

## WORKSHEET for PROPOSED Evidence-Based GUIDELINE RECOMMENDATIONS

<b>Worksheet Author:</b>	<b>Taskforce/Subcommittee:</b> __BLS __ACLS x PEDS __ID __PROAD __X__Other: NRP
<b>Author's Home Resuscitation Council:</b> __X__AHA __ANZCOR __CLAR __ERC __HSFC __HSFC __RCSA __IAHF __Other:	<b>Date Submitted to Subcommittee:</b> 5/1/04

**STEP 1: STATE THE PROPOSAL.** State if this is a proposed new guideline; revision to current guideline; or deletion of current guideline.

**Existing guideline, practice or training activity, or new guideline:** Revision to current guideline

The data regarding the effects of high dose epinephrine for resuscitation of newly born infants is inadequate to support routine use of higher doses of epinephrine ( Class indeterminate LOE 7)

**Step 1A: Refine the question; state the question as a positive (or negative) hypothesis. State proposed guideline recommendation as a specific, positive hypothesis. Use single sentence if possible. Include type of patients; setting (in/out-of-hospital); specific interventions (dose, route); specific outcomes (ROSC vs. hospital discharge).**

There are insufficient data to support the routine use of High Dose Epinephrine for the resuscitation of the newly born infant.

**Step 1B: Gather the Evidence; define your search strategy.** Describe search results; describe best sources for evidence. Key words used included the following:

High dose epinephrine, adrenaline, standard dose epinephrine, cardiac arrest, graded doses, CPR, resuscitation

The best yield was for “High Dose Epinephrine” only- Embase- 100 hits of which 38 articles were reviewed and Medline 116 hits of which 46 articles were reviewed

List electronic databases searched (at least AHA EndNote 7 Master library [<http://ecc.heart.org/>], Cochrane database for systematic reviews and Central Register of Controlled Trials [<http://www.cochrane.org/>], MEDLINE [<http://www.ncbi.nlm.nih.gov/PubMed/> ], and Embase), and hand searches of journals, review articles, and books.

Pubmed, Embase, Cochrane database, ECC EndNote library, Review articles

- State major criteria you used to limit your search; state inclusion or exclusion criteria (e.g., only human studies with control group? no animal studies? N subjects > minimal number? type of methodology? peer-reviewed manuscripts only? no abstract-only studies?)

Any neonatal, pediatric (clinical and animal) adult clinical studies.

- Number of articles/sources meeting criteria for further review: Create a citation marker for each study (use the author initials and date or Arabic numeral, e.g., “Cummins-1”). If possible, please supply file of best references; EndNote 6+ required as reference manager using the ECC reference library.

48 articles met the criteria for further review of which 33 were selected for this worksheet

### STEP 2: ASSESS THE QUALITY OF EACH STUDY

**Step 2A: Determine the Level of Evidence.** For each article/source from step 1, assign a level of evidence—based on study design and methodology.

Level of Evidence	Definitions (See manuscript for full details)
Level 1	
Level 2	
Level 3	

Level 4	
Level 5	
Level 6	Berg, 1994, Berg, 1996, Berkowitz 1991, Brunette, 1990, Chase, 1993
Level 7	Perondi 2004*, Stiell, 1992* , Callaham*, 1992*, Brown, 1992, Gueugniaud*, 1998, Choux, 1995*, Dieckmann, 1995, Carpenter, 1997, Goetting, 1989, Lindner, 1991, Barton, 1991
Level 8	

\* Randomized clinical studies

**Step 2B: Critically assess each article/source in terms of research design and methods.**

Was the study well executed? Suggested criteria appear in the table below. Assess design and methods and provide an overall rating. Ratings apply within each Level; a Level 1 study can be excellent or poor as a clinical trial, just as a Level 6 study could be excellent or poor as an animal study. Where applicable, please use a superscripted code (shown below) to categorize the primary endpoint of each study. For more detailed explanations please see attached assessment form.

Component of Study and Rating	Excellent	Good	Fair	Poor	Unsatisfactory
<b>Design &amp; Methods</b>	Highly appropriate sample or model, randomized, proper controls <b>AND</b> Outstanding accuracy, precision, and data collection in its class	Highly appropriate sample or model, randomized, proper controls <b>OR</b> Outstanding accuracy, precision, and data collection in its class	Adequate, design, but possibly biased <b>OR</b> Adequate under the circumstances	<i>Small or clearly biased population or model</i> <b>OR</b> <i>Weakly defensible in its class, limited data or measures</i>	<i>Anecdotal, no controls, off target end-points</i> <b>OR</b> <i>Not defensible in its class, insufficient data or measures</i>

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

B = Survival of event D = Intact neurological survival

**Step 2C: Determine the direction of the results and the statistics: supportive? neutral? opposed?**

DIRECTION of study by results & statistics:	SUPPORT the proposal	NEUTRAL	OPPOSE the proposal
<b>Results</b>	Outcome of proposed guideline superior, to a clinically important degree, to current approaches	Outcome of proposed guideline no different from current approach	Outcome of proposed guideline inferior to current approach

**Step 2D: Cross-tabulate assessed studies by a) level, b) quality and c) direction** (ie, supporting or neutral/ opposing); **combine and summarize.** Exclude the *Poor* and *Unsatisfactory* studies. Sort the *Excellent*, *Good*, and *Fair* quality studies by both *Level and Quality of evidence*, and *Direction of support* in the summary grids below. Use citation marker (e.g. author/ date/source). In the *Neutral or Opposing* grid use bold font for *Opposing* studies to distinguish them from merely neutral studies. Where applicable, please use a superscripted code (shown below) to categorize the primary endpoint of each study.

## Supporting Evidence

There are insufficient data to support the routine use of High Dose Epinephrine for the resuscitation of the newly born infant.

<b>Quality of Evidence</b>	<b>Excellent</b>									Perondi, 2004 <sup>B</sup> Gueugniaud 1998 <sup>D</sup> Stiell, 1992 <sup>BD</sup> Brown, 1992 <sup>BD</sup> Callaham <sup>CD</sup> Gueugniaud <sup>C</sup>	
	<b>Good</b>										
	<b>Fair</b>									Berg, 1994 <sup>C</sup> Berg, 1996 <sup>C</sup> Chase, 1993 <sup>E</sup>	Dieckmann, 1995 <sup>B</sup> Carpenter, 1997 <sup>B</sup> Lindner, 1991 <sup>C</sup>
		1	2	3	4	5	6		7	8	
<b>Level of Evidence</b>											

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

B = Survival of event D = Intact neurological survival

## Neutral or Opposing Evidence

There are insufficient data to support the routine use of High Dose Epinephrine for the resuscitation of the newly born infant.



<ul style="list-style-type: none"> <li>• <b>Class IIa:</b> <i>Acceptable and useful</i></li> </ul> <p><b>Good</b> evidence provides support</p>	<ul style="list-style-type: none"> <li>• Safe, acceptable</li> <li>• Clinically useful</li> <li>• Considered treatments of choice</li> </ul>	<ul style="list-style-type: none"> <li>• Generally higher levels of evidence</li> <li>• Results are consistently positive</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Class IIb:</b> <i>Acceptable and useful</i></li> </ul> <p><b>Fair</b> evidence provides support</p>	<ul style="list-style-type: none"> <li>• Safe, acceptable</li> <li>• Clinically useful</li> <li>• Considered optional or alternative treatments</li> </ul>	<ul style="list-style-type: none"> <li>• Generally lower or intermediate levels of evidence</li> <li>• Generally, but not consistently, positive results</li> </ul>
<p><b>Class III:</b> <i>Not acceptable, not useful, may be harmful</i></p>	<ul style="list-style-type: none"> <li>• Unacceptable</li> <li>• Not useful clinically</li> <li>• May be harmful.</li> </ul>	<ul style="list-style-type: none"> <li>• No positive high level data</li> <li>• Some studies suggest or confirm harm.</li> </ul>
<p><b>Indeterminate</b></p>	<ul style="list-style-type: none"> <li>• Research just getting started.</li> <li>• Continuing area of research</li> <li>• No recommendations until further research</li> </ul>	<ul style="list-style-type: none"> <li>• Minimal evidence is available</li> <li>• Higher studies in progress</li> <li>• Results inconsistent, contradictory</li> <li>• Results not compelling</li> </ul>

**STEP 3: DETERMINE THE CLASS OF RECOMMENDATION.** State a **Class of Recommendation** for the Guideline Proposal. State either **a) the intervention**, and then the conditions under which the intervention is either Class I, Class IIA, IIB, etc.; or **b) the condition**, and then whether the intervention is Class I, Class IIA, IIB, etc.

Indicate if this is a    **Condition** or  **Intervention**

**Final Class of recommendation:**    **Class I-Definitely Recommended**    **Class IIa-Acceptable & Useful; good evidence**    **Class IIb-Acceptable & Useful; fair evidence**    **Class III – Not Useful; may be harmful** or

**Indeterminate-minimal evidence or inconsistent**

**REVIEWER’S PERSPECTIVE AND POTENTIAL CONFLICTS OF INTEREST:** Briefly summarize your professional background, clinical specialty, research training, AHA experience, or other relevant personal background that define your perspective on the guideline proposal. List any potential conflicts of interest involving consulting, compensation, or equity positions related to drugs, devices, or entities impacted by the guideline proposal. Disclose any research funding from involved companies or interest groups. State any relevant philosophical, religious, or cultural beliefs or longstanding disagreements with an individual.

Neonatologist with 25 years of postgraduate experience. Research training in cerebral blood flow and metabolism. Have served on the Neonatal Resuscitation Program (NRP) for six years, and on the pediatric subcommittee of the AHA. I have a no potential conflict of interest.

**REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:** Summarize your final evidence integration and the rationale for the class of recommendation. Describe any mismatches between the evidence and your final Class of Recommendation. “Mismatches” refer to selection of a class of recommendation that is heavily influenced by other factors than just the evidence. For example, the evidence is strong, but implementation is difficult or expensive; evidence weak, but future definitive evidence is unlikely to be obtained. Comment on contribution of animal or mechanical model studies to your final recommendation. Are results within animal studies homogeneous? Are animal results consistent with results from human studies? What is the frequency of adverse events? What is the possibility of harm? Describe any value or utility judgments you may have made, separate from the evidence. For example, you believe evidence-supported interventions should be limited to in-hospital use because you think proper use is too difficult for pre-hospital providers. Please include relevant key figures or tables to support your assessment.

A consistent observation in both experimental and adult clinical studies is that higher doses of epinephrine (100µg/kg) are necessary to achieve higher plasma epinephrine levels as well as to have sustained improvements in myocardial and cerebral blood flow in models of prolonged cardiac arrest (Brown CG, 1986,1987, Gonzales 1989, Brunette 1990, Paradia 1991, Linder 1991)(LOE 7). Although high dose epinephrine improves ROSC, and myocardial and cerebral perfusion pressure in adult human cardiac arrest victims, this has not translated into clinical benefit in either survival or neurologic outcomes. (Stiell 1992, Brown 1992, Callaham 1992, Choux 1995, Gueugniaud 1998(LOE 7))

The data in children also shows no benefit to high dose therapy. Thus, in a recent blinded, randomized

study (Peroni 2004) (LOE 7) no benefit to high dose epinephrine was shown – indeed the data suggest a worse outcome in children with in-hospital cardiac arrest receiving high-dose epinephrine. Prior retrospective studies also failed to demonstrate a benefit of high dose epinephrine (Dieckman 1995, Carpenter 1997 ) (LOE 7) **There are no data specific to the neonatal population.**

Some experimental and adult studies have raised the possibility of adverse effects associated with high dose epinephrine including detrimental effects on cardiac function following resuscitation (Horchen 1995, Tang 1995)(LOE 6), myocardial necrosis ( Berg 1994)(LOE 6), and post-resuscitation hyperadrenergic states with prolonged systemic hypertension, tachycardia and greater early mortality and poorer neurologic recovery-the latter perhaps due to negative effects on cortical blood flow. (Behringer 1998, Berg 1994,)(LOE 6). Asphyxiated neonatal swine treated with high dose epinephrine frequently demonstrated severe tachycardia and hypertension resulting in marked increases in myocardial oxygen demand (Berg 1994, 1996,, Gedenberg 2000)(LOE 6). The acute hypertension associated with high dose epinephrine increases the potential risk for intraventricular hemorrhage in the preterm infant. Given these observations there are no data to support the routine use of High Dose epinephrine in the resuscitation of the newly born infant.

**Preliminary draft/outline/bullet points of Guidelines revision:** Include points you think are important for inclusion by the person assigned to write this section. Use extra pages if necessary.

Attachments:

Bibliography in electronic form using the Endnote Master Library. It is recommended that the bibliography be provided in annotated format. This will include the article abstract (if available) and any notes you would like to make providing specific comments on the quality, methodology and/or conclusions of the study.

### *Citation List*

Citation Marker	Full Citation*
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{Berg, 1996 #184}	Berg, R. A., C. W. Otto, et al. A randomized, blinded trial of high-dose epinephrine versus standard-dose epinephrine in a swine model of pediatric asphyxial cardiac arrest. <u>Crit Care Med</u> 1996; 24(10): 1695-700.
{Berg, 1994 #185}	Berg, R. A., C. W. Otto, et al. High-dose epinephrine results in greater early mortality after resuscitation from prolonged cardiac arrest in pigs: a prospective, randomized study. <u>Crit Care Med</u> 1994; 22(2): 282-90.
{Berkowitz, 1991 #208}	Berkowitz, I. D., H. Gervais, et al. Epinephrine dosage effects on cerebral and myocardial blood flow in an infant swine model of cardiopulmonary resuscitation. <u>Anesthesiology</u> 1991; 75(6): 1041-1050.
{Carpenter, 1997 #181}	Carpenter, T. C. and K. R. Stenmark . High-dose epinephrine is not superior to standard-dose epinephrine in pediatric in-hospital cardiopulmonary arrest. <u>Pediatrics</u> 1997;99(3): 403-8.
{Dieckmann, 1995 #180}	Dieckmann, R. A. and R. Vardis . High-dose epinephrine in pediatric out-of-hospital cardiopulmonary arrest. <u>Pediatrics</u> 1995;95(6): 901-13.
{Goetting, 1989 #182}	Goetting, M. G. and N. A. Paradis. High dose epinephrine in refractory pediatric cardiac arrest. <u>Crit Care Med</u> 1991; 17(12): 1258-62.
{Perondi, 2004 #196}	Perondi, M. B. M., A. G. Reis, et al A Comparison of High-Dose and Standard-Dose Epinephrine in Children with Cardiac Arrest. <u>N Engl J Med</u> 2004 350(17): 1722-1730.
{Barton, 1991 #189}	Barton, C. and M. Callaham High-dose epinephrine improves the return of spontaneous circulation rates in human victims of cardiac arrest. <u>Ann Emerg Med</u> 1991 ;20(7): 722-5.
{Behringer, 1998 #215}	Behringer, W., H. Kittler, et al. Cumulative epinephrine dose during cardiopulmonary resuscitation and neurologic outcome. <u>Ann Intern Med</u> 1998; 129(6): 450-6.
{Brown, 1992 #213}	Brown, C. G., D. R. Martin, et al. A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital. The Multicenter High-Dose Epinephrine Study Group. <u>N Engl J Med</u> 1992; 327(15): 1051-5.
{Callaham, 1992 #186}	Callaham, M., C. D. Madsen, et al. A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest. <u>Jama</u> 1992;268(19): 2667-72.
{Choux, 1995 #188}	Choux, C., P. Y. Gueugniaud, et al. Standard doses versus repeated high doses of epinephrine in cardiac arrest outside the hospital. <u>Resuscitation</u> 1995; 29(1): 3-9.
{Gonzalez, 1989 #211}	Gonzalez, E. R., J. P. Ornato, et al. Dose-dependent vasopressor response to epinephrine during CPR in human beings. " <u>Ann Emerg Med</u> 1989 ;18(9): 920-6.
	Gueugniaud, P. Y., P. Mols, et al. A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. European Epinephrine Study Group. <u>N Engl J Med</u> 1998 339(22): 1595-601.
	Lindner, K. H., F. W. Ahnefeld, et al. Comparison of standard and high-dose adrenaline in the resuscitation of asystole and electromechanical dissociation. <u>Acta Anaesthesiol Scand</u> 1991; 35(3): 253-6.
	Paradis, N. A., G. B. Martin, et al. The effect of standard- and high-dose epinephrine on coronary perfusion pressure during prolonged cardiopulmonary

<p>{Gueugniaud, 1998 #187}</p>	<p>resuscitation." <u>Jama</u> 1991;265(9): 1139-44.</p> <p>Stiell, I. G., P. C. Hebert, et al. High-dose epinephrine in adult cardiac arrest. <u>N Engl J Med</u> 1992;327(15): 1045-50.</p>
<p>{Lindner, 1991 #212}</p>	<p>Brunette, D. D. and S. J. Jameson Comparison of standard versus high-dose epinephrine in the resuscitation of cardiac arrest in dogs. <u>Ann Emerg Med</u> 1990;19(1): 8-11.</p>
<p>{Paradis, 1991 #214}</p>	<p>Chase, P. B., K. B. Kern, et al. Effects of graded doses of epinephrine on both noninvasive and invasive measures of myocardial perfusion and blood flow during cardiopulmonary resuscitation. <u>Crit Care Med</u> 1993 ;21(3): 413-9.</p>
<p>{Stiell, 1992 #195}</p>	<p>Gedeborg, R., H. C. Silander, et al. Adverse effects of high-dose epinephrine on cerebral blood flow during experimental cardiopulmonary resuscitation." <u>Crit Care Med</u> 2000; 28(5): 1423-30.</p>
<p>{Brunette, 1990 #183}</p>	<p>Hornchen, U., C. Lussi, et al. Potential risks of high-dose epinephrine for resuscitation from ventricular fibrillation in a porcine model. <u>J Cardiothorac Vasc Anesth</u> 1993;7: 184-7.</p>
<p>{Chase, 1993 #192}</p>	<p>Lindner, K. H., F. W. Ahnefeld, et al. Comparison of different doses of epinephrine on myocardial perfusion and resuscitation success during cardiopulmonary resuscitation in a pig model. <u>Am J Emerg Med</u> 1991;9(1): 27-31.</p>
<p>{Gedeborg, 2000 #216}</p>	<p>Tang, W., M. H. Weil, et al. Epinephrine increases the severity of postresuscitation myocardial dysfunction. <u>Circulation</u> 1995 92(10): 3089-93.</p>
<p>{Hornchen, 1993 #194}</p>	<p>Schmitz, B., M. Fischer, et al Resuscitation from cardiac arrest in cats: influence of epinephrine dosage on brain recovery. <u>Resuscitation</u> 1995; 30(3): 251-62.</p>
<p>{Lindner, 1991 #190}</p>	
<p>{Tang, 1995 #193}</p>	
<p>{Schmitz, 1995 #191}</p>	

\*Type the citation marker in the first field and then paste the full citation into the second field. You can copy the full citation from EndNote by selecting the citation, then copying the FORMATTED citation using the short cut, Ctrl-K. After you copy the citation, go back to this document and position the cursor in the field, then paste the citation into the document (use Ctrl-V). For each new citation press Tab to move down to start a new field.

*NRP Literature Review Database - Epinephrine*

### **Pediatric Animal Studies**

Berg, R. A., C. W. Otto, et al. (1996). "A randomized, blinded trial of high-dose epinephrine versus standard-dose epinephrine in a swine model of pediatric asphyxial cardiac arrest." *Crit Care Med* **24**(10): 1695-700.

**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. **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.

**Comments:** High dose epinephrine was not more effective in improving outcome at 24 hours. High dose epinephrine was associated with higher adrenergic manifestations, which may have contributed to the initial higher mortality.

#### **Level of Evidence 6**

**Quality –Good**

**Evidence - Supportive**

Berg, R. A., C. W. Otto, et al. (1994). "High-dose epinephrine results in greater early mortality after resuscitation from prolonged cardiac arrest in pigs: a prospective, randomized study." *Crit Care Med* **22**(2): 282-90.

**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. **RESULTS:** Electrocardiogram, aortic blood pressure, right atrial blood pressure, and end-tidal CO<sub>2</sub> 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.

**Comments:** High dose epinephrine was not more effective than standard dose epinephrine in improving outcome at 24 hours. High dose epinephrine can induce a hyperadrenergic state that includes hypertension and tachycardia.

**Level of Evidence 6**  
**Quality –Good**  
**Evidence - Supportive**

Berkowitz, I. D., H. Gervais, et al. (1041). "Epinephrine dosage effects on cerebral and myocardial blood flow in an infant swine model of cardiopulmonary resuscitation." *Anesthesiology* **75**(6): 1041-1050.

Although epinephrine increases cerebral blood flow (CBF) and left ventricular blood flow (LVBF) during cardiopulmonary resuscitation (CPR), the effects of high dosages on LVBF and CBF and cerebral O<sub>2</sub> uptake have not been examined during prolonged CPR. We determined whether log increment dosages of epinephrine would enhance LVBF and CBF and cerebral O<sub>2</sub> uptake in an infant swine CPR model. **Methods** We compared these responses with epinephrine to those with the alpha-adrenergic agonist, phenylephrine. CPR was performed in five groups ( $n = 6$ ) of pentobarbital-anesthetized piglets (3.5-5.6 kg) receiving a continuous epinephrine infusion (0, 1, 10, and 100  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) or phenylephrine infusion (40  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ). Plasma epinephrine concentrations increased 10-100-fold in the control group during CPR and in a stepwise manner such that concentrations were increased by more than 104 in the 100  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  epinephrine group. In the control group with no epinephrine infusion, LVBF decreased to  $<10$   $\text{ml}\cdot\text{min}^{-1}\cdot 100$   $\text{g}^{-1}$  by 5 min of CPR. With epinephrine in dosages of 10 and 100  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , LVBF at 5 min was  $75 \pm 19$  and  $44 \pm 15$   $\text{ml}\cdot\text{min}^{-1}\cdot 100$   $\text{g}^{-1}$ , respectively, which was significantly greater than values in the control group. With more prolonged CPR, LVBF remained significantly greater than that in the control group but only at 10  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  of epinephrine. Phenylephrine also increased LVBF for 10 min of CPR when compared with the control group. All dosages of epinephrine and phenylephrine maintained CBF close to prearrest values for 20 min of CPR. With prolonged CPR, 10 and 100  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  epinephrine resulted in significantly greater CBF than that in the control group. Incremental dosages of epinephrine did not statistically increase cerebral O<sub>2</sub> uptake or lower the cerebral fractional O<sub>2</sub> extraction when compared with the control group, despite the higher CBF that was generated. In this immature animal CPR model, 10  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  epinephrine is an optimal dosage for maximizing both CBF and LVBF, a dosage that substantially exceeds the current recommended epinephrine dosage for human infant CPR. In addition, for short periods of CPR, 40  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  phenylephrine increases CBF and LVBF to levels similar to those generated by high dosages of epinephrine.

**Comments:** In this immature animal model, a dose of 10 mcg-g•kg-1•min-1 is an optimal dose to increase LVBF and CBF. However, this is a substantial increase above the current NRP recommended dose. Several differences in this model as compared to the asphyxiated neonate should be noted: a) the PaCO<sub>2</sub> ranged from 36-39 mmHg; whereas in the asphyxiated fetus the PaCO<sub>2</sub> values are much higher; b) the pH was maintained in the normal range, whereas in the asphyxiated fetus the pH is low, and c) the hemoglobin was 8.5 g/dl, whereas the hemoglobin in the fetus is frequently higher.

**Level of Evidence 6**

**Quality –Good-Fair**

**Evidence – Neutral to Opposing**

### **Pediatric Studies-Clinical**

Carpenter, T. C. and K. R. Stenmark (1997). "High-dose epinephrine is not superior to standard-dose epinephrine in pediatric in-hospital cardiopulmonary arrest." *Pediatrics* **99**(3): 403-8.

**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.

**Comments:** Retrospective study- This study failed to demonstrate benefit from high dose epinephrine therapy.

**Level of Evidence 7 (for neonates)**

**Quality of evidence-fair**

**Evidence Supportive**

Dieckmann, R. A. and R. Vardis (1995). "High-dose epinephrine in pediatric out-of-hospital cardiopulmonary arrest." *Pediatrics* **95**(6): 901-13.

**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. **Results.** 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.

**Comments:** Retrospective study. Overall outcome including survival was dismal.

**Level of Evidence 7 (for neonates)**

**Quality of evidence-fair**

**Evidence Supportive**

Goetting, M. G. and N. A. Paradis (1989). "High dose epinephrine in refractory pediatric cardiac arrest." *Crit Care Med* 17(12): 1258-62.

Cardiac arrest has a poor prognosis, regardless of age group. Children who fail to respond to two standard doses of epinephrine (0.01 mg/kg) rarely survive to hospital discharge, and most die without the return of spontaneous circulation (ROSC). We treated seven consecutive children in cardiac arrest with high dose epinephrine (0.2 mg/kg) after failure to respond to two standard doses. Six had prompt and sustained ROSC. By comparison, in the previous 20 consecutive pediatric patients with cardiac arrest in which there was no response to two standard doses of epinephrine, none had ROSC. Previous animal data as well as anecdotal human experience suggest that the standard epinephrine dose (0.01 mg/kg) may be much too low.

**Comments:** Uncontrolled study. Poor outcome.

**Level of Evidence 7 (for neonates)**  
**Quality of evidence-fair**  
**Evidence Supportive**

Goetting, M. G. and N. A. Paradis (1991). "High-dose epinephrine improves outcome from pediatric cardiac arrest." *Ann Emerg Med* **20**(1): 22-6.

**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.

**Level of Evidence 7 (for neonates)**  
**Quality of evidence-fair**  
**Evidence Supportive**

\* Perondi, M. B. M., A. G. Reis, et al. A Comparison of High-Dose and Standard-Dose Epinephrine in Children with Cardiac Arrest. *N Engl J Med* **2004; 350**(17): 1722-1730.

**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** 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 was performed. 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** No benefit of high-dose epinephrine rescue therapy for in-hospital cardiac arrest in children after failure of an initial standard dose of epinephrine was found. The data suggest that high-dose therapy may be worse than standard-dose therapy.

\* [Randomized clinical study](#)

**Level of Evidence 7 (for neonates)**  
**Quality of evidence-Excellent**  
**Evidence Supportive**

## **Adult Studies - Clinical**

Barton, C. and M. Callaham (1991). "High-dose epinephrine improves the return of spontaneous circulation rates in human victims of cardiac arrest." Ann Emerg Med **20**(7): 722-5.

**OBJECTIVES:** To evaluate the return of spontaneous circulation (RSC) rates in human victims of cardiac arrest treated with standard doses of epinephrine (SDE) or high-dose epinephrine (HDE). **DESIGN:** Prospective case series. **SETTING:** A university hospital emergency department during 1987 through 1989. **PARTICIPANTS:** Forty-nine adult victims of nontraumatic cardiac arrest. **INTERVENTIONS:** At the discretion of the treating physician, patients received epinephrine in bolus doses ranging from 1 to 15 mg. HDE was defined as a dose of at least 0.2 mg/kg; smaller doses were defined as SDE. Patients were grouped as +RSC if they developed a sustained spontaneous palpable pulse or blood pressure and as -RSC if they did not develop a pulse or blood pressure. **MEASUREMENTS:** Patients were grouped as +RSC if they developed a sustained spontaneous palpable pulse or blood pressure and as -RSC if they did not develop a pulse or blood pressure. Patients were also grouped by their presenting rhythm. Potentially perfusing rhythm was electromechanical dissociation or ventricular tachycardia. Nonperfusing rhythm was asystole or ventricular fibrillation. Rates were analyzed using the Fisher exact test and the two-tailed unpaired t test. HDE improved the rate of initial resuscitation ( $P = .008$ ). The effect was greatest in patients with nonperfusing rhythms ( $P = .014$ ) and disappeared when evaluating patients with potentially perfusing rhythms. No patient survived to hospital discharge. **CONCLUSION:** High-dose epinephrine improves initial resuscitation rates in human victims of cardiac arrest. Its greatest effect is in patients with a nonperfusing rhythm.

**Comments:** Although HDE improves initial resuscitation; it had no effect on outcome.

**Level of Evidence 7 (for neonates)**

**Quality of evidence-Fair**

**Evidence Supportive**

**Behringer, W., H. Kittler, et al. (1998). "Cumulative epinephrine dose during cardiopulmonary resuscitation and neurologic outcome." Ann Intern Med **129**(6): 450-6.**

**BACKGROUND:** Epinephrine is the drug of choice in advanced cardiac life support, but it can have deleterious side effects after restoration of spontaneous circulation. **OBJECTIVE:** To investigate the association between the cumulative epinephrine dose used in advanced cardiac life support and neurologic outcome after cardiac arrest. **DESIGN:** Retrospective cohort study. **SETTING:** University hospital. **PATIENTS:** Adults admitted to the emergency department with witnessed, nontraumatic, normothermic ventricular fibrillation cardiac arrest and unsuccessful initial defibrillation. **MEASUREMENTS:** Functional neurologic outcome was regularly assessed by cerebral performance category (CPC) within 6 months after cardiac arrest. A CPC of 1 or 2 was defined as favorable recovery. **RESULTS:** Among 178 enrolled patients, the median cumulative epinephrine dose administered was 4 mg (range, 0 to 50 mg). In 151 patients (84%), spontaneous circulation was restored; 63 of these 151 patients (42%) had favorable neurologic recovery. Patients with an unfavorable CPC received a significantly higher cumulative dose of epinephrine than did patients with a favorable CPC (4 mg compared with 1 mg;  $P < 0.001$ ). This finding persisted after stratification by duration of resuscitation. After possible cofounders were controlled for, the cumulative epinephrine dose remained an independent predictor of unfavorable neurologic outcome. **CONCLUSIONS:** The results indicate that an increasing cumulative dose of epinephrine administered during resuscitation is independently associated with unfavorable neurologic outcome after ventricular fibrillation cardiac arrest

**Level of Evidence 7 (for neonates)**

**Quality of evidence-Fair**  
**Evidence Supportive**

\* Brown, C. G., D. R. Martin, et al. (1992). "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* 327(15): 1051-5.

**BACKGROUND.** Experimental and uncontrolled clinical evidence suggests that intravenous epinephrine in doses higher than currently recommended may improve outcome after cardiac arrest. This was 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.** No 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 was demonstrated.

**Level of Evidence 7 (for neonates)**

**Quality of evidence-Excellent**  
**Evidence Supportive**

\* Callahan, M., C. D. Madsen, et al. (1992). "A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest." *Jama* 268(19): 2667-72.

**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.

**Level of Evidence 7 (for neonates)**

**Quality of evidence-Excellent**

**Evidence Supportive**

\* Choux, C., P. Y. Gueugniaud, et al. (1995). "Standard doses versus repeated high doses of epinephrine in cardiac arrest outside the hospital." *Resuscitation* **29**(1): 3-9.

Among all of the catecholamines 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.

**Comments:** A trend towards increased survival was noted in the HDE group, although this was not significant.

**Level of Evidence 7 (for neonates)**

**Quality of evidence-Excellent**

**Evidence Supportive**

**Gonzalez, E. R., J. P. Ornato, et al. (1989). "Dose-dependent vasopressor response to epinephrine during CPR in human beings." *Ann Emerg Med* **18**(9): 920-6.**

The optimal dose of epinephrine during CPR in human beings is unknown. We studied ten prehospital cardiac arrest patients (six men and four women; mean age, 54 +/- 5 years) to determine the vasopressor response and change in the end-tidal carbon dioxide concentration (PetCO<sub>2</sub>) after incremental (1-, 3-, and 5-mg) doses of IV epinephrine given five minutes apart during closed-chest CPR. All patients were in ventricular fibrillation on arrival of the paramedics and did not respond to standard advanced cardiac life support. CPR was performed with a computerized Thumper; all patients were intubated and ventilated at 12 times a minute at an FiO<sub>2</sub> of 0.8. Radial artery pressure was measured with a 20 angiocath inserted by radial artery cutdown. Paramedic response time was 4.3 +/- 0.5 minutes; elapsed time to emergency department arrival was 40.0 +/- 9.5 minutes. Initial blood gases were paO<sub>2</sub>, 241 +/- 50 mm Hg; pH, 7.23 +/- 0.08; paCO<sub>2</sub>, 27 +/- 5 mm Hg; and HCO<sub>3</sub>, 11 +/- 2 mEq/L. Baseline systolic and diastolic blood pressures were 47 +/- 5 mm Hg and 18 +/- 2 mm Hg, respectively. Systolic blood pressure was directly related to the dose of epinephrine (P less than .0001), rising to 69 +/- 7 mm Hg, 74 +/- 8 mm Hg, and 85 +/- 8 mm Hg after 1-, 3-, and 5-mg doses of epinephrine, respectively. (

**Level of Evidence 7 (for neonates)**

**Quality of evidence-Fair**

**Evidence Supportive**

\* Gueugniaud, P. Y., P. Mols, et al. (1998). "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* **339**(22): 1595-601.

**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.

**Comments:** Although HDE improved spontaneous return of the circulation, long term survival did not differ between groups.

**Level of Evidence 7 (for neonates)**

**Quality of evidence-Excellent**

**Evidence Supportive**

Lindner, K. H., F. W. Ahnefeld, et al. (1991). "Comparison of different doses of epinephrine on myocardial perfusion and resuscitation success during cardiopulmonary resuscitation in a pig model." Am J Emerg Med 9(1): 27-31.

Published results of dose-response effects of adrenergic drugs (epinephrine [E]) vary so much between studies because of differences in animal models and duration of ischemia before drug administration. In this investigation the effects of different doses of E on coronary perfusion pressure (CPP), left ventricular myocardial blood flow (MBF) and resuscitation success were compared during closed-chest cardiopulmonary resuscitation (CPR) after a 4-minute period of ventricular fibrillation in 28 pigs. MBF was measured during normal sinus rhythm using tracer microspheres. After 4 minutes of ventricular fibrillation CPR was performed with the use of a pneumatic piston compressor. After 4 minutes of mechanical measures only, the animals were randomly allocated into four groups of seven, receiving 0.015, 0.030, 0.045, and 0.090 mg/kg E intravenously respectively. MBF measurements were started 45 seconds after E administration; hemodynamic measurements after 90 seconds. Four minutes after the first administration, the same E dose was given before defibrillation. The CPP of animals given 0.015, 0.030, 0.045 and 0.090 mg/kg E were as follows: 16.3 +/- 6.1, 25.6 +/- 5.8, 33.2 +/- 8.4 and 30.4 +/- 6.3 mm Hg. The left ventricular MBF values were: 14 +/- 9, 27 +/- 11, 43 +/- 6, 46 +/- 10 mL/min/100 g. The differences between the groups receiving 0.015 and 0.045 mg/kg and between the groups receiving 0.015 mg/kg and 0.090 mg/kg were statistically significant ( $P$  less than .05). Resuscitation success was 14.3%, 42.9%, 100% and 86.7% respectively. A significant difference in resuscitation success was found only between 0.015 mg/kg and 0.045 mg/kg E

**Comments:** High dose adrenaline improved spontaneous return of the circulation but had no effect on outcome.

**Level of Evidence 7 (for neonates)**

**Quality of evidence-Fair**

**Evidence Supportive**

Paradis, N. A., G. B. Martin, et al. (1991). The effect of standard- and high-dose epinephrine on coronary perfusion pressure during prolonged cardiopulmonary resuscitation." Jama 265(9): 1139-44.

**Objective** The effect of standard and high doses of epinephrine on coronary perfusion pressure during cardiopulmonary resuscitation in 32 patients whose cardiac arrest was refractory to advanced cardiac life support was evaluated. **Methods** Simultaneous aortic and right atrial pressures were measured and plasma

epinephrine levels were sampled. Patients remaining in cardiac arrest after multiple 1-mg doses of epinephrine received a high dose of 0.2 mg/kg. **Results** The increase in the coronary perfusion pressures was 3.7 +/- 5.0 mm Hg following a standard dose, not a statistically significant change. The increase after a high dose was 11.3 +/- 10.0 mm Hg; this was both statistically different than before administration and larger than after a standard dose. High-dose epinephrine was more likely to raise the coronary perfusion pressure above the previously demonstrated critical value of 15 mm Hg. The highest arterial plasma epinephrine level after a standard dose was 152 +/- 162 ng/mL, and after a high dose, 393 +/- 289 ng/mL. **Conclusions** Because coronary perfusion pressure is a good predictor of outcome in cardiac arrest, the increase after high-dose epinephrine may improve rates of return of spontaneous circulation.

**Level of Evidence 7 (for neonates)**

**Quality of evidence-Fair**

**Evidence Supportive**

\* Stiell, I. G., P. C. Hebert, et al. (1992). "High-dose epinephrine in adult cardiac arrest." N Engl J Med 327(15): 1045-50.

**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.

**Comments:** High dose epinephrine was not associated with improved survival or neurologic outcome in adults with cardiac arrest.

**Level of Evidence 7 (for neonates)**

**Quality of evidence-Excellent**

**Evidence Supportive**

## Experimental Adult animals – Side Effects of High Dose Epinephrine

Chase, P. B., K. B. Kern, et al. (1993). "Effects of graded doses of epinephrine on both noninvasive and invasive measures of myocardial perfusion and blood flow during cardiopulmonary resuscitation." Crit Care Med 21(3): 413-9.

**OBJECTIVES:** Epinephrine administered during cardiopulmonary resuscitation (CPR) is known to increase aortic diastolic and myocardial perfusion pressures, while enhancing myocardial blood flow. Optimal dosing of epinephrine during CPR is less certain. Interest in high-dose epinephrine use under such circumstances is increasing. The effect of different doses of epinephrine on simultaneously measured perfusion pressures, myocardial blood flow, cardiac output, and end-tidal CO<sub>2</sub> (PCO<sub>2</sub>) (used as an indirect measure of cardiac output during CPR) is unknown. **DESIGN:** Prospective, sequential evaluation of no epinephrine, standard dose epinephrine, and high-dose epinephrine. **SETTING:** An experimental

resuscitation laboratory. **SUBJECTS: Twelve domestic swine.** INTERVENTIONS: Myocardial perfusion pressure, myocardial blood flow, cardiac output, and end-tidal PCO<sub>2</sub> were studied after various doses of epinephrine were administered during prolonged CPR. After 3 mins of untreated ventricular fibrillation, each animal received 5 mins of CPR without epinephrine, 5 mins of CPR after standard dose epinephrine (0.02 mg/kg), and 5 mins of CPR after high-dose epinephrine (0.2 mg/kg). Cardiac output and regional myocardial blood flow values were measured with nonradioactive, colored microspheres.

MEASUREMENTS AND MAIN RESULTS: Myocardial perfusion pressure (aortic diastolic minus right atrial diastolic) was significantly ( $p < .05$ ) increased over baseline with high-dose epinephrine (35 +/- 8 vs. 14 +/- 4 mm Hg), but not with standard dose epinephrine (20 +/- 5 vs. 14 +/- 4 mm Hg). Epinephrine's effect on myocardial blood flow was similar, increasing after the high dose (71 +/- 21 vs. 20 +/- 5 mL/min/100 g;  $p > .05$ ), but not with the standard dose (23 +/- 6 vs. 20 +/- 5 mL/min/100 g). Cardiac output decreased significantly ( $p < .05$ ) after high-dose epinephrine (7 +/- 1 vs. 13 +/- 1 mL/min/kg). Mean end-tidal PCO<sub>2</sub> levels were lower after high-dose epinephrine (15 +/- 2 vs. 20 +/- 2 mm Hg;  $p < .05$ ) but not after standard dose epinephrine (19 +/- 2 vs. 20 +/- 2 mm Hg). **CONCLUSIONS:** Standard dose epinephrine had minimal effect on myocardial perfusion pressure, myocardial blood flow, cardiac output, or end-tidal PCO<sub>2</sub>. High-dose epinephrine enhanced myocardial perfusion pressure and myocardial blood flow despite significantly decreasing cardiac output.

**Comments:** High dose epinephrine enhanced myocardial perfusion. However, it was associated with decreased cardiac output.

**Level of Evidence 6**

**Quality of evidence-Good to fair**

**Evidence Supportive**

**Gedeborg, R., H. C. Silander, et al. (2000). "Adverse effects of high-dose epinephrine on cerebral blood flow during experimental cardiopulmonary resuscitation." Crit Care Med 28(5): 1423-30.**

**OBJECTIVE:** To study the effects of high-dose epinephrine, compared with standard-dose epinephrine, on the dynamics of superficial cortical cerebral blood flow as well as global cerebral oxygenation during experimental cardiopulmonary resuscitation. The **hypothesis** was that high-dose epinephrine might be unable to improve cerebral blood flow during cardiopulmonary resuscitation as compared with standard-dose epinephrine. **Methods:** Randomized controlled study. A total of 20 male anesthetized piglets. Were subjected to ventricular fibrillation. A nonintervention interval of 8 mins was followed by open-chest cardiopulmonary resuscitation. The animals were randomized to receive repeated bolus injections of either 20 microg/kg (standard-dose group, n = 10) or 200 microg/kg (high-dose group, n = 10) of epinephrine. Focal cortical cerebral blood flow was measured continuously by using laser Doppler flowmetry. **Results** The duration of blood flow increase was significantly shorter in the high-dose group after the second dose of epinephrine. In the high-dose group there was also a consistent tendency for lower peak levels and shorter duration of flow increase in response to repeated bolus doses of epinephrine. Cerebral oxygen extraction ratio was significantly lower in the high-dose group after administration of epinephrine.

**CONCLUSIONS:** Repeated bolus doses of epinephrine 200 microg/kg, as compared with 20 microg/kg, do not improve superficial cortical cerebral blood flow during experimental open-chest cardiopulmonary resuscitation. **High-dose epinephrine appears to induce vasoconstriction of cortical cerebral blood vessels resulting in redistribution of blood flow from superficial cortex.** This might be one explanation for the failure of high-dose epinephrine to improve overall outcome in clinical trials.

**Level of Evidence 6**

**Quality of evidence-Good to fair**

**Evidence Supportive**

Hornchen, U., C. Lussi, et al. (1993). "Potential risks of high-dose epinephrine for resuscitation from ventricular fibrillation in a porcine model." J Cardiothorac Vasc Anesth 7(2): 184-7.

The arterial plasma concentrations and hemodynamic effects of epinephrine, 10 micrograms/kg, IV (group

A, N = 8) and 50 micrograms/kg, IV (group B, N = 8) were compared in a porcine resuscitation model after 3 minutes of circulatory arrest induced by ventricular fibrillation. All animals in group A were successfully resuscitated after 4.9 +/- 2.8 minutes and 2.8 +/- 1.6 defibrillations. In group B, only 6 of 8 animals were successfully resuscitated after 6.3 +/- 1.1 minutes and 4.0 +/- 2.7 defibrillations (mean +/- SD). During CPR, cardiac output (CO), left ventricular systolic pressure (LVSP), and mean arterial pressure (MAP) were nearly identical in the groups. The hemodynamic situation during the first hour after restitution of spontaneous circulation in group B was characterized by a significantly higher heart rate, combined with significantly lower values for cardiac inotropy, CO, LVSP, and MAP compared to group A. Mean arterial peak epinephrine concentrations (group A 197 +/- 133 ng/mL, group B 1173 +/- 298 ng/mL) were approximately fivefold higher in group B. After resuscitation, plasma concentrations returned to baseline levels within 7 minutes in group A and 15 minutes in group B. Later hemodynamic differences between the groups are thereby attributed to a detrimental impact of high-dose epinephrine on the heart during resuscitation.

**Comments:** Detrimental effects on cardiac function following resuscitation appear to be related to high dose epinephrine.

**Level of Evidence 6**

**Quality of evidence-Good to fair**

**Evidence Supportive**

**Lindner, K. H., F. W. Ahnefeld, et al. (1991). "Comparison of different doses of epinephrine on myocardial perfusion and resuscitation success during cardiopulmonary resuscitation in a pig model." Am J Emerg Med 9(1): 27-31.**

Published results of dose-response effects of adrenergic drugs (epinephrine [E]) vary so much between studies because of differences in animal models and duration of ischemia before drug administration. In this investigation the effects of different doses of E on coronary perfusion pressure (CPP), left ventricular myocardial blood flow (MBF) and resuscitation success were compared during closed-chest cardiopulmonary resuscitation (CPR) after a 4-minute period of ventricular fibrillation in 28 pigs. MBF was measured during normal sinus rhythm using tracer microspheres. After 4 minutes of ventricular fibrillation CPR was performed with the use of a pneumatic piston compressor. After 4 minutes of mechanical measures only, the animals were randomly allocated into four groups of seven, receiving 0.015, 0.030, 0.045, and 0.090 mg/kg E intravenously respectively. MBF measurements were started 45 seconds after E administration; hemodynamic measurements after 90 seconds. Four minutes after the first administration, the same E dose was given before defibrillation. The CPP of animals given 0.015, 0.030, 0.045 and 0.090 mg/kg E were as follows: 16.3 +/- 6.1, 25.6 +/- 5.8, 33.2 +/- 8.4 and 30.4 +/- 6.3 mm Hg. The left ventricular MBF values were: 14 +/- 9, 27 +/- 11, 43 +/- 6, 46 +/- 10 mL/min/100 g. The differences between the groups receiving 0.015 and 0.045 mg/kg and between the groups receiving 0.015 mg/kg and 0.090 mg/kg were statistically significant (P less than .05). Resuscitation success was 14.3%, 42.9%, 100% and 86.7% respectively. A significant difference in resuscitation success was found only between 0.015 mg/kg and 0.045 mg/kg

**Level of Evidence 6**

**Quality of evidence-Good**

**Evidence. Supportive**

Tang, W., M. H. Weil, et al. (1995). Epinephrine increases the severity of postresuscitation myocardial dysfunction." Circulation 92(10): 3089-93.

**BACKGROUND:** Epinephrine has been the mainstay for cardiac resuscitation for more than 30 years. Its vasopressor effect by which it increases coronary perfusion pressure is likely to favor initial resuscitation. Its beta-adrenergic action, however, may have detrimental effects on postresuscitation myocardial function when administered before resuscitation because it increases myocardial oxygen consumption. In the present study, our focus was on postresuscitation effects of epinephrine when this adrenergic agent was

administered during cardiopulmonary resuscitation. Postresuscitation myocardial functions were compared with those of a selective alpha-adrenergic agent, phenylephrine, when epinephrine was combined with a beta 1-adrenergic blocking agent, esmolol, and saline placebo. **METHODS AND RESULTS:** Ventricular fibrillation was induced in 40 Sprague-Dawley rats. Mechanical ventilation and precordial compression was initiated either 4 or 8 minutes after the start of ventricular fibrillation. The adrenergic drug or saline placebo was administered as a bolus after 4 minutes of precordial compression. Defibrillation was attempted 4 minutes later. Left ventricular pressure, dP/dt40, and negative dP/dt were continuously measured for an interval of 240 minutes after successful cardiac resuscitation. Except for saline placebo, comparable increases in coronary perfusion pressure were observed after each drug intervention. The number of countershocks required for restoration of spontaneous circulation was significantly greater for epinephrine-treated animals (10 +/- 8) when compared with phenylephrine-treated animals (1.8 +/- 0.4, P < .01) and with animals treated with epinephrine combined with esmolol (1.6 +/- 0.9, P < .01). After resuscitation, dP/dt40 and negative dP/dt were significantly decreased and left ventricular end-diastolic pressure was significantly increased in each animal when compared with prearrest levels. However, the greatest impairment followed epinephrine, and this was associated with significantly greater heart rate and the shortest interval of postresuscitation survival of 8 +/- 4 hours, whereas placebo controls survived for 12 +/- 11 hours. Phenylephrine-treated animals survived for 41 +/- 10 hours (P < .01 versus epinephrine), and animals that received a combination of epinephrine and esmolol survived for 35 +/- 11 hours (P < .01 versus epinephrine). When the duration of untreated cardiac arrest was increased from 4 to 8 minutes, the severity of postresuscitation left ventricular dysfunction was magnified, but disproportionate decreases in postresuscitation survival were again observed with placebo and epinephrine when compared with alpha-adrenergic agonists. **CONCLUSIONS:** In an established rodent model after resuscitation following cardiac arrest, **epinephrine significantly increased the severity of postresuscitation myocardial dysfunction** and decreased duration of survival. More selective alpha-adrenergic agonist or blockade of beta 1-adrenergic actions of epinephrine reduced postresuscitation myocardial impairment and prolonged survival.

**Comments:** Epinephrine increased the severity of post-resuscitation myocardial dysfunction and decreased the duration of survival.

**Level of Evidence 6**

**Quality of evidence-Good**

**Evidence. Supportive**

Schmitz, B., M. Fischer, et al. (1995). "Resuscitation from cardiac arrest in cats: influence of epinephrine dosage on brain recovery." Resuscitation **30**(3): 251-62.

The quality of brain recovery after cardiac arrest depends crucially on the speed of cardiac resuscitation because the low cerebral perfusion pressure during the resuscitation procedure facilitates the development of no-reflow. To accelerate return of spontaneous circulation, high dose epinephrine has been recommended but the effect on the dynamics of early brain recovery is still unknown. We, therefore, studied the dynamics of brain resuscitation after cardiopulmonary resuscitation (CPR) with standard and high dose epinephrine using non-invasive NMR techniques. Fifteen min cardiac arrest was induced in normothermic cats by ventricular fibrillation. CPR was performed using an inflatable pneumatic vest for cyclic chest compression. With the beginning of CPR the standard dose group received 0.02 mg/kg epinephrine (n = 6) and the high dose group received 0.2 mg/kg (n = 8). Brain recovery was monitored by magnetic resonance imaging of the apparent diffusion coefficient (ADC) of water for 3 h. Although high dose epinephrine treatment led to a significantly higher blood pressure during early reperfusion, rapidly changing heterogeneities of early brain recovery were observed in both groups. **High dose epinephrine thus does not improve the quality of post-cardiac arrest brain recovery during the first 3 h of reperfusion.**

**Level of Evidence 6**

**Quality of evidence-Good**

**Evidence. Supportive**