WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

Worksheet author(s)

Amelia Reis	**Date Submitted for review:**

Clinical question.

In adult and pediatric patients with cardiac arrest (pre-hospital [OHCA] or in-hospital [IHCA) (P), does the use of any specific alternative dosing regimen for epinephrine (I) compared with standard recommendations (C), improve outcome (e.g. ROSC, survival to hospital discharge, survival with favorable neurologic outcome) (O)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention therapy

State if this is a proposed new topic or revision of existing worksheet: new topic

Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet?

no financial conflict of interest

one scientific conflict of interest: co-author in an article that address this subject

Search strategy (including electronic databases searched).

PUBMED: "(("Epinephrine"[Mesh])) AND (("Heart Arrest"[Mesh]) OR ("Cardiopulmonary Resuscitation"[Mesh]))) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

EMBASE: [cardiopulmonary AND 'resuscitation'/exp AND [humans]/lim AND [embase]/lim AND [<1966-2008]/py] and [('epinephrine'/exp OR 'epinephrine') AND [humans]/lim AND [<1966-2008]/py]

AHA Endnote Master Library "(epinephrine as title) and (resuscitation as keyword)"

Cochrane database for systematic reviews "(epinephrine or adrenaline) and ("cardiopulmonary resuscitation" or "heart arrest" or "cardiac arrest")

Web of Science. "Title=(epinephrine) and Title=(cardiopulmonary resuscitation" or "cardiac arrest" or "heart arrest")

LILACS "Title=(epinephrine or adrenaline)

- **State inclusion and exclusion criteria**

Exclusion criteria: Not true cardiac arrest models (e.g., cardiac pacing), not intravenous or intraosseous epinephrine (e.g., endotracheal, intra aortic, nasal), epinephrine for newborn resuscitation, articles published in different languages from English, Portuguese or Spanish.

Inclusion criteria: studies were included if they addressed cardiopulmonary resuscitation or cardiac arrest and specified the doses of epinephrine used.

- **Number of articles/sources meeting criteria for further review:**

46 studies met criteria for further review. Of these ten were LOE 1 (RCTs), three LOE 2 (non-randomised, concurrent controls), seven LOE 3 (retrospective controls), nine LOE 4 (no controls), and seventeen LOE 5 (not directly related; all animal studies).

Summary of evidence

Evidence Supporting Clinical Question

Good	Callaham 1992 [A,B] Gueugniaud 1998 [A,B] *Vandycke 2000 [A]			Gonzalez 1989 [E] Wortsman 1993 [E]	*Brown 1986* [E] *Brown 1987* [E] *Brunette 1990* [A] ***Burchfield 1993*** [A,E] *Lindner 1991* [E]
Fair	Lindner 1991 [A]		**Goetting** 1989 [A,B,E] **Goetting** 1991 [A,B,D,E]	Barton 1991 [A]	*Hoekstra 1993* [E] *Chase 1993* [E]
Poor				Koscove 1988 [A] Paradis 1991 E Cipolotti 1991 [D]	***Brown 1988*** [E]
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event
Bold = Pediatric studies
C = Survival to hospital discharge
D = Intact neurological survival
* = meta-analysis
E = Other endpoint
Italics = *Animal studies*

Evidence Neutral to Clinical question

Good	Brown 1992 [A,B,C,D] Callaham 1992 [,C,D] Choux 1995 [A,B,C,D] Gueugniaud 1998 [C,D] Stiell 1992 [A,C,D,E] *Vandycke 2000[B,C] **Patterson** 2005 [A,B,C,D]	Callaham 1991 [,B,C,D,E] **Carpenter,** 1997 [A,B,C,E] Woodhouse 1995 [B,C,E] **Dieckmann** 1995 [A,B,C,D]	Carvolth, 1996 [B,C]		***Berkowitz 1991*** [E] *DeBehnke 1992* [E]
Fair	Lindner 1991 [C] Lipman 1993 [A, B, C] Sherman 1997 [A,C,D]	**Rodriguez Nunez** 2005 [A,C]			
Poor				Martin 1990 [E]	
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event
Bold = Pediatric studies
C = Survival to hospital discharge
D = Intact neurological survival
* = meta-analysis
E = Other endpoint
Italics = *Animal studies*

Evidence Opposing Clinical Question

Good	**Perondi** 2004 [ABC]		Behringer 1998 [D]		*Berg 1994* [B, D, E] ***Berg 1996*** [B, D, E] ***Gedeborg 2000*** [E] *McCaul 2006 E*
Fair		Rivers 1994 [B,C,D,E]	Marwick 1988 [A,B,C]		*Bar-Joseph 2000* [E] *Hornchen 1993* [A,E] *Schmitz 1995* [E]
Poor					
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Animal studies
Bold = Pediatric studies

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

Epinephrine is the main drug used in cardiopulmonary resuscitation. It is recommended for all arrest rhythms: asystole, pulseless electrical activity, ventricular fibrillation and pulseless ventricular tachycardia. In pediatric patients it is also used for bradycardia with signs of hypoperfusion, as this rhythm often precedes cardiac arrest.

The main effect of epinephrine in cardiac arrest is through activation of α receptors, causing intense peripheral vasoconstriction. As a result of the vasoconstriction in descending aorta, there is an increase in the flow in the coronary and carotid artery, thus improving myocardial and cerebral perfusion. Additionally, activation of β1 receptors causes positive inotropic and chronotropic effects and β2 receptors promote bronchodilation.

The efficacy of epinephrine for resuscitation from cardiac arrest in animals has been documented since 1890. However, several controversies about its use persist: a primary one is the appropriate or optimal dosage standard dose epinephrine (SDE) or high dose epinephrine (HDE). Controversy exists as to the definitions of SDE and HDE. As with other vasoactive medications, the best dose for epinephrine is the one that causes the desired effect in a particular patient with a specific clinical condition meaning, that the dose should be individualized. During CPR, it is difficult to determine the best vasoactive drug dose, as it is not possible to measure the drug effect, without invasive hemodynamic monitoring.

Physiologically, higher doses increase coronary perfusion, but also increase myocardial oxygen consumption and promote a hyperadrenergic post-resuscitation state. So, the best epinephrine dose is the one between the desired effect and adverse effects, and is associated with improvement in CPR outcomes.

The ILCOR 2005 CPR guidelines recommend 0.01mg/kg/dose for pediatric patients and 1mg/dose for adults. The clinical question for this worksheet is: in adult and pediatric patients with cardiac arrest (pre-hospital or in-hospital), does the use of any specific alternative dosing regimen for epinephrine, compared with standard recommendations, improve outcome (ROSC, survival to hospital discharge, survival with favorable neurologic outcome)?

Evidence supporting clinical question:

A meta-analysis (Vandycke and Martens 2000) reviewed five randomized controlled trials in adults. Two studies compared 1mg vs. 5mg epinephrine (Brown, Martin et al. 1992; Choux, Gueugniaud et al. 1995; Gueugniaud, Mols et al. 1998), one compared 0.2mg/kg/dose vs 0.03mg/kg/dose (Brown, Martin et al. 1992), one compared 1mg vs 7mg (Stiell, Hebert et al. 1992) and one compared 1mg vs 15mg. Using return of spontaneous circulation (ROSC) as the outcome, the results favored HDE (table 1).

Table 1 (Vandycke and Martens 2000)

OR and 95% confidence interval for ROSC in the different studies, and the pooled OR and 95% confidence interval

Studies included	Odds ratio and 95% confidence interval	*P* value
N. Engl. J. Med., 1998	1.19 (1.03–1.37)	0.01933
Resuscitation, 1995	1.16 (0.79–1.69)	0.4665
N. Engl. J. Med., 1992 (Stiell)	1.17 (0.92–1.49)	0.2093
N. Engl. J. Med., 1992 (Brown)	0.72 (0.48–1.09)	0.1241
J. Am. Med. Assoc., 1992	1.60 (0.89–2.94)	0.1248
Overall	1.14 (1.02–1.27)	0.01632

One LOE 2,two LOE 3 and seven LOE 4 studies support the use of epinephrine doses higher than 1mg or 0.01mg/kg. Four of these (Koscove and Paradis 1988; Goetting and Paradis 1989; Barton and Callaham 1991; Goetting and Paradis 1991) reported increased ROSC rates. Three (Gonzalez and Ornato 1991; Paradis, Martin et al. 1991; Wortsman, Paradis et al. 1993) reported improved hemodynamic parameters. Both studies from Goeting and Paradis prospectively gave 0.2mg/kg to 20 pediatric cardiac arrest victims who had failed to respond to two standard 0.01mg/kg doses of epinephrine. Twelve had ROSC and 8 survived to discharge, six apparently regained their previous neurologic status, although only three were neurologically normal. The quality of those studies was fair and flawed by the lack of concurrent controls.

There are eight experimental studies (Brown, Werman et al. 1986; Brown, Werman et al. 1987; Brunette and Jameson 1990; Lindner, Ahnefeld et al. 1991; Lindner, Ahnefeld et al. 1991; Burchfield, Preziosi et al. 1993; Chase, Kern et al. 1993; Hoekstra, Griffith et al. 1993) that support the clinical question proposed.

No level one, two or three studies recorded better results in outcome survivals (event, hospital discharge or intact neurological) with different dose than that is recommended by ILCOR 2005 guidelines for adults. There are no studies in pediatric resuscitation which support doses other than SDE.

Evidence neutral to clinical question:

Seven good and one fair LOE 1 randomized controlled trials found no differences in outcomes with different dosing regimens for epinephrine. One (Vandycke and Martens 2000), was a meta-analysis of five level one studies (Brown, Martin et al. 1992; Callaham, Madsen et al. 1992; Stiell, Hebert et al. 1992; Choux, Gueugniaud et al. 1995; Gueugniaud, Mols et al. 1998), and demonstrated no improvement in survival of event or survival to hospital discharge (Tables 2 and 3).

Lipman et al (Lipman, Wilson et al. 1993), analyzed forty intensive care unit patients, and found no survival differences between 1mg and 10mg of epinephrine during cardiopulmonary resuscitation. No adverse effect of high dose was reported.

Sherman et al (Sherman, Munger et al. 1997), in an multicenter trial of eight academic emergency departments, and Lindner, et al (Lindner, Ahnefeld et al. 1991), compared SDE vs. HDE in patients with cardiac arrest in asystole or PEA and observed no advantage to HDE.

Table 2 (Vandycke and Martens 2000)

OR and 95% confidence interval for admission to the hospital in the different studies, and the pooled OR and 95% confidence interval

Studies include	Odds ratio and 95% confidence interval	*P* value
N. Engl. J. Med., 1998	1.03 (0.82–1.31)	0.8207
Resuscitation, 1995	1.20 (0.62–2.33)	0.6636
N. Engl. J. Med., 1992 (Stiell)	0.80 (0.51–1.25)	0.3532
N. Engl. J. Med., 1992 (Brown)	No data available	
J. Am. Med. Assoc., 1992	0.20 (0.004–1.82)	0.2391
Overall	1.03 (0.86–1.24)	0.7485

Table 3 (Vandycke and Martens 2000)

OR and 95% confidence interval for hospital discharge in the different studies, and the pooled OR and 95% confidence interval

Studies included	Odds ratio and 95% confidence interval	*P* value
N. Engl. J. Med., 1998	0.70 (0.43–1.12)	0.1482
Resuscitation, 1995	1.89 (0.38–12.22)	0.6009
N. Engl. J. Med., 1992 (Stiell)	1.15 (0.62–2.16)	0.7478
N. Engl. J. Med., 1992 (Brown)	0.82 (0.30–2.12)	0.8198
J. Am. Med. Assoc., 1992	1.20 (0.20–8.70)	1.000
Overall	0.74 (0.53–1.03)	0.08006

Two good LOE 2 (Woodhouse, Cox et al. 1995) reported no significant differences in immediate survival or hospital discharge between 1mg or 10mg of epinephrine vs. placebo. Two retrospective adult studies (Callaham, Barton et al. 1991 and Carvolth and Hamilton 1996), one case series (Martin, Werman et al. 1990) and two experimental studies (Brunette and Jameson 1990; Berkowitz, Gervais et al. 1991; DeBehnke, Angelos et al. 1992) observed similar results.

Two studies, described in table 4, retrospectively compared the prognosis in pediatric cardiopulmonary resuscitation with HDE and SDE. Dieckman and Vardis (Dieckmann and Vardis 1995) studied 65 children with out-of-hospital cardiac arrest and while Carpenter and Stenmark (Carpenter and Stenmark 1997) analyzed 51 children with in-hospital cardiac arrest. Epinephrine dosage did not influence outcome in those nonrandomized series of pediatric cardiac arrests, however the majority of patients in the Dieckman (Dieckmann and Vardis 1995) study were not salvageable and therefore their participation in the therapeutic trial is questionable. A LOE 1 pediatric trial (Patterson, Boenning et al. 2005) showed that 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 refractory to prehospital interventions.

Table 4. High doses x standard dose: meta-analysis. Hospital discharge

	High dose	Standard dose
Dieckmann et al, 1995	2.5%	7.7%
Carpenter et al, 1997	26%	23%

Evidence opposing to clinical question

One randomized controlled trial (Perondi, Reis et al. 2004) addressed in-hospital pediatric CPR prognosis with HDE vs. SDE as rescue therapy, after a first dose of 0.01mg/kg. None of the patients in the HDE group, but four in SDE group, survived to hospital discharge. Among the patients whose cardiac arrest was caused by asphyxia, 24h survival rates were statistically significant better in SDE group. This data suggested that HDE was worse than SDE.

One nonrandomized control trial (Rivers, Wortsman et al. 1994), two retrospective (Marwick, Case et al. 1988) and seven animal studies (Hornchen, Lussi et al. 1993; Berg, Otto et al. 1994; Schmitz, Fischer et al. 1995; Berg, Otto et al. 1996; Bar-Joseph, Weinberger et al. 2000; Gedeborg, Silander et al. 2000; McCaul, McNamara et al. 2006) also reported survival outcomes rates unfavorable to HDE.

Conclusions

Although optimal epinephrine dose during CPR has been the subject of extensive research, questions about dosing regimen are far from answered. Almost a century of clinical experience confirms the benefits of epinephrine use in patients, but current dosage recommendations for epinephrine administration during cardiac arrest controversial

Publications to date show no improvement in survival outcomes of victims of cardiopulmonary arrest with doses other than that recommended by ILCOR 2005 guidelines. Moreover, there are concerns that HDE is associated with increased post-resuscitation complications. It is essential to consider the purposes and disadvantages of this medication. The repeated use of high doses can cause organ damage superior to beneficial effect of improved coronary and cerebral perfusion.

Some data demonstrate increased ROSC with higher doses, but with no increase in survival or neurological recovery. ROSC is considered the primary goal by some few researchers as they argue that without a heartbeat, the brain cannot be perfused; the counterargument is that patients may ultimately have beating hearts but nonfunctioning brains, and those frequently die after an extensive and expensive medical care. Probably, patients who have already sustained irreversible neurologic injury can be resuscitated with HDE.

The hypothesis that the use of HDE results in improved rates of ROSC, long-term survival and neurological function is not supported by the data; however, there is no evidence that the use of HDE results in more survivors with severe neurological deficits (Patterson, Boenning et al. 2005).

Other related questions about epinephrine dose must be mentioned. The effects of hypoxia and energy failure on either reuptake or enzymatic degradation of catecholamines is not completely understood. The duration of action, the dosing interval, and the pharmacokinetics of variable epinephrine dosages in such conditions has not been sufficiently investigated. There are some data showing variability of catecholamine pharmacokinetics and pharmacodynamics among ill and normal subjects. So, it is likely that similar variability exists during cardiac arrest and CPR. A life-saving dose for one patient may be life-threatening for another. The ideal treatment is to titrate epinephrine doses to achieve adequate myocardial perfusion pressure by monitoring continuous arterial and central venous pressure or other physiologic variables, such as end tidal CO_2

The SDE has been a subject of intense debate, but, the limit of subsequent doses every 3 to 5 min without assessment has not been questioned by most literature data available. ROSC without consideration of neurologic recovery should not be a limit of subsequent epinephrine doses in ACLS and PALS. Probably it not a good practice to give a lot of epinephrine doses without thinking about neurologic outcome.

Extrapolation of catecholamine doses from experimental studies is difficult., Adult cardiac arrest frequently occurs in patients with underlying heart diseases, while pediatric cardiac arrest is usually secondary to hypoxemia, asphyxia or shock. Animal data is usually derived from controlled situations of fibrillatory cardiac arrest in healthy myocardium. Another difficulty is the different definitions of HDE range from 3mg (Lindner, Ahnefeld et al. 1991) to 100mg (Brown, Werman et al. 1987).

Finally, Berkowitz and Gervais (Berkowitz, Gervais et al. 1991) raise the question of using a pure α agonist rather than epinephrine with both α and β agonistic actions, since the essential mechanism of action of epinephrine during CPR is due to α receptor stimulation. Studies that compare different doses of pure α agonists with epinephrine demonstrated either equivalence or poorer results.

Acknowledgements:

Citation List

1. Bar-Joseph, G., T. Weinberger, et al. (2000). "Response to repeated equal doses of epinephrine during cardiopulmonary resuscitation in dogs." Ann Emerg Med **35**(1): 3-10.

LOE 5 fair opposed

Comments: - it is a secondary analysis of a canine study; - the primary purpose was to compare various buffer agents and all animals received the same epinephrine protocol (0,1mg/kg every 5 min); - the results only speculate about other dosing regimens; -the authors suggest that frequent administration of high dose results in a very high, potentially detrimental cumulative dose.

2. 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): 722-725.

LOE 4 fair supportive

Comments: -case series of cardiac arrest patients received different doses of epi (1 to 15mg) selected by the physician;-the definition of HDE was 0.2mg/kg or more, and SDE was less than that.

3. Behringer, W., H. Kittler, et al. (1998). "Cumulative epinephrine dose during cardiopulmonary resuscitation and neurologic outcome." Ann Intern Med **129**(6): 450-456.

LOE 3 good opposed

Comments: -retrospective cohort study in ventricular fibrillation, the retrospective design of the study has several limitations; -lack of comparable groups; -increasing cumulative dose of epinephrine (4mg) during ACLS was independently associated with unfavorable neurologic function when compared with smaller doses (1mg); -no patient who received a cumulative dose of more 13mg achieved good neurologic recovery; -from 44 patients whose cumulative dose of epinephrine was more than 6mg, 36 achieved ROSC and 2 left hospital without severe neurologic impairment; - the authors pointed an adverse effect of epi that was independent from the no-flow or low-flow duration.

4. 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): 1695-1700.

LOE 5 good opposed

Comments: a swine model of ***pediatric*** *asphyxia cardiac arrest comparing 0.02mg/kg with 0,2mg/kg of epinephrine; -the paper analyzes survival to event, neurologic recovery and hemodynamic parameters; -4/13 HDE piglets died in the ICU vs. 0/10 SDE piglets ($p \leq 0.05$); -HDE piglets had, after resuscitation, higher heart rates and aortic diastolic pressures ($p \leq 0.05$); -the authors comments that hyperadrenergic condition, in HDE group, contributed to higher mortality rate; -the investigation suggests that HDE may improve*

ROSC due increasing myocardial perfusion pressure during CPR, however this result did not translate into improved long-term survival or neurologic outcome;: cross-species catecholamine pharmacokinetics and pharmacodynamics are not well established; -the study utilized long downtime and relatively short period of chest compressions; -the sample size is small for outcome data, resulting in large β errors; -the CPR provided was excellent, so, further increases in myocardial perfusion pressure from HDE were not necessary.

5. 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): 282-290.

LOE 5 good opposed

Comments: -swine fibrillatory cardiac arrest mode comparing 0.02mg/kg to 0.2mg/kg of epinephrine; -some animals treated with HDE experienced a lethal toxic hyperadrenergic state, with severe SVT, VT and hypertension 10 min after ROSC; -the improved hemodynamic with HDE was irrelevant to outcome; -species catecholamine pharmacokinetics and pharmacodynamics are not well established; -the application of catecholamine doses from animals to humans is hardly appropriate; -

6. Berkowitz, I. D., H. Gervais, et al. (1991). "Epinephrine dosage effects on cerebral and myocardial blood flow in an infant swine model of cardiopulmonary resuscitation." Anesthesiology **75**(6): 1041-1050.

LOE 5 good neutral

*Comments: the study evaluates the effects of graded epinephrine continuous infusions on cerebral and myocardial vascular pressures and blood flow during prolonged CPR (50 min) in a **infant** swine fibrillatory cardiac arrest mode; - compared with a control group (no epinephrine), myocardial perfusion pressure and myocardial blood flow improved with 0.01mg/kg/min of epinephrine, and, improved less markedly with 0.001mg/kg/min or 0.1mg/kg/min, but this difference was not significant; -cerebral blood flow was maintained during the first 20 min of CPR with all three epinephrine dosage; --it is the first report of plasma epinephrine concentrations made during CPR in a infant animal model*

7. Brown, C. G., H. A. Werman, et al. (1986). "Comparative effect of graded doses of epinephrine on regional brain blood flow during CPR in a swine model." Ann Emerg Med **15**(10): 1138-1144.

LOE 5 good supportive

Comments: - study design is pretty similar to the next one; -this study evaluated the effects of graded doses of epinephrine on regional brain blood flow during CPR in a swine fibrillatory cardiac arrest model; -the epinephrine doses tested were 0.02, 0.2, and 2.0mg/kg; -higher doses (0.2 and 2.0mg/kg) significantly increased regional CBF; -the applicability of the model to cardiac arrest is debatable; -the variables measured may not be associated with better outcome

8. Brown, C. G., H. A. Werman, et al. (1987). "The effects of graded doses of epinephrine on regional myocardial blood flow during cardiopulmonary resuscitation in swine." Circulation **75**(2): 491-497.

LOE 5 good supportive

Comments: - this study evaluated the effects of graded doses of epinephrine on myocardial blood flow during CPR in a swine fibrillatory cardiac arrest model; -myocardial blood flow improved markedly with HDE (0.2mg/kg and 2.0 mg/kg) compared with 0.02mg/kg; -concerns regarding the ultrastructural changes in the myocardium promoted by HDE not were solved; -the applicability of the model to cardiac arrest is debatable, as the previous study;- animals received dipyridamole to induce maximal coronary vasodilatation

9. Brown, C. G., R. B. Taylor, et al. (1988). "Effect of standard doses of epinephrine on myocardial oxygen delivery and utilization during cardiopulmonary resuscitation." Crit Care Med **16**(5): 536-539.

LOE 5 fair supportive

Comments: -study with only five miniature swine that measure the effect of SDE on myocardial blood flow and myocardial oxygen consumption

10. 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): 1051-1055.

LOE 1 good neutral

Comments: -multicenter randomized controlled trial; -no differences were reported on outcomes (ROSC, survival of event, hospital discharge, and neurologic function) using 0.02mg/kg or 0.2mg/kg of epinephrine; -in patients with electromechanical dissociation the rate of ROSC was higher when patients were treated with HDE than SDE; -maybe there are some sub group of cardiac arrest patients who would benefit from higher doses; -the authors found no adverse effects of HDE; -more than 60% or cardiac arrests were not witnessed, so the length of time to receive epinephrine may have interfered on results; -the time to receive the first epinephrine dose was long in all patients (averaged 17 min); -subtle differences in neurologic outcome may be difficult to detect using this retrospective approach; -a type II error is likely because the rate of survival among patients given SDE is quite low

11. Brunette, D. D. and S. J. Jameson (1990). "Comparison of standard versus high-dose epinephrine in the resuscitation of cardiac arrest in dogs." Ann Emerg Med **19**(1): 8-11.

LOE 5 good supportive

Comments: -experimental study where dogs in cardiac arrest were randomized to receive saline, 0.014mg/kg by central venous line, 0.014mg/kg by intra-cardiac injection, 0.071mg/kg by central venous line, 0.071mg/kg by intra-cardiac injection; -animals receiving HDE had significantly shorter resuscitation times.

12. Burchfield, D. J., M. P. Preziosi, et al. (1993). "Effects of graded doses of epinephrine during asphxia-induced bradycardia in newborn lambs." Resuscitation **25**(3): 235-244.

LOE 5 good supportive

Comments: -experimental model with newborn lambs in hypoxemic bradycardia; -epinephrine doses higher than 0.01mg/kg but smaller than 0.1mg/kg were more effective, than different doses, to revert this rhythmus.

13. Callaham, M., C. W. Barton, et al. (1991). "Potential complications of high-dose epinephrine therapy in patients resuscitated from cardiac arrest." JAMA **265**(9): 1117-1122.

LOE 2 good neutral

Comments: -patients (68) were enrolled for pos resuscitation complications attributable to epinephrine; -no differences in outcomes were observed, neither a harmful effect of epinephrine when higher doses were used; - the doses of epinephrine were not randomly assigned (they were chosen at clinicians' decision); -the HDE patients seems to be sicker (may have increased the likelihood of complications in that group); -part of the data was obtained by retrospective chart review, as all retrospective studies; -possibility of type II error, because of small number of cases

14. Callaham, 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): 2667-2672.

LOE 1 good supportive (ROSC and survival of event) neutral (survival to hospital discharge and intact neurological survival)

Comments: this study analyzed three different groups: 15mg of epinephrine (HDE) vs. 15mg of norepinephrine vs. 1mg of epinephrine (SDE), the prognosis was better in HDE when ROSC (P=0.01) and survival to event (P=0.02) were analyzed; -there were no differences related to hospital discharge rates and Cerebral Performance Category scores; - A tendency toward a higher frequency of postresuscitation ventricular tachycardia after HDE was observed compared to SDE (P=0.08); -the study size was sufficient to provide a power of only 0.61 for outcome of hospital discharge (only 1.8% were discharged); - patients enrolled in this study were not a complete spectrum of cardiac arrest victims, but only those with ominous rhythms or having failed to defibrillation; -the total epinephrine dose range had a great variation (3mg to 35mg)

15. 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): 403-408.

LOE 2 good neutral

Comments: -it is a pediatric in-hospital CPR study; -HDE was defined as 0.12+/-0.05mg/kg and SDE as 0.01+/-0.01mg/kg; -HDE was used as both initial and rescue therapy, which may have played a role in results; -no differences were noted in measured outcomes (ROSC, short-term survival, survival to hospital discharge; -); -the time to ROSC was significant longer in HDE group; -retrospective study;- the sample size is relatively small reducing the power of the study and increasing the possibility of a type II error; -HDE group may have been initially more ill than SDE, there was a higher proportion of patients with cardiac disease in the HDE group; -there was a trend for more SDE patients being in the PICU, maybe these patients were closer monitored and treated by more skilled personnel

16. Carvolth, R. D. and A. J. Hamilton (1996). "Comparison of high-dose epinephrine versus standard-dose epinephrine in adult cardiac arrest in the prehospital setting." Prehospital Disaster Med **11**(3): 219-222.

LOE 3 good neutral

Comments:-retrospective adult CPR study that compared SDE (1mg bolus) to HDE (5, 10 and 15 mg bolus), -no differences were observed in survival to event or at hospital discharge

17.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): 413-419.

LOE 5 fair supportive

Comments: -animal study; - increasing in myocardial perfusion pressure and blood flow with 0.2mg/kg compared with 0.02 mg/kg was found; - cardiac output decreased after HDE compared to baseline cardiac output during CPR in group without epinephrine, -repeated-measure design was not randomized as to the dose of epinephrine; -the study was performed in a healthy porcine model of cardiac arrest

18. 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.

LOE 1 fair neutral

Comments: randomized controlled trial with adult cardiac arrest patients; -repeated epinephrine dose of 1mg was compared with repeated 5mg; -ROSC, hospital admission, survival at 6 months and neurological outcome were equivalent in both groups; -the authors did not observe adverse effects postresuscitation (neurologic or ventricular dysrhythmias);- time to epinephrine was statistically different and unfavorable to the high-dose group; -CPR took too long to be initiated; -

19. Cipolotti, G., A. Paccagnella, et al. (1991). "Successful cardiopulmonary resuscitation using high doses of epinephrine." Int J Cardiol **33**(3): 430-431.

LOE 5 poor
Comments: HDE were used in two cardiac arrest patients during an open heart surgery.

20. DeBehnke, D. J., M. G. Angelos, et al. (1992). "Use of cardiopulmonary bypass, high-dose epinephrine, and standard-dose epinephrine in resuscitation from post-countershock electromechanical dissociation." Ann Emerg Med **21**(9): 1051-1057.

LOE 5 good neutral

Comments: controlled laboratory study using a canine arrest model; -no differences in survival were noticed between groups

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

LOE 2 good neutral

Comments: -pediatric out-of-hospital CPR; - HDE (> 0.1 mg/kg), SDE (< 0.1 mg/kg), or no epinephrine

(NE), was administered by paramedics based on base hospital physician order and availability of access for drug ; - epinephrine dosage did not influence outcome; - the majority of patients were not salvageable and therefore did not respond to epinephrine administration; -1 of 44 patients given HDE survived to hospital admission, compared with 1 of 13 given SDE; the authors pointed that the low survival rate (3%) reflected deficiencies in overall treatment of pediatric CPR patients on that community; -retrospective, small number of patients were enrolled (65)

22. 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): 1423-1430.

LOE 5 good opposed

Comments: -experimental CPR in piglets; -dynamics or superficial cortical cerebral blood flow and global cerebral oxygenation was observed with HDE (0.2mg/kg) and SDE (0.02mg/kg); -vasoconstriction of cortical cerebral blood vessels may have contribute to failure to improve outcomes.

23. Goetting, M. G. and N. A. Paradis (1989). "High dose epinephrine in refractory pediatric cardiac arrest." Crit Care Med **17**(12): 1258-1262.

LOE 4 fair supportive

Comments: -anecdotal report of successful ROSC with HDE; -prospectively HDE (0.2mg/kg) was given to 7 pediatric cardiac arrest victims who had failed to respond to two SDE(0.01 mg/kg); -6 had ROSC

24. Goetting, M. G. and N. A. Paradis (1991). "High-dose epinephrine improves outcome from pediatric cardiac arrest." Ann Emerg Med **20**(1): 22-26.

LOE 4 fair supportive

Comments: -anecdotal report of successful ROSC with HDE; -prospectively HDE (0.2mg/kg) was given to 20 pediatric cardiac arrest victims who had failed to respond to two SDE(0.01 mg/kg); -12 had ROSC and 8 survived to discharge, six apparently regained their premorbid neurologic status, although only three were neurologically normal

25. Gonzalez, E. R. and J. P. Ornato (1991). "The dose of epinephrine during cardiopulmonary resuscitation in humans: what should it be?" DICP **25**(7-8): 773-777.

LOE 4 good supportive

Comments: studied the effect of incremental (1mg, 3mg and 5mg) dose of epinephrine on human blood pressure during CPR; -systolic and diastolic pressures increased in direct relationship to epinephrine dosage; -end-tidal CO2 concentration decreased progressively with each dose of epinephrine; -cardiac output also decreased with increasing epinephrine dose

26. 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): 1595-1601.

LOE 1 good neutral

Comments: -multicenter randomized clinical trial comparing repeated HDE with repeated standard doses in cases of out-of-hospital cardiac arrest adult patients; -the ROSC and hospital admission rates were better in HDE group, P=0.02 and P=0.05 respectively; -no statistically difference was noted when the outcome measure was hospital discharge, in fact the hospital mortality was higher in HDE; -there was no difference in neurologic status; -it is important to point that overall survival rate was poor in both groups and the long duration of cardiac arrest before advanced CPR could explain those rates

27. Hoekstra, J. W., R. Griffith, et al. (1993). "Effect of standard-dose versus high-dose epinephrine on myocardial high-energy phosphates during ventricular fibrillation and closed-chest CPR." Ann Emerg Med **22**(9): 1385-1391.

LOE 5 fair supportive

Comments:- nonrandomized controlled study; -prolonged ventricular fibrillation in a porcine model; -testing 0.02mg/kg of epinephrine vs.0.2mg/kg; -HDE did not deplete myocardial high energy phosphate when given in this model, and did replete phosphocreatine during closed-chest CPR (increasing myocardial energy stores)

28. 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): 184-187.

LOE 5 fair opposed

Comments:- in ventricular fibrillation in a porcine model; animal study testing 0.01mg/kg of epinephrine vs.0.05mg/kg; -the hemodynamic parameters were worse with HDE; -as other fibrillatory animal model studies, this paper have demonstrated adverse effects from HDE during CPR, including a toxic adrenergic state immediately after ROSC…

29. Koscove, E. M. and N. A. Paradis (1988). "Successful resuscitation from cardiac arrest using high-dose epinephrine therapy. Report of two cases." JAMA **259**(20): 3031-4.

LOE 4 fair supportive

Comments: - report of only two cases of successful ROSC when HDE was administered after standard doses failed to result in resuscitation

30. 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.

LOE 5 good supportive

Comments: Animal study (pig model); - benefit on myocardial perfusion was higher in HDE group; -the

animals were allocated to receive 0.015 or 0.030 or 0.045 or 0.09 mg/kg of epinephrine, the rates of resuscitation success was respectively 14.3%, 42.9%, 100%, 86.7%.

31. Lindner, K. H., F. W. Ahnefeld, et al. (1991). "Comparison of standard and high-dose adrenaline in the resuscitation of asystole and electromechanical dissociation." Acta Anaesthesiol Scand **35**(3): 253-6.

LOE 1 fair supportive to ROSC and neutral to hospital discharge

Comments: -randomized controlled trial comparing 1mg to 5mg of epinephrine dose; -cardiac arrest patient were in asystole or electromechanical dissociation; -ROSC rates were better with HDE; -hospital discharge rates were similar between HDE and SDE

32. Lipman, J., W. Wilson, et al. (1993). "High-dose adrenaline in adult in-hospital asystolic cardiopulmonary resuscitation: a double-blind randomised trial." Anaesth Intensive Care **21**(2): 192-6.

LOE 1 fair neutral

Comments: -randomized controlled trial with 40 adult cardiac arrest patients; -there was no significant difference in the response between the HDE and SDE group; -groups were different: -the acute physiological score, 24 hours prior to arrest, was significant higher in HDE; -the degree of inotropic support (dobutamine) were significantly higher in the HDE; the leading cause of cardiac arrest were sepsis in the vast majority of patients (80%), as the predicted mortality is 45% in those patients, cardiac arrest in this situation is probably manifestation of severely diseased myocardium

33. Martin, D., H. A. Werman, et al. (1990). "Four case studies: high-dose epinephrine in cardiac arrest." Ann Emerg Med **19**(3): 322-326.

LOE 4 fair neutral

Comments: report of four patients which standard AHA protocol failure to resuscitate; -HDE (0.12 to 0.22 mg/kg) was administered after prolonged RCP (at least 20 min)

34. Marwick, T. H., C. Case, et al. (1988). "Adverse effect of early high-dose adrenaline on outcome of ventricular fibrillation." Lancet **2**(8602): 66-8.

LOE 3 Opposed fair

Comments: observational study looking at the effect on survival with the introduction of HDE protocol to ventricular fibrillation; -there was a significant reduction in the immediate survival; obs: 1mg was considered HDE

35. McCaul, C. L., P. J. McNamara, et al. (2006). "Epinephrine increases mortality after brief asphyxial cardiac arrest in an in vivo rat model." Anesth Analg **102**(2): 542-8.

LOE 5 good opposed

Comments: animal study using an in vivo rat model; -animals were allocated to receive 0.01mg or 0.03mg/kg

of epinephrine or saline; -the mortality rates were 33.3%, zero, 72.8% respectively; -the animals that received 0.03mg/kg of epinephrine developed more hypertension, tachycardia and cardiac disfuncion.

36. 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): 1139-1144.

LEO 4 poor supportive

Comments: HDE (0.2mg/kg) was more likely increase coronary perfusion pressure, -the cumulative effect of multiple doses was not considered; no survival outcome were observed

37. Patterson, M. D., D. A. Boenning, et al. (2005). "The use of high-dose epinephrine for patients with out-of-hospital cardiopulmonary arrest refractory to prehospital interventions." Pediatr Emerg Care **21**(4): 227-237.

LOE 2 good neutral

Comments: -multicenter collaborative trial involving 7 tertiary pediatric centers; - it is the first prospective randomized controlled trial that examine the use of HDE in out-hospital pediatric cardiac arrest, -ages ranged from newborn to 22 years; -HDE group received first dose of 0.1mg/kg and subsequent doses of 0.2mg/kg, SDE group received first dose of 0.01mg/kg and subsequent doses of 0.2mg/kg; -there was a trend toward an increase rate of ROSC in HDE group, there was no significant improvement in survival to discharge or neurological outcome; -wide variability of patient presentation at emergency department; -the study was blinded in some but not all centers; there was inability to enroll as many patients as originally planned

38. Perondi, M. B., A. G. Reis, et al. (2004). "A comparison of high-dose and standard-dose epinephrine in children with cardiac arrest." N Engl J Med **350**(17): 1722-1730.

LOE 1 good opposed

Comments: -randomized prospective controlled trial in pediatric CPR; -the patients were randomized to receive 0.01mg/kg or 0.1mg/kg as rescue epinephrine dose, -ROSC similar in both groups, survival at 24h were 3% in HDE group and 21% in SDE group (P=0.05); no patient in HDE group and 12%in SDE group survived to hospital discharge (P=0.11); in a subgroup of patients with cardiac arrest precipitated by Asphyxia no one survived at 24h in HDE group and 39% survived in SDE group (P=0.02); -the results suggested that HDE is worse and SDE in pediatric cardiac arrest patients; -small sample size, -occurrence of protocol violations,

39. Rivers, E. P., J. Wortsman, et al. (1994). "The effect of the total cumulative epinephrine dose administered during human CPR on hemodynamic, oxygen transport, and utilization variables in the postresuscitation period." Chest **106**(5): 1499-1507.

LOE 2 fair opposed

Comments: -comparative study in a large emergency department and intensive care unit; -the epinephrine

dose was 0.01 to 0.2mg/kg or 1 to 14 mg; -the patients were divided in two groups according to total cumulative dose of epinephrine (group 1: ≤15mg, group 2: >15mg); -outcome measures: hemodynamic, oxygen transport variable; mortality; -epinephrine was associated with impairment of oxygen consumption and oxygen delivery in postresuscitation, the duration and severity of these effects correlated with total cumulative dose; 85% of group one and 41% of group two were alive at 24h (P<0.002)

40. Rodriguez Nunez, A., C. Garcia, et al. (2005). "[Is high-dose epinephrine justified in cardiorespiratory arrest in children?]." An Pediatr (Barc) **62**(2): 113-6.

LOE 2 fair neutral

Comments: -prospective multicenter clinical trial in pediatric cardiac arrest; -secondary analysis of 92 pediatric patients who received epinephrine during CPR; -patients received 0.01mg/kg or 0.1mg/kg as rescue epinephrine dose;-no differences were observed between groups; -the groups were different (number of patients, age, number of epinephrine doses); -no current controls, secondary analysis (the study was not designed to compare different doses of epi)

41. 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.

LOE 5 fair opposed

Comments: -experimental study in cats; -the authors compared 0.02mg/kg to 0.2mg/kg of epinephrine; -when changes of the apparent diffusion coefficient of water in brainstem was measured in cats submitted to 15min cardiac arrest, significant faster recovery in brain stem occurred in animals treated with standard than high dose of epinephrine (P<0.05).

42. Sherman, B. W., M. A. Munger, et al. (1997). "High-dose versus standard-dose epinephrine treatment of cardiac arrest after failure of standard therapy." Pharmacotherapy **17**(2): 242-247.

LOE 1 fair neutral

Comments: -multicenter (eight academic center emergency departments) randomized controlled trial; -no difference was noticed in ROSC between high and standard dose of epinephrine; -no patient survived to hospital discharge

43. Stiell, I. G., P. C. Hebert, et al. (1992). "High-dose epinephrine in adult cardiac arrest." N Engl J Med **327**(15): 1045-1050.

LOE 1 good neutral

Comments: -randomized controlled trial; -adult patients with cardiac arrest received up to five doses of HDE (7mg) or SDE (1mg); -no improvement in survival or neurologic outcome with HDE was found; a subgroup of those who received HDE after 10 min downtime were statistically less likely to survive

44. Vandycke, C. and P. Martens (2000). "High dose versus standard dose epinephrine in cardiac arrest - a meta-analysis." Resuscitation **45**(3): 161-166.

LOE 1 good supportive (ROSC) neutral (survival of event and survival to hospital discharge)

Comments: -meta-analysis; -searching the Medline database online (January 1988 to December 1998); -five randomized double blind controlled trial were analyzed; -considering ROSC as an outcome; high or escalating dose epinephrine have shown better results;-no significant improvement in hospital admission or hospital discharge; -differences in the experimental treatment (different HDE were tested); -variability in the investigated population; -the intervals between doses are not standardized

45. Woodhouse, S. P., S. Cox, et al. (1995). "High dose and standard dose adrenaline do not alter survival, compared with placebo, in cardiac arrest." Resuscitation **30**(3): 243-9.

LOE 2 good neutral

Comments: the trial was designed to compare placebo, SDE and HDE in human cardiac arrest; -no differences were observed in immediate survival, or, hospital discharge; -the study power has been severely limited by the number of eligible patients not entered; -

46. Wortsman, J., N. A. Paradis, et al. (1993). "Functional responses to extremely high plasma epinephrine concentrations in cardiac arrest." Crit Care Med **21**(5): 692-697.

LOE 4 good supportive

Comments: case series of eighteen patients with out-of-hospital cardiac arrest; -endpoints measured were: related to hemodynamic variables; -with HDE was observed an increase in Aortic diastolic pressure and plasma Epinephrine and Norepinephrine.