WORKSHEET for Evidence-Based Review of Science for Veterinary CPCR

1. Basic Demographics

Worksheet author(s)

Rosalind S. Chow	**Date Submitted for review:** 7/10/11

[redacted]

2. Clinical question:

In dogs and cats with cardiac arrest (P), does the use of any specific alternative dosing regimen for epinephrine (I) compared with standard recommendations (0.01 mg/kg IV q 3-5 minutes) (C), improve outcome (e.g. ROSC, survival to hospital discharge, survival with favorable neurologic outcome) (O)?

3. Conflict of interest specific to this question:

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet?
- No

4. Search strategy (including electronic databases searched):

4a. Databases

i) PUBMED (1977 to May 2011) (updated on June 5, 2011)

1. epinephrine (adrenaline)
   - adrenaline appears to be cross-referenced with epinephrine so separate searches using both terms were not performed
2. resuscitation
3. cardiopulmonary arrest
4. high-dose

1, 2 and 4: 71 relevant hits out of 147
1, 3 and 4: 8 additional relevant hits

ii) PubMed MeSH (Medical Subject Headings) Database - Search strategy limited to controlled subject key words used for indexing Pubmed citations.

1. Epinephrine
2. Dose-response relationship, drug
3. Heart arrest
4. Cardiopulmonary resuscitation

1 additional hit

iii) CAB (1910 to May 2011)

No additional hits

4b. Other sources

References of review articles identified from the above literature search were evaluated for relevance.

4c. State inclusion and exclusion criteria for choosing studies and list number of studies excluded per criterion

Inclusion criteria

Comparison of two or more doses of epinephrine in patients with cardiac arrest or cardiopulmonary arrest (defined as lack of spontaneous respiration and of a palpable pulse), including ventricular fibrillation studies. Patient outcome must be described (eg. overall survival, functional neurological survival). All types of studies may be considered (experimental, clinical, in-hospital and out-of-hospital arrest). For definition purposes, "low dose" is defined as a dose less than or equal to 0.02 mg/kg, or 1 mg per dose. "High dose" is defined as a dose greater than or equal to 0.1 mg/kg, or 5 mg per dose.

Exclusion criteria

Multi-drug or multi-intervention studies that do not allow determination of the efficacy of different doses of epinephrine in isolation. Abstracts only. Editorials. Review articles. Small case studies not in the target species. Hypoxia studies without cardiac arrest. Cardiac arrest studies that do not evaluate clinical outcome measures/end point as specified in the clinical question (ie studies that evaluate cerebral blood flow or hemodynamic effects, and do not report survival rate or other clinical outcome measures).

4d. Number of articles/sources meeting criteria for further review: 28

Relevant Studies in Target Species:
- 3 randomized experimental studies in dogs were identified: (Brunette et al. 1990; DeBehnke et al 1992; Perondi et al. 2004)
- 0 clinical studies in dogs were identified
- 0 relevant studies in cats was identified

Relevant Studies in Non-Target Species:
- 1 meta-analysis in humans was identified:
- 10 randomized trials in humans were identified:
- 5 non-randomized trials in humans were identified:
- 5 randomized experimental trials in non-target animal species were identified:
- 1 non-randomized experimental trials in non-target animal species were identified:
- 0 randomized clinical trials in non-target animal species were identified.

5. Summary of evidence

Evidence Supporting Clinical Question (High-dose better)

Good						
Fair						
Poor						*Goetting, 1991 ACE*
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint

B = Survival of event D = Intact neurological survival *Italics = Non-target species studies*

Evidence Neutral to Clinical question (equivocal)

Good			Brunette, 1990 AE DeBehnke, 1992 AB Roberts, 1990 BE			*Berg, 1996 ABDE* *Berg, 1994 ABDE* *Brown, 1992 ABCD* *Callaham, 1992 ABCD* *Chen, 2010 AE* *Choux , 1995 ABDE* *Gueugniaud, 1998 ACDE* *Jeung, 2011 ADE* *Lindner, 1991 AC* *Lipman, 1993 ACE* *Patterson, 2005 ACDE* *Sherman, 1997 ABCD* *Stiell, 1992BCD* *Vandycke, 2000 ACD*
Fair						*Callaham, 1991 CDE* *Carpenter, 1997 ABCDE* *Woodhouse, 1995 AC*
Poor						*Carvolth, 1996 ABC* *Dieckmann, 1995 ACDE*
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Non-target species studies

Evidence Opposing Clinical Question (High dose worse)

Good						*Neumar, 1995* ABD *Perondi, 2004* ABCD
Fair						*McCaul, 2006* AB
Poor						*Guay, 2004* AB
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = *Non-target species studies*

6. REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

When administered during cardiac arrest, epinephrine improves myocardial and cerebral perfusion predominantly through its stimulatory action on alpha-adrenergic receptors (Roberts, 1990). In the late 1980's and early 1990's, a number of human case studies (Goettig 1989; Barton 1991) and experiments in animal models suggested a potential benefit to administration of higher than standard doses of epinephrine. Many prospective, randomized clinical trials were subsequently performed to determine whether high-dose epinephrine produced a better clinical outcome, as determined by resuscitation rates, neurological outcome, and short and long term survival, compared to standard doses of epinephrine. Most studies considered a dose equal to or less than 1 mg or 0.02 mg/kg to represent a "standard" dose, compared to a "high" dose of epinephrine of greater than or equal to 5 mg or 0.1 mg/kg.

Of these studies, only three small randomized, controlled experimental trials were performed in dogs (Brunette 1990; DeBehnke 1992; Roberts 1990. Each compared the standard dose to a high dose of epinephrine during CPR. None reported a survival benefit with high-dose epinephrine.

In humans, although a few studies have found no significant difference in outcome measures between standard and high-dose epinephrine during cardiopulmonary resuscitation, the majority of prospective, controlled clinical trials and one meta-analysis (Vandycke 2000) on the subject have reported improvements in resuscitation time, rate of ROSC and rate of hospital admission with out-of-hospital cardiac arrest following epinephrine doses of 0.1 mg/kg or greater. However, despite these early benefits, no change in 24-hour survival or rates of discharge from hospital have been seen (Gueugniaud 1998; Lindner 1991; Neumar 1995; Stiell 1992) due to a trend toward higher in-hospital mortality rate in the high-dose group. Several reasons have been advanced to explain this discrepancy, including a greater tendency for high-dose epinephrine to lead to tachycardia, sustained ventricular arrhythmias, more severe metabolic acidosis (attributed to vasoconstriction) (Neumar 1995; Jeung 2011), and hyperglycemia (Jeung 2011) in the post-arrest period. These factors may increase patient mortality by increasing myocardial oxygen demand in the presence of unchanged oxygen supply (Roberts 1990), thus opposing any beneficial effects epinephrine may have on resuscitation rates. If so, there is a potential ethical concern that although more patients may be successfully resuscitated with high-dose epinephrine in the short term, they may lack sufficient functional neurological recovery or longevity to survive to hospital discharge (Brown 1992). This may contribute to the emotional toll on families, as well as increase the diversion of medical resources toward patients that ultimately will fail to survive.

In humans, three studies reported reduced survival rates with high doses of epinephrine (McCaul, Neumar 1995, Perondi 2004). Only one study in favor of high-dose epinephrine over standard-dose epinephrine was found (Goettig 1991), and in this case, high-dose epinephrine proved to be beneficial when it was administered as a third dose after two unsuccessful standard doses had failed to achieve ROSC.

7. Conclusion

In summary, there is insufficient evidence to justify a change in the standard dose of epinephrine administered to veterinary patients during cardiopulmonary arrest. High-dose epinephrine may have a neutral effect or mildly beneficial effect on ROSC, but results in exaggerated adrenergic effects that can subsequently cause patient harm. There were few clinical studies in dogs (and none in cats) investigating the effect of variable doses of epinephrine in cardiopulmonary and cardiac arrest, and it is not known whether the findings from human studies can be directly applied to veterinary patients. Prospective, randomized clinical trials in small animal patients are needed.

8. Acknowledgement

The author extends her appreciation to Dr. Rush and Dr. Rozanski for their assistance.

9. Citation list

1: Berg RA, Otto CW, Kern KB, Hilwig RW, Sanders AB, Henry CP, Ewy GA. A randomized, blinded trial of high-dose epinephrine versus standard-dose epinephrine in a swine model of pediatric asphyxial cardiac arrest. Crit Care Med. 1996 Oct;24(10):1695-700. PubMed PMID: 8874308.

2: Berg RA, Otto CW, Kern KB, Sanders AB, Hilwig RW, Hansen KK, Ewy GA. High-dose epinephrine results in greater early mortality after resuscitation from prolonged cardiac arrest in pigs: a prospective, randomized study. Crit Care Med. 1994 Feb;22(2):282-90. PubMed PMID: 8306688.

3: Brown CG, Martin DR, Pepe PE, Stueven H, Cummins RO, Gonzalez E, Jastremski M. A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital. The Multicenter High-Dose Epinephrine Study Group. N Engl J Med. 1992 Oct 8;327(15):1051-5. PubMed PMID: 1522841.

4: Brunette DD, Jameson SJ. Comparison of standard versus high-dose epinephrine in the resuscitation of cardiac arrest in dogs. Ann Emerg Med. 1990 Jan;19(1):8-11. PubMed PMID: 2297160.

5: Callaham M, Barton CW, Kayser S. Potential complications of high-dose epinephrine therapy in patients resuscitated from cardiac arrest. JAMA. 1991 Mar 6;265(9):1117-22. PubMed PMID: 1995996.

6: Callaham M, Madsen CD, Barton CW, Saunders CE, Pointer J. A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest. JAMA. 1992 Nov 18;268(19):2667-72. PubMed PMID: 1433686.

7: Carpenter TC, Stenmark KR. High-dose epinephrine is not superior to standard-dose epinephrine in pediatric in-hospital cardiopulmonary arrest. Pediatrics. 1997 Mar;99(3):403-8. PubMed PMID: 9041296.

8: Carvolth RD, Hamilton AJ. Comparison of high-dose epinephrine versus standard-dose epinephrine in adult cardiac arrest in the prehospital setting. 1996 Jul-Sep;11(3):219-22. PubMed PMID: 10163386.

9: Chen MH, Lu JY, Xie L, Zheng JH, Song FQ. What is the optimal dose of

epinephrine during cardiopulmonary resuscitation in a rat model? Am J Emerg Med. 2010 Mar;28(3):284-90. Epub 2010 Jan 28. PubMed PMID: 20223384.

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11: DeBehnke DJ, Angelos MG, Leasure JE. Use of cardiopulmonary bypass, high-dose epinephrine, and standard-dose epinephrine in resuscitation from post-countershock electromechanical dissociation. Ann Emerg Med. 1992 Sep;21(9):1051-7. PubMed PMID: 1514715.

12: Dieckmann RA, Vardis R. High-dose epinephrine in pediatric out-of-hospital cardiopulmonary arrest. Pediatrics. 1995 Jun;95(6):901-13. PubMed PMID: 7761219.

13: Goetting MG, Paradis NA. High-dose epinephrine improves outcome from pediatric cardiac arrest. Ann Emerg Med. 1991 Jan;20(1):22-6. PubMed PMID: 1984722.

14: Guay J, Lortie L. An evaluation of pediatric in-hospital advanced life support interventions using the pediatric Utstein guidelines: a review of 203 cardiorespiratory arrests. Can J Anaesth. 2004 Apr;51(4):373-8. PubMed PMID: 15064267.

15: Gueugniaud PY, Mols P, Goldstein P, Pham E, Dubien PY, Deweerdt C, Vergnion M, Petit P, Carli P. A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. European Epinephrine Study Group. N Engl J Med. 1998 Nov 26;339(22):1595-601. PubMed PMID: 9828247.

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17: Lindner KH, Ahnefeld FW, Prengel AW. Comparison of standard and high-dose adrenaline in the resuscitation of asystole and electromechanical dissociation. Acta Anaesthesiol Scand. 1991 Apr;35(3):253-6. PubMed PMID: 2038933.

18: McCaul CL, McNamara PJ, Engelberts D, Wilson GJ, Romaschin A, Redington AN, Kavanagh BP. Epinephrine increases mortality after brief asphyxial cardiac arrest in an in vivo rat model. Anesth Analg. 2006 Feb;102(2):542-8. PubMed PMID: 16428558.

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20: Patterson MD, Boenning DA, Klein BL, Fuchs S, Smith KM, Hegenbarth MA, Carlson DW, Krug SE, Harris EM. The use of high-dose epinephrine for patients with out-of-hospital cardiopulmonary arrest refractory to prehospital interventions. Pediatr Emerg Care. 2005 Apr;21(4):227-37. PubMed PMID: 15824681.

21: Perondi MB, Reis AG, Paiva EF, Nadkarni VM, Berg RA. A comparison of high-dose and standard-dose epinephrine in children with cardiac arrest. N Engl J Med. 2004 Apr 22;350(17):1722-30. PubMed PMID: 15102998.

22: Roberts D, Landolfo K, Dobson K, Light RB. The effects of methoxamine and epinephrine on survival and regional distribution of cardiac output in dogs with prolonged ventricular fibrillation. Chest. 1990 Oct;98(4):999-1005. PubMed PMID: 2209164.

23: Stiell IG, Hebert PC, Weitzman BN, Wells GA, Raman S, Stark RM, Higginson LA, Ahuja J, Dickinson GE. High-dose epinephrine in adult cardiac arrest. N Engl J Med. 1992 Oct 8;327(15):1045-50. PubMed PMID: 1522840.

24: Vandycke C, Martens P. High dose versus standard dose epinephrine in cardiac arrest - a meta-analysis. Resuscitation. 2000 Aug 1;45(3):161-6. PubMed PMID: 10959014.

25: Woodhouse SP, Cox S, Boyd P, Case C, Weber M. High dose and standard dose adrenaline do not alter survival, compared with placebo, in cardiac arrest. Resuscitation. 1995 Dec;30(3):243-9. PubMed PMID: 8867714.

Citation List with Abstracts:

1. Crit Care Med. 1996 Oct;24(10):1695-700.

A randomized, blinded trial of high-dose epinephrine versus standard-dose epinephrine in a swine model of pediatric asphyxial cardiac arrest.

Berg RA, Otto CW, Kern KB, Hilwig RW, Sanders AB, Henry CP, Ewy GA.

Department of Pediatrics, Steele Memorial Children's Research Center, Tucson, AZ, USA.

OBJECTIVE: To determine whether high-dose epinephrine administration during cardiopulmonary resuscitation (CPR) in a swine pediatric asphyxial cardiac arrest model improves outcome (i.e., resuscitation rate, survival rate, and neurologic function) compared with standard-dose epinephrine.
DESIGN: A randomized, blinded study.
SETTING: A large animal cardiovascular laboratory at a university.
SUBJECTS: Thirty domestic piglets (3 to 4 months of age) were randomized to receive standard-dose epinephrine (0.02 mg/kg) or high-dose epinephrine (0.2 mg/kg) during CPR after 10 mins of cardiac standstill with loss of aortic pulsation after endotracheal tube clamping.
INTERVENTIONS: Two minutes of CPR were provided, followed by advanced pediatric life support. Successfully resuscitated animals were supported in an intensive care unit (ICU) setting for 2 hrs and then observed for 24 hrs.
MEASUREMENTS AND MAIN RESULTS: Electrocardiogram, thoracic aortic blood pressure, and right atrial blood pressure were monitored continuously until the intensive care period ended. Survival rate and neurologic outcome were determined. Return of spontaneous circulation was obtained in 13 of 15 high-dose epinephrine piglets vs. ten of 15 standard-dose epinephrine piglets ($p < .20$). Four of 13 high-dose piglets died in the ICU period after initial resuscitation vs. 0 of ten standard-dose piglets ($p < \text{or} = .05$). Nine high-dose piglets survived 2 hrs vs. ten standard-dose piglets. Three piglets in each group survived for 24 hrs, but all were severely neurologically impaired. Two minutes after resuscitation, piglets treated with high-dose epinephrine had higher heart rates (210 +/- 24 vs. 189 +/- 40 beats/min, $p < .05$) and higher aortic diastolic pressures (121 +/- 39 vs. 74 +/- 40 mm Hg, $p < .01$). Within 10 mins of return of spontaneous circulation, severe tachycardia (> 240 beats/min) was more frequently noted in the high-dose group than in the standard-dose group ($p < .05$). All four high-dose piglets that died in the ICU period experienced ventricular fibrillation within 10 mins of return of spontaneous circulation.
CONCLUSIONS: High-dose epinephrine did not improve 2-hr survival rate, 24-hr survival rate, or neurologic outcome. High-dose epinephrine resulted in severe tachycardia and hypertension immediately after resuscitation and in a higher mortality rate immediately after resuscitation.

PMID: 8874308 [PubMed - indexed for MEDLINE]

2. Crit Care Med. 1994 Feb;22(2):282-90.

High-dose epinephrine results in greater early mortality after resuscitation from prolonged cardiac arrest in pigs: a prospective, randomized study.

Berg RA, Otto CW, Kern KB, Sanders AB, Hilwig RW, Hansen KK, Ewy GA.

Department of Pediatrics, University of Arizona College of Medicine, Tucson.

Comment in
Crit Care Med. 1994 Feb;22(2):194-5.

OBJECTIVE: To determine whether high-dose epinephrine (0.2 mg/kg) during cardiopulmonary resuscitation (CPR) results in improved outcome, compared with standard-dose epinephrine (0.02 mg/kg).
DESIGN: A prospective, randomized, blinded study.
SETTING: Research laboratory of a university medical center.
SUBJECTS AND INTERVENTIONS: Thirty domestic swine were randomized to receive standard- or high-dose epinephrine during CPR after 15 mins of fibrillatory cardiac arrest. Three minutes of CPR were provided, followed by advanced cardiac life support per American Heart Association guidelines. Animals that were successfully resuscitated were supported for 2 hrs in an intensive care unit (ICU) setting, and then observed for 24 hrs.
MEASUREMENTS AND MAIN RESULTS: Electrocardiogram, aortic blood pressure, right atrial blood pressure, and end-tidal CO2 were monitored continuously until the intensive care period ended. Survival and neurologic outcome were determined. Return of spontaneous circulation was attained in 14 of 15 animals in each group. Four of 14 high-dose epinephrine pigs died during the ICU period after return of spontaneous circulation vs. zero of the 14 standard-dose pigs ($p < .05$). Six standard-dose pigs survived 24 hrs vs. four high-dose pigs. Twenty-four-hour survival rate and neurologic outcome were not significantly different. Within 10 mins of defibrillation, severe hypertension (diastolic pressure > 120 mmHg) occurred in 12 of 14 high-dose pigs vs. two of 14 standard-dose pigs ($p < .01$). Severe tachycardia (heart rate > 250 beats/min) occurred in seven of 14 high-dose pigs vs. zero of 14 standard-dose pigs ($p < .01$). All four high-dose epinephrine pigs that died during the ICU period experienced both severe hypertension and tachycardia immediately postresuscitation.
CONCLUSIONS: High-dose epinephrine did not improve 24-hr survival rate or neurologic outcome. Immediately after return of spontaneous circulation, most animals in the high-dose epinephrine group exhibited a hyperadrenergic state that included severe hypertension and tachycardia. High-dose epinephrine resulted in a greater early mortality rate.

PMID: 8306688 [PubMed - indexed for MEDLINE]

3. N Engl J Med. 1992 Oct 8;327(15):1051-5.

A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital. The Multicenter High-Dose Epinephrine Study Group.

Brown CG, Martin DR, Pepe PE, Stueven H, Cummins RO, Gonzalez E, Jastremski M.

Department of Emergency Medicine, Ohio State University, Columbus 43210.

Comment in
N Engl J Med. 1993 Mar 11;328(10):735; author reply 735-6.

BACKGROUND: Experimental and uncontrolled clinical evidence suggests that intravenous epinephrine in doses higher than currently recommended may improve outcome after cardiac arrest. We conducted a prospective, multicenter study comparing standard-dose epinephrine with high-dose epinephrine in the management of cardiac arrest outside the hospital.
METHODS: Adult patients were enrolled in the study if they remained in ventricular fibrillation, or if they had asystole or electromechanical dissociation, at the time the first drug was to be administered to treat the cardiac arrest. Patients were randomly assigned to receive either 0.02 mg of epinephrine per kilogram of body weight (standard-dose group, 632 patients) or 0.2 mg per kilogram (high-dose group, 648 patients), both given intravenously.
RESULTS: In the standard-dose group 190 patients (30 percent) had a return of spontaneous circulation, as compared with 217 patients (33 percent) in the high-dose group; 136 patients (22 percent) in the standard-dose group and 145 patients (22 percent) in the high-dose group survived to be admitted to the hospital. Twenty-six patients (4 percent) in the standard-dose group and 31 (5 percent) in the high-dose group survived to discharge from the hospital. Ninety-two percent of the patients discharged in the standard-dose group and 94 percent in the high-dose group were conscious at the time of hospital discharge. None of the differences in outcome between the groups were statistically significant.
CONCLUSIONS: In this study, we were unable to demonstrate any difference in the overall rate of return of spontaneous circulation, survival to hospital admission, survival to hospital discharge, or neurologic outcome between patients treated with a standard dose of epinephrine and those treated with a high dose.

PMID: 1522841 [PubMed - indexed for MEDLINE]

4. Ann Emerg Med. 1990 Jan;19(1):8-11.

Comparison of standard versus high-dose epinephrine in the resuscitation of cardiac arrest in dogs.

Brunette DD, Jameson SJ.

Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, Minnesota 55415.

A prospective, randomized, blinded study was conducted to evaluate the efficacy of standard compared with high-dose epinephrine in cardiac arrest in dogs. Twenty-five mongrel dogs were anesthetized and monitored by central venous catheter, intra-arterial catheter, and ECG. A left lateral thoracotomy was performed, and the proximal left anterior descending artery was ligated. After ten minutes of myocardial ischemia, ventricular fibrillation was obtained by application of 6-V AC. Mechanical ventilation was stopped. Total arrest time was ten minutes. All animals were randomized into one of five resuscitation protocols; each protocol was identical except for the dose and route of epinephrine administration. Group 1 animals comprised the control group and received normal saline. Group 2 and 3 animals received epinephrine in doses of 0.014 mg/kg by central venous and intracardiac injection, respectively. Group 4 and 5 animals received epinephrine in doses of 0.071 mg/kg by central venous and intracardiac injection, respectively. None of the dogs receiving normal saline had a return of spontaneous circulation, defined as a spontaneous systolic blood pressure of more than 50 mm Hg. Nine of the ten animals from groups 2 and 3 and all of the ten animals from groups 4 and 5 had a return of spontaneous circulation. However, animals receiving the standard dose of epinephrine had a significantly longer resuscitation time compared with the high-dose group (P = .05) and required more doses of epinephrine for successful resuscitation than did animals receiving high doses (P less than .02).(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 2297160 [PubMed - indexed for MEDLINE]

5. JAMA. 1991 Mar 6;265(9):1117-22.

Potential complications of high-dose epinephrine therapy in patients resuscitated from cardiac arrest.

Callaham M, Barton CW, Kayser S.

Department of Medicine, University of California, San Francisco.

Comment in
JAMA. 1991 Mar 6;265(9):1160-1.
JAMA. 1991 Aug 7;266(5):656-7.

Adults resuscitated from nontraumatic cardiac arrest who received intravenous epinephrine in doses chosen by the treating physician and who survived at least 6 hours were studied to determine if high-dose epinephrine produced more complications than standard-dose. A total of 68 patients were enrolled and evaluated for postresuscitation complications attributable to epinephrine, using a two-tailed t test, and contingency analysis. The 33 patients receiving

high-dose epinephrine and 35 patients receiving standard-dose epinephrine were similar in demographics and variables known to affect outcome. There was no difference in potential complications between groups except serum calcium, which was 1.97 mmol/L (SD, 0.20) in the high-dose epinephrine group and 2.10 (SD, 0.20) in the standard-dose group. Hospital discharge rates (18% in the high-dose vs 30% in the standard-dose group) and neurological status on discharge were not significantly different. High-dose epinephrine did not produce increased direct complications in this cardiac arrest population compared with standard-dose epinephrine.

PMID: 1995996 [PubMed - indexed for MEDLINE]

6. JAMA. 1992 Nov 18;268(19):2667-72.

A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest.

Callaham M, Madsen CD, Barton CW, Saunders CE, Pointer J.

Division of Emergency Medicine, University of California, San Francisco.

Comment in
JAMA. 1993 Mar 17;269(11):1383; author reply 1383-4.
JAMA. 1993 Mar 17;269(11):1383.

OBJECTIVE: To determine the relative efficacy of high- vs standard-dose catecholamines in initial treatment of prehospital cardiac arrest.
DESIGN: Randomized, prospective, double-blind clinical trial.
SETTING: Prehospital emergency medical system of a major US city.
PATIENTS: All adults in nontraumatic cardiac arrest, treated by paramedics, who would receive epinephrine according to American Heart Association advanced cardiac life support guidelines.
INTERVENTIONS: High-dose epinephrine (HDE, 15 mg), high-dose norepinephrine bitartrate (NE, 11 mg), or standard-dose epinephrine (SDE, 1 mg) was blindly substituted for advanced cardiac life support doses of epinephrine.
MAIN OUTCOME MEASURES: Restoration of spontaneous circulation in the field, admission to hospital, hospital discharge, and Cerebral Performance Category score.
RESULTS: Of 2694 patients with cardiac arrests during the study period, resuscitation was attempted on 1062 patients. Of this total, 816 patients met study criteria and were enrolled. In the entire cardiac arrest population, 63% of the survivors were among the 11% of patients who were defibrillated by first responders. The three drug treatment groups were similar for all independent variables. Thirteen percent of patients receiving HDE regained a pulse in the field vs 8% of those receiving SDE (P = .01), and 18% of HDE patients were admitted to the hospital vs 10% of SDE patients who were admitted to the hospital

(P = .02). Similar trends for NE were not significant. There were 18 survivors; 1.7% of HDE patients and 2.6% of NE patients were discharged from the hospital compared with 1.2% of SDE patients, but this was not significant (P = .37; beta = .38). There was a nonsignificant trend for Cerebral Performance Category scores to be worse for HDE (3.2) and NE patients (3.7) than for SDE patients (2.3) (P = .10; beta = .31). No significant complications were identified. High-dose epinephrine did not produce longer hospital or critical care unit stays.
CONCLUSIONS: High-dose epinephrine significantly improves the rate of return of spontaneous circulation and hospital admission in patients who are in prehospital cardiac arrest without increasing complications. However, the increase in hospital discharge rate is not statistically significant, and no significant trend could be determined for neurological outcome. No benefit of NE compared with HDE was identified. Further study is needed to determine the optimal role of epinephrine in prehospital cardiac arrest.

PMID: 1433686 [PubMed - indexed for MEDLINE]

7. Pediatrics. 1997 Mar;99(3):403-8.

High-dose epinephrine is not superior to standard-dose epinephrine in pediatric in-hospital cardiopulmonary arrest.

Carpenter TC, Stenmark KR.

Department of Pediatrics, University of Colorado Health Sciences Center, Denver 80262, USA.

OBJECTIVE: To compare the efficacy of high-dose epinephrine (HDE) with that of standard-dose epinephrine (SDE) for resuscitation from in-hospital pediatric cardiopulmonary arrest (CPA).
DESIGN: Fifty-four-month retrospective study of all pediatric patients who had a CPA while hospitalized at a tertiary care children's hospital. Standard pediatric advanced life support techniques were used for all patients. Patients received HDE or SDE in accordance with physician orders and standard protocols at the time of CPA. Primary outcome measures were the return of spontaneous circulation (ROSC), the duration of survival after resuscitation, survival to hospital discharge, and Pediatric Overall Performance Category scores at the time of discharge.
RESULTS: During the study period, 51 patients met entry criteria and had a total of 58 CPAs. Twenty-one patients received HDE during resuscitation from 24 arrests, at a dose of 0.12 +/- 0.05 mg/kg (mean +/- SD); 30 patients received SDE during resuscitation from 34 arrests, at a dose of 0.01 +/- 0.01 mg/kg (mean +/- SD). The HDE and SDE groups were not significantly different in terms of gender, initial cardiac rhythm, location of CPA, primary diagnoses at the time of CPA, initial pH, or additional resuscitation medications received; the SDE group had a significantly higher mean age, although the median ages were not different.

Fourteen of 24 resuscitations using HDE resulted in ROSC (58%) with a mean time to ROSC of 19 minutes; 7 (29%) of 24 led to survival for 24 hours, and 6 (26%) of 23 patients survived to hospital discharge, all with moderate to severe neurologic and functional impairment. Twenty-four of 34 resuscitations using SDE resulted in ROSC (71%) with a mean time to ROSC of 12 minutes; 17 (50%) of 34 led to survival for 24 hours; and 7 (23%) of 30 patients survived to hospital discharge, 4 with mild to moderate neurologic impairment. No significant differences in rates of ROSC, survival rates, or Pediatric Overall Performance Category scores of survivors were found between the two groups. The mean time to ROSC was significantly longer in the HDE group.
CONCLUSIONS: In this study, the use of HDE did not improve the rates of ROSC, short-term survival, or long-term survival after pediatric in-hospital CPA, nor did it improve overall outcome scores. Given the conflicting evidence surrounding possible detrimental effects of HDE use, a large, blinded, prospective trial of HDE use in this setting is necessary to clarify the appropriate role for HDE in pediatric resuscitation.

PMID: 9041296 [PubMed - indexed for MEDLINE]

8. Prehosp Disaster Med. 1996 Jul-Sep;11(3):219-22.

Comparison of high-dose epinephrine versus standard-dose epinephrine in adult cardiac arrest in the prehospital setting.

Carvolth RD, Hamilton AJ

Department of Health and Human Services, Emergency Medical Services Office, County of Marin, San Rafael, California, USA.

OBJECTIVE:
To compare the efficacy of high-dose epinephrine (HDE) with standard-dose epinephrine (SDE) in the management of cardiac arrest in adults in the prehospital setting.

HYPOTHESIS:
The use of HDE will improve the outcome of adult patients in cardiac arrest.

METHODS:
In a general population of 700,000 persons, in a mixed geographical area of 2,200 square miles, a 12-month retrospective study of SDE and a 12-month prospective trial of HDE were conducted involving adult patients in cardiac arrest in the prehospital setting. Treatment was provided by paramedic-level clinicians. In the control group, patients were treated according to existing American Heart Association cardiac resuscitation guidelines using SDE (defined as 1.0 mg boluses to a maximum dose of 4 mg). In the test group, the same guidelines were revised to use HDE (defined as a rapid sequence of 5, 10, and 15 mg boluses to a total dose of 30 mg).

RESULTS:
The control group included 594 patients; the test group consisted of 580 patients. The overall survival rate to hospital admission in the control group was 14.5% (84 patients) and in the test group 15.3% (89 patients). The survival rate to hospital discharge in the control group was 4.9% (29 patients) versus 4.8% (28 patients) in the

test group. For patients whose initial rhythms were ventricular fibrillation, survival to admission in the control group was 20.4% (39 patients) versus 24.4% (43 patients) in the test group. Survival to discharge for patients with ventricular fibrillation in the control group was 8.9% (17 patients) versus 10.8% (19 patients) in the test group.

CONCLUSION:
There was no statistically significant difference in overall rate of survival to hospital admission or discharge between patients treated with SDE and those treated with HDE, regardless of the initial rhythm.

PMID:10163386

9. Am J Emerg Med. 2010 Mar;28(3):284-90. Epub 2010 Jan 28.

What is the optimal dose of epinephrine during cardiopulmonary resuscitation in a rat model?

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OBJECTIVE: Because different species may require different doses of drug to produce the same physiologic response, we were provoked to evaluate the dose-response of epinephrine during cardiopulmonary resuscitation (CPR) and identify what is the optimal dose of epinephrine in a rat cardiac arrest model.
METHODS: Rat cardiac arrest was induced via asphyxia, and then the effects of different doses of epinephrine (0.04, 0.2, and 0.4 mg/kg IV, respectively) and saline on the outcome of CPR were compared (n = 10/each group). The primary outcome measure was restoration of spontaneous circulation (ROSC), and the secondary was the change of spontaneous respiration and hemodynamics after ROSC.
RESULTS: Rates of ROSC were 9 of 10, 8 of 10, 7 of 10, and 1 of 10 in the low-dose, medium-dose, and high-dose epinephrine groups and saline group, respectively. The rates of withdrawal from the ventilator within 60 minutes in the low-dose (7 of 9) and medium-dose epinephrine groups (7 of 8) were higher than in the high-dose epinephrine group (1 of 7, $P < .05$). Mean arterial pressures were comparable, but the heart rate in the high-dose epinephrine group was the lowest among epinephrine groups after ROSC. These differences in part of time points reached statistical significance ($P < .05$).
CONCLUSION: Different doses of epinephrine produced the similar rate of ROSC, but high-dose epinephrine inhibited the recovery of spontaneous ventilation and caused relative bradycardia after CPR in an asphyxial rat model. Therefore, low and medium doses of epinephrine were more optimal for CPR in a rat asphyxial cardiac arrest model.

PMID: 20223384 [PubMed - indexed for MEDLINE]

10. Resuscitation. 1995 Feb;29(1):3-9.

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

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Among all of the cathecolamines used for cardiac arrest treatment, epinephrine injection during cardio-pulmonary resuscitation is currently the most powerful means of enhancing effectiveness; however, deliberations about the optimal dosage have recently become intense. In the SAMU of Lyon (F), we conducted a double blind prospective randomized study over an 18-month period, comparing repeated standard-dose epinephrine (1 mg) and repeated high-dose epinephrine (5 mg) in the management of cardiac arrest outside the hospital. Five-hundred thirty-six patients were enrolled with 265 in the standard-dose group and 271 in the high-dose group; both groups are globally similar. One-hundred eighty-one (33.8%) patients returned to spontaneous circulation (R.O.S.C.); 85 in the standard-dose group (32%) and 96 in the high-dose group (35.5%). One-hundred nineteen patients (22.2%) were admitted; 54 in the standard-dose group (20.4%) and 65 in the high-dose group (24%). At 6 months nine patients (7.6%) were alive; three patients from the standard-dose group (5.5%) and six from the high-dose group (9.2%). We never noticed cardiac or neurologic adverse effects with the high doses. The results of this study are not statistically significant, but we observed a marginal trend towards repeated 5 mg epinephrine doses. A large French multicentre study is now necessary.

PMID: 7784720 [PubMed - indexed for MEDLINE]

11. Ann Emerg Med. 1992 Sep;21(9):1051-7.

Use of cardiopulmonary bypass, high-dose epinephrine, and standard-dose epinephrine in resuscitation from post-countershock electromechanical dissociation.

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STUDY OBJECTIVE: To determine the effects of cardiopulmonary bypass with standard-dose epinephrine, high-dose epinephrine, and standard-dose epinephrine on perfusion pressures, myocardial blood flow, and resuscitation from post-countershock electromechanical dissociation.
DESIGN: Prospective, controlled laboratory investigation using a canine cardiac arrest model randomized to receive one of three resuscitation therapies.
INTERVENTIONS: After the production of post-countershock electromechanical

dissociation, 25 animals received ten minutes of basic CPR and were randomized to receive cardiopulmonary bypass with standard-dose epinephrine, high-dose epinephrine, or standard-dose epinephrine.
MEASUREMENTS AND MAIN RESULTS: Myocardial blood flow was measured using a colored microsphere technique at baseline, during basic CPR, and after intervention. Immediate and two-hour resuscitation rates were determined for each group. Return of spontaneous circulation was achieved in eight of eight cardiopulmonary bypass with standard-dose epinephrine compared with four of eight high-dose epinephrine and three of eight standard-dose epinephrine animals (P less than .04). One animal was resuscitated with CPR alone and was excluded. Survival to two hours was achieved in five of eight cardiopulmonary bypass with standard-dose epinephrine, four of eight high-dose epinephrine, and three of eight standard-dose epinephrine animals (NS). Coronary perfusion pressure increased significantly in the cardiopulmonary bypass with standard-dose epinephrine group when compared with the other groups (cardiopulmonary bypass with standard-dose epinephrine, 76 +/- 45 mm Hg; high-dose epinephrine, 24 +/- 12 mm Hg; standard-dose epinephrine, 3 +/- 14 mm Hg; P less than .005). Myocardial blood flow was higher in cardiopulmonary bypass with standard-dose epinephrine and high-dose epinephrine animals compared with standard-dose epinephrine animals but did not reach statistical significance. Cardiac output increased during cardiopulmonary bypass with standard-dose epinephrine (P = .001) and standard-dose epinephrine (NS) compared with basic CPR but decreased after epinephrine administration in the high-dose epinephrine group (NS).
CONCLUSION: Resuscitation from electromechanical dissociation was improved with cardiopulmonary bypass and epinephrine compared with high-dose epinephrine or standard-dose epinephrine alone. However, there was no difference in survival between groups. Cardiopulmonary bypass with standard-dose epinephrine resulted in higher cardiac output, coronary perfusion pressure, and a trend toward higher myocardial blood flow. A short period of cardiopulmonary bypass with epinephrine after prolonged post-countershock electromechanical dissociation cardiac arrest can re-establish sufficient circulation to effect successful early resuscitation.

PMID: 1514715 [PubMed - indexed for MEDLINE]

12. Pediatrics. 1995 Jun;95(6):901-13.

High-dose epinephrine in pediatric out-of-hospital cardiopulmonary arrest.

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OBJECTIVE: To compare the efficacy of high-dose epinephrine (HDE) and standard-dose epinephrine (SDE) for out-of-hospital treatment of pediatric cardiopulmonary arrest (CPA).
DESIGN: Forty-eight-month retrospective cohort study.

SETTING: Prehospital emergency medical services (EMS) system of a large metropolitan region.
PATIENTS: All children younger than 18 years of age, who suffered nontraumatic CPA, did not meet local EMS criteria for death in the field, and were treated by paramedics according to EMS pediatric CPA protocols.
INTERVENTIONS: Paramedics administered HDE (> 0.1 mg/kg), SDE (< 0.1 mg/kg), or no epinephrine (NE), based on base hospital physician order and availability of access for drug delivery. Protocols permitted either HDE or SDE. The drug was given through an endotracheal tube, intraosseous line, or intravenous line.
MAIN OUTCOME MEASURES: Return of spontaneous circulation (ROSC) and return of an organized electrical rhythm (ROER) in the ambulance and emergency department, hospital admission, hospital discharge, and short- and long-term neurologic outcome by pediatric cerebral performance category (PCPC) score.
RESULTS: During the study period, 65 children met inclusion criteria and underwent attempted out-of-hospital resuscitation. Forty patients (62%) received HDE (mean dose +/- SD, 0.19 +/- 0.06 mg/kg); 13 patients (20%) received SDE (mean dose +/- SD, 0.02 +/- 0.02 mg/kg); and 12 patients (18%) received NE. The HDE and SDE groups were statistically different only in epinephrine dose but not in age, gender, proportion of asystolic presenting rhythms, success of endotracheal tube intubation or intraosseous line insertion, rate of ROSC, rate of ROER, survival, or proportion of sudden infant death syndrome final diagnoses. Fifty-four children (83%) presented in asystole, 5 (8%) had pulseless electrical activity (PEA), and 6 (9%) had ventricular fibrillation (VF). None presented with either supraventricular tachycardia or ventricular tachycardia. Thirty-nine patients receiving HDE had asystole or VF as presenting rhythms, 4 (10%) had ROER, and 1 had ROSC. The single child receiving HDE presenting with PEA did not have ROSC. Ten patients receiving SDE had asystole or VF, 2 (20%) had ROER, and none had ROSC. There were 3 children receiving SDE who had PEA, and 1 had ROSC. Eleven patients receiving NE had asystole or VF, and none had ROER. One child receiving NE had PEA and ROSC. Altogether, 1 patient receiving HDE, 1 receiving SDE, and 1 receiving NE had ROSC in the field, which continued in the emergency department; all 3 were admitted to the hospital. Two children (3%), 1 receiving HDE and 1 receiving SDE, survived to hospital discharge. The survivor receiving HDE had spastic quadriplegia and profound neurologic handicaps at discharge, with a PCPC score of 4 (severe disability with daily living milestones below the 10th percentile and excessive dependence on others for provision of activities of daily living); at a 1-year follow-up, she had a PCPC score of 4. The survivor receiving SDE was neurologically healthy at discharge; at discharge and at follow-up at age 1 year, she had a PCPC score of 1 (age-appropriate level of functioning and developmentally appropriate).
CONCLUSIONS: HDE does not seem to improve the rates of ROER and ROSC, hospital admission, survival, or neurologic outcome when compared with SDE for treatment of out-of-hospital pediatric CPA. A large, blinded prospective clinical trial testing different epinephrine doses is necessary to determine drug efficacy and safety. Future pediatric CPA studies must standardize reporting of core data elements, using the adult Utstein criteria modified for pediatrics, to allow valid treatment comparisons. Overall, survival in out-of-hospital pediatric CPA is dismal.(ABSTRACT TRUNCATED)

PMID: 7761219 [PubMed - indexed for MEDLINE]

13. Ann Emerg Med. 1991 Jan;20(1):22-6.

High-dose epinephrine improves outcome from pediatric cardiac arrest.

Goetting MG, Paradis NA.

Department of Pediatrics, Henry Ford Hospital, Detroit, Michigan 48202.

Comment in
Ann Emerg Med. 1993 Apr;22(4):758-9.
Ann Emerg Med. 1991 Jan;20(1):104-5.

STUDY OBJECTIVE: Animal studies suggest that the standard dose of epinephrine (SDE) for treatment of cardiac arrest in human beings may be too low. We compared the outcome after SDE with that after high-dose epinephrine (HDE) in children with refractory cardiac arrest.
DESIGN: Prospective intervention versus historic control groups.
TYPE OF PARTICIPANTS: Two similar groups of 20 consecutive patients each (median ages, 2.5 and 3 years) with witnessed cardiac arrest who remained in arrest after at least two SDEs (0.01 mg/kg).
INTERVENTIONS: Treatment with an additional SDE versus HDE (0.2 mg/kg).
MEASUREMENTS AND MAIN RESULTS: The rates of return of spontaneous circulation and long-term survival were compared. Fourteen of the HDE group (70%) had return of spontaneous circulation, whereas none of the SDE group did (P less than .001). Eight children survived to discharge after HDE, and three were neurologically intact at follow-up. No significant toxicity from HDE was observed.
CONCLUSION: HDE provided a higher return of spontaneous circulation rate and a better long-term outcome than SDE in our series of pediatric cardiac arrest. HDE may warrant incorporation into standard resuscitation protocols at an early enough point to prevent irreversible brain injury.

PMID: 1984722 [PubMed - indexed for MEDLINE]

14. Can J Anaesth. 2004 Apr;51(4):373-8.

An evaluation of pediatric in-hospital advanced life support interventions using the pediatric Utstein guidelines: a review of 203 cardiorespiratory arrests.

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PURPOSE: Evaluate the efficacy of advanced life support interventions using the pediatric Utstein guidelines.
METHODS: Charts from all patients for whom a cardiorespiratory arrest code was called during a six-year period in a university affiliated centre were reviewed. Data were recorded according to the pediatric Utstein guidelines and a $P < 0.05$ was considered significant.
RESULTS: Of the 234 calls, 203 were retained for analysis. The overall survival rate at one year was 26.0% of which 10% had deterioration of their neurologic status compared to the pre-cardiorespiratory arrest evaluation. Time to achieve sustained return of spontaneous circulation (ROSC; $P < 0.0001$) and sustained measurable blood pressure ($P = 0.002$), to perform endotracheal intubation ($P = 0.04$) and the dose of sodium bicarbonate ($P < 0.0001$) were indicators of long-term survival. Two patients were alive at one year with unchanged neurologic status despite a time to achieve sustained ROSC longer than 30 min (38 and 44 min). The mean first epinephrine dose of patients for whom ROSC was achieved but unsustained was higher than those for whom ROSC was achieved and sustained (0.038 +/- 0.069 mg*kg(-1) vs 0.011 +/- 0.006 mg*kg(-1); $P = 0.004$). Survival rate and mean first epinephrine dose of patients who received their first epinephrine dose endotracheally (13.3%; 0.011 +/- 0.004 mg*kg(-1)) were comparable to those of patients who received their first epinephrine dose intravenously (7%; 0.015 +/- 0.027 mg*kg(-1)).
CONCLUSIONS: For intravenously administered epinephrine, a dose of 0.01 mg*kg(-1) seems appropriate as the first dose. The endotracheal route is a valuable alternative for epinephrine administration and, for infants, the dose does not need to be increased. A minimal resuscitation duration time of 30 min can be misleading if ROSC is used as the indicator.

PMID: 15064267 [PubMed - indexed for MEDLINE]

15. N Engl J Med. 1998 Nov 26;339(22):1595-601.

A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. European Epinephrine Study Group.

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Comment in
N Engl J Med. 1999 Jun 3;340(22):1763-4; author reply 1765.
N Engl J Med. 1999 Jun 3;340(22):1764; author reply 1765.

BACKGROUND: Clinical trials have not shown a benefit of high doses of epinephrine in the management of cardiac arrest. We conducted a prospective, multicenter, randomized study comparing repeated high doses of epinephrine with repeated standard doses in cases of out-of-hospital cardiac arrest.
METHODS: Adult patients who had cardiac arrest outside the hospital were enrolled if the cardiac rhythm continued to be ventricular fibrillation despite the administration of external electrical shocks, or if they had asystole or pulseless electrical activity at the time epinephrine was administered. We randomly assigned 3327 patients to receive up to 15 high doses (5 mg each) or standard doses (1 mg each) of epinephrine according to the current protocol for advanced cardiac life support.
RESULTS: In the high-dose group, 40.4 percent of 1677 patients had a return of spontaneous circulation, as compared with 36.4 percent of 1650 patients in the standard-dose group (P=0.02); 26.5 percent of the patients in the high-dose group and 23.6 percent of those in the standard-dose group survived to be admitted to the hospital (P=0.05); 2.3 percent of the patients in the high-dose group and 2.8 percent in the standard-dose group survived to be discharged from the hospital (P=0.34). There was no significant difference in neurologic status according to treatment among those discharged. High-dose epinephrine improved the rate of successful resuscitation in patients with asystole, but not in those with ventricular fibrillation.
CONCLUSIONS: In our study, long-term survival after cardiac arrest outside the hospital was no better with repeated high doses of epinephrine than with repeated standard doses.

PMID: 9828247 [PubMed - indexed for MEDLINE]

16. Resuscitation. 2011 Jul;82(7):932-6. Epub 2011 Mar 23.

Variable effects of high-dose adrenaline relative to standard-dose adrenaline on resuscitation outcomes according to cardiac arrest duration.

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AIM OF THE STUDY: Adjustment of adrenaline (epinephrine) dosage according to cardiac arrest (CA) duration, rather than administering the same dose, may theoretically improve resuscitation outcomes. We evaluated variable effects of high-dose adrenaline (HDA) relative to standard-dose adrenaline (SDA) on resuscitation outcomes according to CA duration.
METHODS: Twenty-eight male domestic pigs were randomised to the following 4 groups according to the dosage of adrenaline (SDA 0.02mg/kg vs. HDA 0.2mg/kg) and duration of CA before beginning cardiopulmonary resuscitation (CPR): 6min SDA, 6min HDA, 13min SDA, or 13min HDA. After the predetermined duration of untreated

ventricular fibrillation, CPR was provided.
RESULTS: All animals in the 6min SDA, 6min HDA, and 13min HDA groups were successfully resuscitated, while only 4 of 7 pigs in the 13min SDA group were successfully resuscitated (p=0.043). HDA groups showed higher right atrial pressure, more frequent ventricular ectopic beats, higher blood glucose, higher troponin-I, and more severe metabolic acidosis than SDA groups. Animals of 13min groups showed more severe metabolic acidosis and higher troponin-I than animals of 6min groups. All successfully resuscitated animals, except two animals in the 13min HDA group, survived for 7 days (p=0.121). Neurologic deficit score was not affected by the dose of adrenaline.
CONCLUSION: HDA showed benefit in achieving restoration of spontaneous circulation in 13min CA, when compared with 6min CA. However, this benefit did not translate into improved long-term survival or neurologic outcome.

PMID: 21482013 [PubMed - in process]

17. Acta Anaesthesiol Scand. 1991 Apr;35(3):253-6.

Comparison of standard and high-dose adrenaline in the resuscitation of asystole and electromechanical dissociation.

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Sixty-eight adults with cardiac arrest (asystole and electromechanical dissociation) were randomly allocated for treatment with standard (1 mg) or high-dose epinephrine (5 mg). If the first dose of adrenaline (1 or 5 mg) failed, standardized advanced life-support was applied in all cases. High-dose adrenaline was associated with higher initial resuscitation success rates (16 of 28) than standard-dose adrenaline (6 of 40), whereas hospital discharge rates were not significantly different between the groups. Blood pressure was significantly higher in the high-dose adrenaline group in comparison to the standard dose at 1 and 5 min after resuscitation. Although high-dose adrenaline appears to improve cardiac resuscitation success, the duration of global cerebral ischaemia seems to determine the ultimate outcome.

PMID: 2038933 [PubMed - indexed for MEDLINE]

18. Anesth Analg. 2006 Feb;102(2):542-8.

Epinephrine increases mortality after brief asphyxial cardiac arrest in an in vivo rat model.

McCaul CL, McNamara PJ, Engelberts D, Wilson GJ, Romaschin A, Redington AN, Kavanagh BP.

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Epinephrine may be detrimental in cardiac arrest. In this laboratory study we sought to characterize the effect of epinephrine and concomitant calcium channel blockade on postresuscitation myocardial performance after brief asphyxial cardiac arrest. Anesthesized rats were disconnected from mechanical ventilation, resulting in cardiac arrest. Resuscitation was attempted after 1 min with mechanical ventilation, oxygen, chest compressions, and IV medication. In experimental series 1 and 2, animals were allocated to 10 or 30 microg/kg epinephrine or 0.9% saline. In series 3, animals received 30 microg/kg of epinephrine and were randomized to 0.1 mg/kg of verapamil or to 0.9% saline. In series 1 and 3, left ventricular function was assessed using transthoracic echocardiography. In series 2, left atrial pressure was measured. Epinephrine was associated with increased mortality (0/8 [0%] in controls, 4/12 [33.3%] in 10 microg/kg animals, and 16/22 [72.8%] in 30 microg/kg animals; $P < 0.05$), hypertension ($P < 0.001$), tachycardia ($P = 0.004$), early transient left atrial hypertension, and dose-related reduction in left ventricular end diastolic diameter ($P < 0.05$). Verapamil prevented mortality associated with large-dose epinephrine (0% versus 100%) and attenuated early diastolic dysfunction and postresuscitation hypertension ($P = 0.001$) without systolic dysfunction. Epinephrine appears to be harmful in the setting of brief cardiac arrest after asphyxia.

PMID: 16428558 [PubMed - indexed for MEDLINE]

19. Resuscitation. 1995 Jun;29(3):249-63.

Epinephrine and sodium bicarbonate during CPR following asphyxial cardiac arrest in rats.

Neumar RW, Bircher NG, Sim KM, Xiao F, Zadach KS, Radovsky A, Katz L, Ebmeyer E, Safar P.

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Although high-dose epinephrine during CPR improves coronary perfusion pressure (CoPP) and rate of return of spontaneous circulation (ROSC) in some models, its impact on long term outcome (> or = 72 h) has not been evaluated. Previous studies of sodium bicarbonate ($NaHCO_3$) therapy during CPR indicate that beneficial effects may be dependent on epinephrine (EPI) dose. We hypothesized that EPI and $NaHCO_3$ given during CPR have a significant impact on long term outcome. One hundred male Sprague-Dawley rats were prospectively studied in a

block randomized placebo controlled trial. Rats were anesthetized, paralyzed, mechanically ventilated, instrumented, and each underwent 10 min of asphyxia, resulting in 6.8 +/- 0.4 min of circulatory arrest. Resuscitation was performed by mechanical ventilation and manual external chest compressions. EPI 0.0 (placebo), 0.01, 0.1, or 1.0 mg/kg IV was given at the onset of CPR, followed by NaHCO3 0.0 (placebo) or 1.0 mEq/kg IV. Successfully resuscitated rats were monitored and ventilated for 1 h without hemodynamic support. Neurologic deficit scores (NDS), cerebral histopathologic damage scores (CHDS) and myocardial histopathologic damage scores (MHDS) were determined in rats that survived 72 h. EPI improved CoPP and ROSC in a dose-dependent manner up to 0.1 mg/kg. Rats receiving EPI 0.1 and 1.0 mg/kg during CPR exhibited prolonged post-ROSC hypertension and metabolic acidemia, increased A-a O2 gradient, and an increased incidence of post-ROSC ventricular tachycardia or fibrillation. Overall survival was lower with EPI 0.1 and 1.0 mg/kg compared to 0.01 mg/kg. Although NDS was significantly less with EPI 0.1 mg/kg compared to placebo, there was no difference in CHDS between groups. In contrast, MDS was significantly higher with EPI 0.1 mg/kg compared to placebo or EPI 0.01 mg/kg. There was an overall trend toward improved survival at 72 h in rats that received NaHCO3 which was most evident in the EPI 0.1 mg/kg group. We conclude that (1) EPI during CPR has a biphasic dose/response curve in terms of survival, when post-resuscitation effects are left untreated and (2) NaHCO3 doses greater than 1.0 mEq/kg may be necessary to treat the side-effects of high-dose EPI. Further work is needed to determine if treating the immediate post-resuscitation effects of high-dose EPI can prevent detrimental effects on long-term outcome.

PMID: 7667556 [PubMed - indexed for MEDLINE]

20. Pediatr Emerg Care. 2005 Apr;21(4):227-37.

The use of high-dose epinephrine for patients with out-of-hospital cardiopulmonary arrest refractory to prehospital interventions.

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OBJECTIVE: To determine if high-dose epinephrine (HDE) used during out-of-hospital cardiopulmonary arrest refractory to prehospital interventions improves return of spontaneous circulation, 24-hour survival, discharge survival, and neurological outcomes.
METHODS: A multicenter randomized controlled trial was conducted between May 1991 and October 1996 to compare the effectiveness of HDE versus standard-dose epinephrine (SDE) in patients having out-of-hospital cardiopulmonary arrest refractory to prehospital resuscitation efforts. Cardiopulmonary arrest was

classified as "medical" or "traumatic." Two hundred thirty patients were enrolled in 7 pediatric emergency departments. Ages ranged from newborn to 22 years. Seventeen patients met exclusion criteria. Patients were assigned to receive HDE (0.1 mg/kg for the initial dose and 0.2 mg/kg for subsequent doses) or SDE (0.01 mg/kg). The main end points evaluated were return of spontaneous circulation, 24-hour survival, discharge survival, and neurological outcome.
RESULTS: One hundred twenty-seven patients received HDE (32 trauma patients), and 86 patients received SDE (27 trauma patients). Among medical patients, 24 (25%) of 95 experienced return of spontaneous circulation in the HDE group as compared with 9 (15%) of 59 in the SDE group (P = 0.14, chi2 = 2.17, relative risk = 1.66 [0.83-3.31]). Sixteen (17%) of 95 HDE patients and 5 (8%) of 59 SDE patients survived at least 24 hours (P = 0.14, chi2 = 2.16, relative risk = 1.99 [0.77-5.14]). Nine survivors to discharge received HDE, and 2 received SDE (P = 0.21, Fisher exact test, relative risk = 2.75 [0.61-12.28]). There were no long-term survivors among the trauma patients. Eight of 11 long-term survivors had severe neurological outcomes defined by the Glasgow Outcome Scale (2/2 SDE, 6/9 HDE; P = 0.51, Fisher exact test).
CONCLUSION: HDE does not improve or diminish return of spontaneous circulation, 24-hour survival, long-term survival, or neurological outcome compared with SDE in out-of-hospital cardiopulmonary arrest.

PMID: 15824681 [PubMed - indexed for MEDLINE]

21. N Engl J Med. 2004 Apr 22;350(17):1722-30.

A comparison of high-dose and standard-dose epinephrine in children with cardiac arrest.

Perondi MB, Reis AG, Paiva EF, Nadkarni VM, Berg RA.

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Comment in
N Engl J Med. 2004 Apr 22;350(17):1708-9.

BACKGROUND: When efforts to resuscitate a child after cardiac arrest are unsuccessful despite the administration of an initial dose of epinephrine, it is unclear whether the next dose of epinephrine (i.e., the rescue dose) should be the same (standard) dose or a higher dose.
METHODS: We performed a prospective, randomized, double-blind trial to compare high-dose epinephrine (0.1 mg per kilogram of body weight) with standard-dose epinephrine (0.01 mg per kilogram) as rescue therapy for in-hospital cardiac arrest in children after failure of an initial, standard dose of epinephrine. The trial included 68 children, and Utstein-style reporting guidelines were used. The primary outcome measure was survival 24 hours after the arrest.
RESULTS: The rate of survival at 24 hours was lower in the group assigned to a

high dose of epinephrine as rescue therapy than in the group assigned to a standard dose: 1 of the 34 patients in the high-dose group survived for 24 hours, as compared with 7 of the 34 patients in the standard-dose group (unadjusted odds ratio for death with the high dose, 8.6; 97.5 percent confidence interval, 1.0 to 397.0; P=0.05). After adjustment by multiple logistic-regression analysis for differences in the groups at the time of arrest, the high-dose group tended to have a lower 24-hour survival rate (odds ratio for death, 7.9; 97.5 percent confidence interval, 0.9 to 72.5; P=0.08). The two treatment groups did not differ significantly in terms of the rate of return of spontaneous circulation (which occurred in 20 patients in the high-dose group and 21 of those in the standard-dose group; odds ratio, 1.1; 97.5 percent confidence interval, 0.4 to 3.0). None of the patients in the high-dose group, as compared with four of those in the standard-dose group, survived to hospital discharge. Among the 30 patients whose cardiac arrest was precipitated by asphyxia, none of the 12 who were assigned to high-dose epinephrine were alive at 24 hours, as compared with 7 of the 18 who were assigned to a standard dose (P=0.02).
CONCLUSIONS: We did not find any benefit of high-dose epinephrine rescue therapy for in-hospital cardiac arrest in children after failure of an initial standard dose of epinephrine. The data suggest that high-dose therapy may be worse than standard-dose therapy.

PMID: 15102998 [PubMed - indexed for MEDLINE]

22. Chest. 1990 Oct;98(4):999-1005.

The effects of methoxamine and epinephrine on survival and regional distribution of cardiac output in dogs with prolonged ventricular fibrillation.

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Comment in
Chest. 1990 Oct;98(4):787-9.

This study compares the effects of methoxamine, a pure alpha 1-agonist, and epinephrine on cerebral and myocardial blood flow, central hemodynamics, and survival in a randomized placebo-controlled fashion during prolonged ventricular fibrillation (VF) in a canine model. Twenty-four anesthetized and ventilated adult mongrel dogs were instrumented for regional blood flow determinations using radio-labeled microspheres. The dogs were randomized to receive either 20 mg of methoxamine as a single intravenous bolus or repeated boluses of 0.02 mg/kg of epinephrine, 0.2 mg/kg of epinephrine, or normal saline solution placebo beginning at three minutes following induction of VF and initiation of closed chest cardiac massage (CCCM). Organ blood flow measurements were determined during normal sinus rhythm and after five and 20 minutes of VF. All six dogs

receiving methoxamine were successfully resuscitated in contrast to only one in each of the epinephrine-treated groups and none of the dogs receiving placebo (p less than .01). Although epinephrine was associated with significantly higher blood pressures than placebo during cardiopulmonary resuscitation (CPR), blood pressures achieved with methoxamine were significantly higher than those observed in the other three treatment groups (p less than .001). Cerebral blood flow was significantly higher with both methoxamine and high-dose epinephrine (p less than .05). Mean left and right ventricular myocardial flows were highest with methoxamine but this did not achieve statistical significance. In contrast, organ flows measured in the animals receiving the lowest dose of epinephrine were not significantly higher than those associated with placebo. Cardiac output after 20 minutes of CPR was significantly lower with high-dose epinephrine than with methoxamine or placebo (p less than .05). Our results suggest that methoxamine significantly improves regional cerebral blood flow and survival during CPR and although high-dose epinephrine is associated with comparable improvements in regional cerebral blood flow, this treatment is associated with deterioration in central hemodynamics during prolonged VF and does not enhance survival.

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High-dose epinephrine in adult cardiac arrest.

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BACKGROUND: Recent studies suggest that doses of epinephrine of 0.1 mg per kilogram of body weight or higher may improve myocardial and cerebral blood flow as well as survival in cardiac arrest. Such studies have called into question the traditional dose of epinephrine (0.007 to 0.014 mg per kilogram) recommended for advanced cardiac life support.
METHODS: We randomly assigned 650 patients who had had cardiac arrest either in or outside the hospital to receive up to five doses of high-dose (7 mg) or standard-dose (1 mg) epinephrine at five-minute intervals according to standard protocols for advanced cardiac life support. Patients who collapsed outside the hospital received no advanced-life-support measures other than defibrillation before reaching the hospital.
RESULTS: There was no significant difference between the high-dose group (n = 317) and the standard-dose group (n = 333) in the proportions of patients who

survived for one hour (18 percent vs. 23 percent, respectively) or who survived until hospital discharge (3 percent vs. 5 percent). Among the survivors, there was no significant difference in the proportions who remained in the best category of cerebral performance (90 percent vs. 94 percent) and no significant difference in the median Mini-Mental State score (36 vs. 37). The exploration of clinically important subgroups, including those with out-of-hospital arrest (n = 335) and those with in-hospital arrest (n = 315), failed to identify any patients who appeared to benefit from high-dose epinephrine and suggested that some patients may have worse outcomes after high-dose epinephrine.
CONCLUSION: High-dose epinephrine was not found to improve survival or neurologic outcomes in adult victims of cardiac arrest.

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