Epi-Phenomenon: The Most Practical Uses of Epinephrine in Resuscitation

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DISCLOSURE STATEMENT

- Board Member, MN Resuscitation Consortium
- Director of Operations, The MN Mobile ECMO Project

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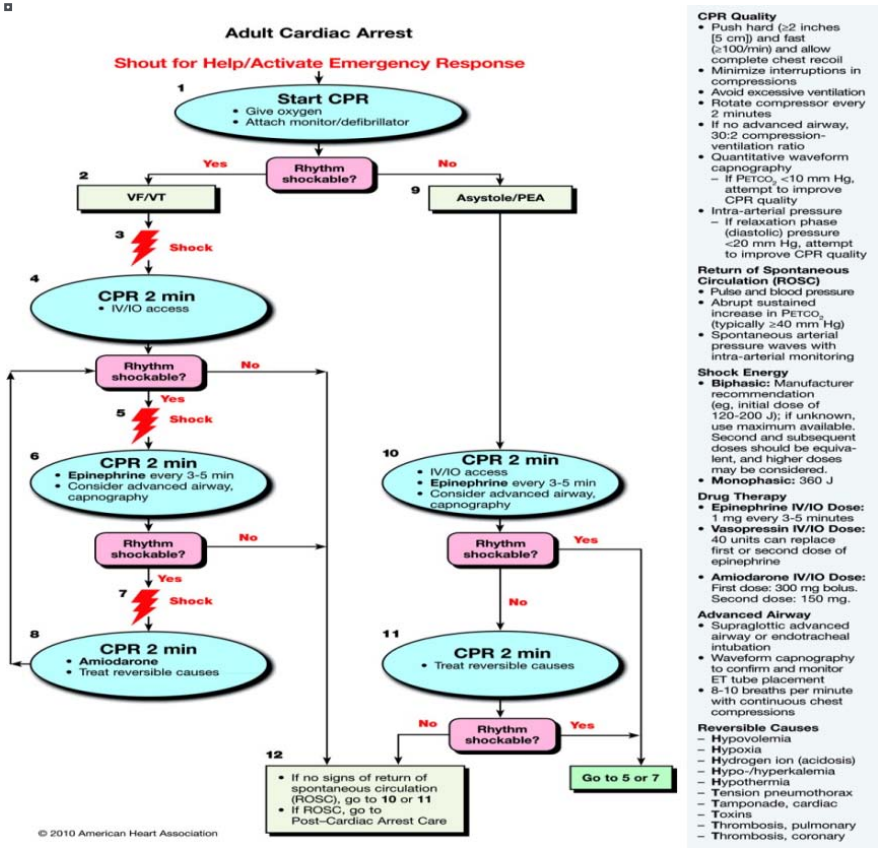
Epinephrine in the treatment of cardiac arrest

- Current AHA guidelines for VF/VT call for three defibrillations with IV/IO epinephrine every 3-5 minutes.
- Amiodarone is then given if unable to convert.
- ***Refractory VF exceeds the current AHA algorithm for VF/VT!!!***



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Epinephrine in the treatment of cardiac arrest

- **How about limiting or eliminating epinephrine?**
  - It has never been shown to improve survival to hospital discharge, and may actually decrease it.
  - Increases oxygen consumption.
  - Increases cerebral and myocardial vasoconstriction, so it impairs critical tissue oxygenation.
  - It is a dysrhythmic catecholamine, so it may actually make Refractory VF harder to break.

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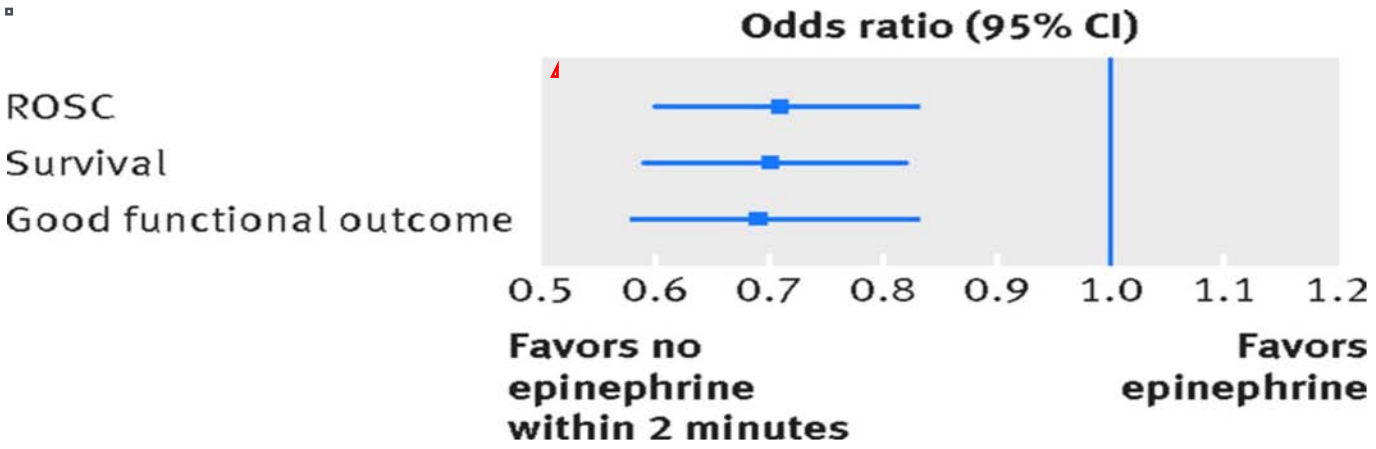
Current Pre-hospital/hospital treatments

Lars W Andersen et al: Early administration of epinephrine (adrenaline) in patients with cardiac arrest with initial shockable rhythm in hospital: propensity score matched analysis: BMJ 2016; 353



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Current Pre-hospital/hospital treatments

- Design: Prospective observational cohort study.
- Intervention: Epinephrine given within two minutes after the first defibrillation.
- Main outcome measures: Survival to hospital discharge. Secondary outcomes included return of spontaneous circulation and survival to hospital discharge with a good functional outcome.
- Results: 2978 patients were matched on the propensity score, and the groups were well balanced. 1510 (51%) patients received epinephrine within two minutes after the first defibrillation, which is contrary to current American Heart Association guidelines. Epinephrine given within the first two minutes after the first defibrillation was associated with decreased odds of survival in the propensity score matched analysis (odds ratio 0.70, 95% confidence interval 0.59 to 0.82; P<0.001). Early epinephrine administration was also associated with a decreased odds of return of spontaneous circulation (0.71, 0.60 to 0.83; P<0.001) and good functional outcome (0.69, 0.58 to 0.83; P<0.001).
- Conclusion: Half of patients with a persistent shockable rhythm received epinephrine within two minutes after the first defibrillation, contrary to current American Heart Association guidelines. The receipt of epinephrine within two minutes after the first defibrillation was associated with decreased odds of survival to hospital discharge as well as decreased odds of return of spontaneous circulation and survival to hospital discharge with a good functional outcome.

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Current Pre-hospital/hospital treatments PARAMEDIC2

- Results
- At 30 days, 130 patients (3.2%) in the epinephrine group and 94 (2.4%) in the placebo group were alive (unadjusted odds ratio for survival, 1.39; 95% confidence interval [CI], 1.06 to 1.82; P=0.02). There was no evidence of a significant difference in the proportion of patients who survived until hospital discharge with a favorable neurologic outcome (87 of 4007 patients [2.2%] vs. 74 of 3994 patients [1.9%]; unadjusted odds ratio, 1.18; 95% CI, 0.86 to 1.61). At the time of hospital discharge, severe neurologic impairment (a score of 4 or 5 on the modified Rankin scale) had occurred in more of the survivors in the epinephrine group than in the placebo group (39 of 126 patients [31.0%] vs. 16 of 90 patients [17.8%]).

Table 2. Intervals between Key Events and Initial Response to Resuscitation.*

Variable	Epinephrine (N=4015)	Placebo (N=3999)
Interval between emergency call and ambulance arrival at scene		
No. of patients in analysis	4015	3999
Median (IQR) — min†	6.7 (4.3–9.7)	6.6 (4.2–9.6)
Interval between emergency call and administration of trial agent		
No. of patients in analysis	3975	3949
Median (IQR) — min†	21.5 (16.0–27.3)	21.1 (16.1–27.4)
Interval between ambulance arrival at scene and departure		
No. of patients in analysis	2039	1226
Mean — min	50.1±21.8	44.5±18.3
Interval between ambulance departure from scene and hospital arrival		
No. of patients in analysis	2038	1225
Mean — min	12.9±9.8	12.4±8.9
Median interval between initiation of advanced life support and cessation (IQR) — min	47.5 (35.1–64.0)	43.1 (33.5–56.1)
Return of spontaneous circulation — no. (%)		
Yes	1457 (36.3)	468 (11.7)
No	2518 (62.7)	3492 (87.3)
Missing data	40 (1.0)	39 (1.0)
Transportation of patient to hospital — no. (%)		
Yes	2041 (50.8)	1227 (30.7)
No	1974 (49.2)	2772 (69.3)
Declaration of death by emergency department staff — no. (%)		
Yes	988 (24.6)	689 (17.2)
No	614 (15.3)	290 (7.3)
Not applicable because not transported	1974 (49.2)	2772 (69.3)
Missing data	439 (10.9)	248 (6.2)

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† Among cardiac arrests that were witnessed by paramedics, the interval between the emergency call and the cardiac event was considered to be 0 minutes.

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Current Pre-hospital/hospital treatments PARAMEDIC2

- Conclusions
- In adults with out-of-hospital cardiac arrest, the use of epinephrine resulted in a significantly higher rate of 30-day survival than the use of placebo, but there was no significant between-group difference in the rate of a favorable neurologic outcome because more survivors had severe neurologic impairment in the epinephrine group.

Table 3. Primary and Secondary Outcomes.*

Outcome	Epinephrine	Placebo	Odds Ratio (95% CI)†	
			Unadjusted	Adjusted
Primary outcome				
Survival at 30 days — no./total no. (%)‡	130/4012 (3.2)	94/3995 (2.4)	1.39 (1.06–1.82)	1.47 (1.09–1.97)
Secondary outcomes				
Survival until hospital admission — no./total no. (%)§	947/3973 (23.8)	319/3982 (8.0)	3.59 (3.14–4.12)	3.83 (3.30–4.43)
Median length of stay in ICU (IQR) — days				
Patients who survived	7.5 (3.0–15.0)	7.0 (3.5–12.5)	NA	NA
Patients who died¶	2.0 (1.0–5.0)	3.0 (1.0–5.0)	NA	NA
Median length of hospital stay (IQR)				
Patients who survived	21.0 (10.0–41.0)	20.0 (9.0–38.0)	NA	NA
Patients who died‖	0	0	NA	NA
Survival until hospital discharge — no./total no. (%)	128/4009 (3.2)	91/3995 (2.3)	1.41 (1.08–1.86)	1.48 (1.10–2.00)
Favorable neurologic outcome at hospital discharge — no./total no. (%)	87/4007 (2.2)	74/3994 (1.9)	1.18 (0.86–1.61)	1.19 (0.85–1.68)
Survival at 3 mo — no./total no. (%)	121/4009 (3.0)	86/3991 (2.2)	1.41 (1.07–1.87)	1.47 (1.08–2.00)
Favorable neurologic outcome at 3 mo — no./total no. (%)	82/3986 (2.1)	63/3979 (1.6)	1.31 (0.94–1.82)	1.39 (0.97–2.01)

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Epinephrine in the treatment of cardiac arrest

Clinical paper

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

Cameron A. Fisk [a], Michele Olsufka [b], Lihua Yin [c], Andrew M. McCoy [c], Andrew J. Latimer [c], Charles Maynard [d], Graham Nichol [e], Jonathan Larsen [f], Leonard A. Cobb [b], Michael R. Sayre [c, f]

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Conclusion:
Reducing the dose of epinephrine administered during out-of-hospital cardiac arrest was not associated with a change in survival to hospital discharge or favorable neurological outcomes after OHCA.

- 2255 patients with OHCA were eligible for analysis. Of these, 24.6% had an initially shockable rhythm.
- Total epinephrine dose per patient decreased from a mean ± standard deviation of 3.4 ± 2.3 mg–2.6 ± 1.9 mg ($p < 0.001$) in the shockable group and 3.5 ± 1.9 mg–2.8 ± 1.7 mg ($p < 0.001$) in the non-shockable group.
- Among those with a shockable rhythm, survival to hospital discharge was 35.0% in the higher dose group vs. 34.2% in the lower dose group.
- Among those with a non-shockable rhythm, survival was 4.2% in the higher dose group vs. 5.1% in the lower dose group.

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Epinephrine in the treatment of cardiac arrest

Source: Loomba RS, Nijhawan K, Aggarwal S, Arora RR. Increased return of spontaneous circulation at the expense of neurologic outcomes: Is prehospital epinephrine for out-of-hospital cardiac arrest really worth it? Journal of Critical Care. 2015;30:1376-1381.

Study Population: Total of 655,853 patients from 13 observational studies and one randomized, controlled trial (RCT) involving patients who experience out-of-hospital cardiac arrest.

Efficacy Endpoints: Pre-hospital ROSC, survival to hospital discharge, survival at one month

Harm Endpoints: Long-term neurological outcome, defined as Cerebral Performance Category (CPC) score of 1-2 (corresponding to independence in Activities of Daily Living)

In summary, we chose a color recommendation of "Red" for epinephrine administration in OHCA. There is no patient-centered benefit and probable harm due to increased survival with worse long-term neurological function.

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Epinephrine in the treatment of cardiac arrest

- So, is the King dead??!!

- The answer is;
  - **It depends.**

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Epinephrine in the treatment of cardiac arrest

BMJ. 2014; 348: g3028.
Published online 2014 May 20. doi: 10.1136/bmj.g3028
PMCID: PMC4027796
PMID: 24846323

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

Conclusions: In patients with non-shockable cardiac arrest in hospital, earlier administration of epinephrine is associated with a higher probability of return of spontaneous circulation, survival in hospital, and neurologically intact survival.

- Results 25,095 adults had in-hospital cardiac arrest with non-shockable rhythms **(55% asystole/45% PEA).** Median time to administration of the first dose of epinephrine was 3 minutes (interquartile range 1-5 minutes).
- There was a stepwise decrease in survival with increasing interval of time to epinephrine (analyzed by three minute intervals): adjusted odds ratio 1.0 for 1-3 minutes (reference group); 0.91 for 4-6 minutes; 0.74 for 7-9 minutes; and 0.63 for >9 minutes.
- A similar stepwise effect was observed across all outcome variables.

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Epinephrine in the treatment of cardiac arrest

- **PSEUDO-PEA**
  - Pseudo-PEA is essentially a severe shock state and is distinct from true electro-mechanical dissociation
- Pseudo-PEA can be detected in the absence of a palpable pulse by:
  - arterial line placement during cardiac arrest (identified by the presence of a blood pressure)
  - high ETCO2 readings in intubated patients
  - echocardiography or Doppler ultrasound demonstrating cardiac pulsatility
- In animal models asynchronous CPR during pseudo-PEA is harmful:
  - raised mean intrathoracic pressure due to chest compression can be expected to reduce rather than to increase cardiac filling

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Epinephrine in the treatment of cardiac arrest

- **Pseudo-PEA is associated with better outcomes than true EMD**
  - •Prosen et al, 2012
  - •in a small trial, ETCO2 and echocardiography were used to confirm pseudo-PEA
  - •These patients were administered vasopressin (an additional vasopressor) and had CPR ceased for 15 seconds
  - •94% of patients received ROSC and 50% had good neurological outcomes
- •Flato et al, 2015
  - •rates of ROSC were 70.4% for those in pseudo-EMD, 20.0% for those in EMD, and 23.5% for those in asystole
  - •Survival upon hospital discharge and after 180 days occurred only in patients in pseudo-EMD (22.2% and 14.8%, respectively)

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Epinephrine in the treatment of cardiac arrest

- **So when should we use epinephrine in cardiac arrest?**
  - As with everything else, timing may matter!
  - In shockable rhythms and especially in Refractory VF, we may actually be making matters worse.
  - Treatment of PEA (or Pseudo-EMD) may be the better choice for epinephrine!

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References

- **Limiting Epinephrine**
  - Tang W et al. Epinephrine increases the severity of postresuscitation myocardial dysfunction: Circulation. 1995;92(10):3089-3093.
  - Ristagno G et al. Epinephrine reduces cerebral perfusion during cardiopulmonary resuscitation: Crit Care Med. 2009;37(4):1408-1415.
  - Akihito Hagihara et al. Prehospital Epinephrine Use and Survival Among Patients With Out-of-Hospital Cardiac Arrest: JAMA. 2012;307(11):1161-1168. doi:10.1001/jama.2012.294
  - Lower Dose Epinephrine and Out-of-hospital Cardiac Arrest Outcomes: Cameron Fisk, BS https://doi.org/10.1016/j.resuscitation.2018.01.004
  - PARAMEDIC2 (July 18, 2018;DOI: 10.1056/NEJMoa1806842)

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