficacy*** : good for heart, but not for brain
- ***Optimal dose*** : Standard dose > High dose
  - low dose : inconclusive
- ***Frequency*** : less frequent may be better
- ***Timing***
  - variable benefit
    - OHCA - early administration a/w increased survival to discharge
    - IHCA, shockable - early administration : not a/w good outcomes
    - IHCA, nonshockable - early administration : a/w good outcomes

- **First priority of CPR : *ROSC !***
  - **No valuable other option for increasing coronary perfusion pressure during closed chest compression**
- **Need research on other modality to improve neurological outcomes**