WORKSHEET for Evidence-Based Review of Science for Veterinary CPCR (1 & 5)

1. Basic Demographics
Worksheet author(s)

Catherine Rogers	**Date Submitted for review:** 6/21/11

[redacted]

2. Clinical question:

Worksheet question ALS03
In dogs and cats with cardiac arrest (P), does the use of vasopressin (I) compared with standard treatment recommendations (e.g., epinephrine) (C), improve outcome (e.g. ROSC, survival to hospital discharge or survival with favorable neurologic outcome)(O)?

3. Conflict of interest specific to this question:
None

4. Search strategy (including electronic databases searched):

4a. Databases

-MEDLINE via PUBMED (1950 to June 2011)
1. Vasopressin
2. Cardiac arrest
3. Cardiopulmonary resuscitation

1 and 2: 279
1 and 3: 245
Significant overlap between the two searches. After exclusions, 26 studies met criteria for further review.

Forward Review: Pub med provides alerts when a new publication fitting either of the above searches is published.

-CAB (1910 to June 2011)
SEARCH: (vasopressin) AND Topic=(cardiac arrest) OR Topic=(cardiopulmonary resuscitation)
No additional hits

4b. other sources
-non published manuscript (in review) also included (Buckley et al).

-In addition all references of identified articles and the references of the following relevant review articles were checked:
1. Schmittinger et al, 2005
2. Scrogin and Quandt, 2009

TOTAL STUDIES: 27

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

Inclusion criteria (*included)*

Randomized control trials
Case reports in target species (dogs)
Meta-analyses of randomized control trials/retrospective studies in humans, pigs, rabbits
Studies investigating vasopressin use in arrest in humans, pigs and rabbits

Exclusion criteria *(excluded)*
Abstracts only
Editorials
Studies where vasopressin was compared to other drugs (except epinephrine)
Case reports from human literature, retrospectives not involving controls from human literature
Studies in animal models investigating primary outcomes other than ROSC, survival to hospital discharge or survival with favorable neurologic outcome (studies addressing physiologic variables such as coronary perfusion pressure, blood pressure)
Studies investigating the use of vasopressin in clinical scenarios other than cardiac arrest or resuscitation
Studies involving non target species with the exception of humans, pigs and rabbits
Studies investigating models of local anesthetic induced arrest

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

5. Summary of evidence

Evidence Supporting Clinical Question

Good						*Stroumpoulis, 2008, A (V +E)* *Wenzel, 2004 BC (V, V+E)* *Voelckel, 2000 AB (V)*
Fair					Hofmeisterm, 2009, (V)	*Mentzelopoulos 2009, AC (V + steroids)* *Grmec, 2008, ABCE (V + HES)* *Grmec, 2006, AB (V, V +E)* *Stadlbauer 2003 AD (V +E)* *Wenzel 2000, AD (V)*
Poor					Schmittinger, 2005 ABCD (V)	*Guyette 2004, AB (V + E)* *Biondi, 2003 AC (V)*
	1	**2**	**3**	**4**	**5**	**6**
(P)						

Evidence Neutral to Clinical question

Good	Buckley, in press, AB (V)					*Ducros, 2010 (in press), AE (E +V)* *Mukoyama, 2009, ABCD (V)* *Callaway 2006, ABC, (V + E)* *Aung, 2005, ABCD (V)* *Babar, 1999, ABCDE (V)* *Steill 2001 ABCD (V)*
Fair						*López-Herce, 2010, A (V + E)* *Linder, 1997, ABCD (V)* *Chen 2007, A (V)* *Grmec, 2006, D (V, V +E)*
Poor						*López-Herce, 2010, A (V)* *Cody, 2010 BC (V +E)* *Meybohm 2007 A (V +E)* *Callaway, 2006 ABC, (V+E)* *Wyer, 2006, CD (V, V+E)*
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

Evidence Opposing Clinical Question

Good						
Fair						
Poor						*Duncan 2009, ABCD (V, V + E)*
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

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

V=vasopressin alone; V + E= vasopressin + epinephrine in compared to epinephrine alone

Summary of studies (supplements table above)

Vasopressin compared to epinephrine

Vfib/VT

Improves- LINDNER, ROSC/SURVIVAL TO 24 HOURS (out of hospital)
VOELCKEL, ROSC (pig model of hypovolemic shock)

No effect- BABAR, ROSC/neurologic (pig model)
LINDNER, NEURO (out of hospital)

W*orsens*

Asystole

Improves
No effect
Worsens

PEA

Improves-
No effect
Worsens

Overall

(no subgroup analysis or no difference)

Improves CHEN, ROSC (rabbit asphyxiation model)

No effect- BUCKLEY, ROSC (in hospital)
MUKOYAMA, ROSC/24 HR/DISCHARGE (out of hospital)

Worsens

Vasopressin+ epinephrine compared to epinephrine

Vfib/VT

Improves STADLBAUER, ROSC/NEURO (pig model, simulated out of hospital arrest)
STROUMPOULIS, ROSC (pig model, simulated out of hospital arrest)
WENZEL (2000), ROSC, NEURO (pig model)

No effect MEYBOHM, ROSC (pig model)

Worsens

Asystole

Improves
No effect
Worsens

PEA

Improves- GRMEC, ROSC (out of hospital, subgroup trauma)
No effect-
Worsens

Overall

(no subgroup analysis or no difference)

Improves- GUYETTE, ROSC/SURVIVAL TO HOSPITAL (out of hospital)

No effect- CALLAWAY, ROSC (out of hospital, vasopressin after first dose of epi);
CODY, ROSC/24 HRS/DISCHARGE (pulseless cardiac arrest, out of hospital)
DUCROS, ROSC, (out of hospital)
GUEGNIARD, ROSC, SURVIVAL TO ADMISSION/DISCHARGE/1 YEAR, NEURO (out of hospital)
MENTZELOPOULOS, ROSC (MPSS included, in hospital)

Worsens

Vasopressin OR vasopressin + epinephrine compared to epinephrine

Vfib/VT

Improves- GRMEC, ROSC, 24 HRS/ DISCHARGE (ESP MI, out of hospital)

No effect- AUNG, (out of hospital);
GREMEC, NEURO, (out of hospital)
WENZEL (2004), SURVIVAL TO ADMISSION (out of hospital)

Worsens

Asystole

Improves- WENZEL (2004), SURIVAL TO HOSPITAL ADMISSION/DISCHARGE (out of hospital)

No effect- AUNG (out of hospital)
Worsens

PEA

Improves- WENZEL, SURVIVAL TO ADMISSION (out of hospital)

No effect- AUNG (out of hospital)

Worsens

Overall

(no subgroup analysis or no difference)

Improves- HOFMEISTER, ROSC (veterinary study, in hospital)

No effect DUNCAN, SURVIVAL 24 HRS/DISCHARGE (in hospital)
LOPEZ-HERCE , ROSC (terlipressin, out-of hospital pig model)
STIELL, ROSC, SURVIVAL 1HR/DISCHARGE/NEURO (in hospital)
WYER, SURVIVAL TO DISCHARGE, NEURO (out of hospital, review study)

Worsens DUNCAN,ROSC (in hospital)

Other

SCHMITTINGER, ROSC/SURVIVAL/SURVIVAL TO DISCHARGE/NEURO(asystole, positive outcome, no control, *veterinary case report*)

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

7. Conclusion

There are 3 clinical veterinary studies that provide information about the use of vasopressin in dogs with cardiac arrest. The single randomized prospective study (Buckley et al) finds neither benefit nor harm in using vasopressin in lieu of epinephrine in an in-hospital arrest. Doses used in this study were not uniform, but most fell within the published recommended doses for vasopressin and epinephrine. Subgroup analysis failed to identify a treatment effect based on rhythm (not powered). In addition, there is a single case report (Schmittinger et al) and a single retrospective study (Hofmeister et al) investigating CPR in small animals that argue that vasopressin may be an effective drug for use in CPR in small animals. The retrospective study suggests that vasopressin may be superior to epinephrine, but the numbers are small (5/8 animals treated with vasopressin achieved ROSC).

In humans, there are several retrospective and prospective studies investigating the use of vasopressin in cardiac arrest. The studies differ in the subgroups analyzed, including location (out-of-hospital versus in-hospital) and initial arrest rhythm. In addition, the methods & materials vary significantly among the studies with some studies using both vasopressin + epinephrine while others compared epinephrine alone to vasopressin alone. Furthermore, the doses of vasopressin and epinephrine (high dose, low dose) are not consistent from study to study thus making it difficult to garner significance from any particular study alone. The overall conclusion is that vasopressin does not worsen outcome (except in one study, Duncan et al), but there is no repeatable evidence that it improves outcome when compared to epinephrine. Vasopressin may be substituted for epinephrine or given concurrently with epinephrine, but the outcomes are similar. Only one study comments on the fact that vasopressin is markedly more expensive than epinephrine and therefore use should be questioned when there does not appear to be a benefit. In animal models (pigs and rabbits), there are several retrospective and prospective studies that compared epinephrine to vasopressin with mixed results. Like the human studies, the doses are not consistent from study to study. The primary model is an induced fibrillation porcine model and in some of those studies, vasopressin may trend towards a better outcome when compared to epinephrine. The significance of these studies is uncertain as the effect of vasopressin does not appear to translate to human studies. Furthermore, ventricular fibrillation is a less common arrest rhythm in veterinary patients compared to humans.

There are two studies (one prospective human study, Gremec et al 2008; one porcine animal model, Voelckel et al 2000) that found vasopressin may be superior to epinephrine in the stratified patient population with underlying hypovolemic shock as a predisposing condition. However, in the Gremec study, patients in the vasopressin group concurrently received hypertonic hetastarch as part of the resuscitative protocol making it difficult to determine true significance in their findings. The porcine model (Voelckel et al, 2000) was not a realistic model as no interventions were made other than a single dose of either vasopressin or epinephrine after induced ventricular fibrillation. However, in this experiment, all the pigs that received vasopressin survived the initial event whereas all pigs receiving epinephrine died.

Overall, it appears that vasopressin is not harmful when compared to epinephrine and does not worsen outcome, but has no proven advantage in the pharmacological role of CPR. However, when different subgroups are assessed, the use of vasopressin in situations of cardiac arrest secondary to hypovolemic shock may warrant further investigation. Further studies are needed in veterinary patients (as well as in people) to determine if vasopressin is superior to epinephrine in particular subpopulations.

9. Citation list

1. Aung K, Htay T. Vasopressin for cardiac arrest: a systematic review and meta-analysis. Arch Intern Med. 2005 Jan 10;165(1):17-24.

BACKGROUND: The current guidelines for cardiopulmonary resuscitation recommend vasopressin as an alternative to epinephrine for the treatment of adult shock-refractory ventricular fibrillation. The objective of this study was to determine the effectiveness of vasopressin in the treatment of cardiac arrest. METHODS: We performed a systematic review and meta-analysis of 1519 patients with cardiac arrest from 5 randomized controlled trials that compared vasopressin and epinephrine. Two reviewers conducted a systematic search of electronic databases, complemented by hand searches, to identify randomized trials. Reviewers evaluated the quality of the trials, extracted data, and derived pooled estimates using a random-effects model. RESULTS: There were no statistically significant differences between the vasopressin and epinephrine groups in failure of return of spontaneous circulation (risk ratio [RR], 0.81; 95% confidence interval [CI], 0.58-1.12), death before hospital admission (RR, 0.72; 95% CI, 0.38-1.39), death within 24 hours (RR, 0.74; 95% CI, 0.38-1.43), death before hospital discharge (RR, 0.96; 95% CI, 0.87-1.05), or combination of number of deaths and neurologically impaired survivors (RR, 1.00; 95% CI, 0.94-1.07). Subgroup analysis based on initial cardiac rhythm showed no statistically significant difference in the rate of death before hospital discharge between the vasopressin and epinephrine groups in any of the 3 subgroups: ventricular fibrillation or ventricular tachycardia (RR, 0.97; 95% CI, 0.79-1.19), pulseless electrical activity (RR, 1.02; 95% CI, 0.95-1.10), or asystole (RR, 0.97; 95% CI, 0.94-1.00). CONCLUSIONS: There is no clear advantage of vasopressin over epinephrine in the treatment of cardiac arrest. Guidelines for Advanced Cardiac Life Support should not recommend vasopressin in resuscitation protocols until more solid human data on its superiority are available.

Comments: LOE 6, Quality- good, Direction –negative (no improvement)

This study is a meta analysis of 5 RCT including the following studies that may be included elsewhere in this worksheet: Linder 1997, li 1999, lee 2000, stiellel, 2001, wenzel 2004). The outcome measures included ROSC, survival to hospital admission (if out-of-hospital), survival to 24 hours, survival to discharge and overall survival including neurological function. There were no statistically significant differences in outcome with the use of vasopressin. The authors point out there was not consistent use of vasopressin in all the studies (epinephrine was used as a rescue agent in some) possibly confounding results. The authors bring up the cost difference between vasopressin versus epinephrine and the difficulty in justifying making this a required drug in crash carts. Importantly, vasopressin did not perform any better than epinephrine in prolonged cardiac arrest (when conditions are more acidotic).

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2. Babar SI, Berg RA, Hilwig RW, Kern KB, Ewy GA. Vasopressin versus epinephrine during cardiopulmonary resuscitation: a randomized swine outcome study. Resuscitation. 1999 Jul;41(2):185-92

In animal models, vasopressin improves short-term outcome after cardiopulmonary resuscitation (CPR) for ventricular fibrillation compared to placebo, and improves myocardial and cerebral hemodynamics during CPR compared to epinephrine. This study was designed to test the hypothesis that vasopressin would improve 24-h neurologically intact survival compared to epinephrine. After a 2-min untreated ventricular fibrillation interval followed by 6 min of simulated bystander CPR, 35 domestic swine (weight, 25+/-1 kg) were randomly provided with a single dose of vasopressin (20 U or approximately 0.8 U kg(-1) intravenously) or with epinephrine (0.02 mg kg(-1) intravenously every 5 min). Ten minutes after initial medication administration (18 min after induction of ventricular fibrillation), standard advanced life support was provided, starting with defibrillation. Animals that were successfully resuscitated received 1 h of intensive care support and were observed for 24 h. Coronary perfusion pressures were higher in the vasopressin group 2 and 4 min after vasopressin administration (28+/-2 versus 18+/-1 mm Hg, P<0.01, and 26+/-3 versus 18+/-2 mm Hg, P<0.05, respectively). The vasopressin group tended to be successfully defibrillated on the first attempt more frequently (8/18 versus 3/17, P = 0.15). Return of spontaneous circulation (ROSC) was attained in 12/18 (67%) vasopressin-treated pigs versus 8/17 (47%) epinephrine-treated pigs, P = 0.24. Twenty-four hour neurologically normal survival occurred in 11/18 (61%) versus 7/17 (41%), respectively, P = 0.24. In conclusion, vasopressin administration during CPR improved coronary perfusion pressure, but did not result in statistically significant outcome improvement.

Comments: LOE 6, quality: good, Direction: negative (vasopressin does not improve neurologic outcome)

This study investigated the use of vasopressin alone versus epinephrine in an animal model of VF. The primary outcome measured in this study is neurologic outcome, secondary outcome was ROSC. Successful defibrillation, ROSC and neurologic outcome showed a trend towards improvement with vasopressin alone, but did not reach statistical significance, possibly partially a result of the small study size. The vasopressin treated pigs had a trend towards more successful defibrillation on the first attempt, but this did not reach statistical significance. Coronary perfusion pressure was statistically improved with vasopressin alone. This study attempted to simulate an out of hospital arrest with "bystander CPR" that occurred for several minutes before debrifillation. Although this is an animal model, the primary outcome of neurologic outcome is unique (vs. ROSC or survival). The endpoint was 24

hours only and neurological performance was assessed by the "Swine Cerebral Performance Category" as follows: "Category 1 indicates a grossly normal, walking, feeding, alert animal. Category 2 is assigned to a slightly disabled, alert animal. Category 3 indicates a severely disabled animal responsive to verbal or noxious stimuli. Category 4 refers to an unresponsive, deeply comatose animal". This is similar to the score used by Buckley et al (below).

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3. Biondi-Zoccai GG, Abbate A, Parisi Q, Agostoni P, Burzotta F, Sandroni C, Zardini P, Biasucci LM. Is vasopressin superior to adrenaline or placebo in the management of cardiac arrest? A meta-analysis. Resuscitation. 2003 Nov;59(2):221-4.

Vasopressin is currently recommended in the management of patients with cardiac arrest, but its efficacy is still incompletely established. We systematically reviewed randomized trials comparing vasopressin to control treatment in the management of cardiac arrest in humans and animals. Two human and 33 animal studies were retrieved. At pooled analysis vasopressin appeared equivalent to adrenaline (epinephrine) in the management of human cardiac arrest (N=240), with, respectively 63 (78/124) vs 59% (68/116) ROSC (P=0.43), and 16 (20/124) vs 14% (16/116) survival to hospital discharge (P=0.52). In animal trials (N=669) vasopressin appeared instead significantly superior to both placebo (ROSC, respectively 93 [98/105] vs 19% [14/72], P<0.001) or adrenaline (ROSC, respectively 84 [225/268] vs 52% [117/224], P<0.001). In conclusion, vasopressin is superior to both placebo and adrenaline in animal models of cardiopulmonary resuscitation. Evidence in humans is still limited and confidence intervals estimates too wide to reliably confirm or disprove results obtained in experimental animal settings.

Comments LOE: 6, Quality: poor (retrospective/metaanalysis), Direction: mixed (positive for animal, negative for human studies)

The primary outcomes in this retrospective analysis of 35 studies (33 animal, 2 people) were ROSC and survival to discharge and compared vasopressin to either placebo or epinephrine. Weaknesses of this retrospective include no assessment of quality and lack of consistency when comparing multiple variables.

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4. Buckley GJ, Rozanski EA, Rush JE. Randomized Blinded Comparison of Epinephrine and vasopressin for treatment of Naturally occurring cardiopulmonary arrest in dogs, J Vet Internal Med, under review,

Background: Administration of epinephrine during CPR is recommended for treatment of cardiopulmonary arrest (CPA) in dogs. Administration of epinephrine during CPR may be associated with deleterious side effects. Vasopressin has been studied for use in cardiopulmonary resuscitation as an alternative to epinephrine in people and experimental animals. **Hypothesis:** That administration of vasopressin in place of epinephrine along with standard CPR techniques will result in improved outcome in dogs with CPA. **Animals:** Client owned dogs identified in the ER or ICU with spontaneous cardiopulmonary arrest were eligible for inclusion. **Methods:** Dogs were randomized to receive epinephrine (0.01-0.02mg/kg) or vasopressin (0.5-1U/kg) in a blinded fashion. Attending veterinarians were asked to follow a standardized CPR protocol for the first six minutes of CPR during which time doses of the study drug were administered at three minute intervals. At the end of the six minute study period, further interventions were left to the discretion of the attending veterinarians.**Results:** Overall rate of return of spontaneous circulation (ROSC) was 60%, 32% of dogs survived to twenty minutes, 18% survived to one hour. No difference was seen in rates of return of spontaneous circulation between the two groups (p=0.2). Dogs receiving epinephrine were more likely to survive to one hour than those receiving vasopressin. (P= 0.027).**Conclusions and clinical importance:** ROSC was similar in dogs receiving epinephrine or vasopressin. In this study, a survival advantage at 1 hour was seen in those animals receiving epinephrine. Based on the results of this study, no advantage of routine use of vasopressin over epinephrine was found. Further studies are required to examine subgroups of dogs which may benefit from specific interventions.

Comment: LOE 1, quality good, direction: negative (no improvement)

This is a prospective, well-randomized clinical trial examining a standard dose of epinephrine versus vasopressin in in-hospital cardiac arrest in dogs. The primary end point of the study was ROSC within the study period (6 minutes). Secondary end points included ROSC, survival for 20 minutes, survival to one hour and survival to hospital discharge. No difference was seen in rates of primary outcome between the two groups. Dogs receiving epinephrine only were more likely to survive to one hour. Unable to analyze sub-groups of rhythms due to number of cases enrolled in the study. Doses of drugs were not entirely consistent due to the blinded and randomized nature of the study.

5 .Callaway CW, Hostler D, Doshi AA, Pinchalk M, Roth RN, Lubin J, Newman DH, Kelly LJ. Usefulness of vasopressin administered with epinephrine during out-of-hospital cardiac arrest. Am J Cardiol. 2006 Nov 15;98(10):1316-21.

Vasopressin administration has been suggested during cardiopulmonary resuscitation, and a previous clinical trial has suggested that vasopressin is most effective when administered with epinephrine. Adult subjects (n = 325) who received > or =1 dose of intravenous epinephrine during cardiopulmonary resuscitation for nontraumatic, out-of-hospital cardiac arrest were randomly assigned to receive 40 IU of vasopressin (n = 167) or placebo (n = 158) as soon as possible after the first dose of epinephrine. The rate of return of pulses was similar between the vasopressin and placebo groups (31% vs 30%), as was the presence of pulses at the emergency department (19% vs 23%). No subgroup appeared to be differentially affected, and no effect of vasopressin was evident after adjustment for other clinical variables. Additional open-label vasopressin was administered by a physician after the study drug for 19 subjects in the placebo group and 27 subjects in the vasopressin group. Results were similar if these subjects were excluded or were assigned to an actual drug received. Survival duration for subjects admitted to the hospital did not differ between groups. In conclusion, vasopressin administered with epinephrine does not increase the rate of return of spontaneous circulation.

Comments LOE 6, quality good, direction: negative (no benefit)
This is a prospective, blinded, placebo-controlled RCT in humans with out-of hospital cardiac arrest. Primary outcomes for this study were ROSC at any time during resuscitation and the presence of pulses at hospital arrival. Secondary outcome was total duration of survival (one day, 1 year). Multivariate logistic regression performed to remove confounding factors. No differences between ECG rhythms or any outcome were seen.
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6. Chen MH, Xie L, Liu TW, Song FQ, He T, Zeng ZY, Mo SR. Epinephrine, but not vasopressin, improves survival rates in an adult rabbit model of asphyxia cardiac arrest. Am J Emerg Med. 2007 Jun;25(5):509-14.
Although vasopressin has been reported to be more effective than epinephrine for cardiopulmonary resuscitation in ventricular fibrillation animal models, its efficacy in asphyxia model remains controversy. The purpose of this study was to investigate the effectiveness of vasopressin vs epinephrine on restoration of spontaneous circulation (ROSC) in a rabbit model of asphyxia cardiac arrest. Cardiac arrest was induced by clamping endotracheal tube. After 5 minutes of basic life-support cardiopulmonary resuscitation, animals who had no ROSC were randomly assigned to receive either epinephrine alone (epinephrine group; 200 microg/kg) or vasopressin alone (vasopressin group; 0.8 U/kg). The coronary perfusion pressure (CPP) was calculated as the difference between the minimal diastolic aortic and simultaneously recorded right atrial pressure. Restoration of spontaneous circulation was defined as an unassisted pulse with a systolic arterial pressure of 60 mm Hg or higher for 5 minutes or longer. We induced arrest in 62 rabbits, 15 of whom had ROSC before drug administration and were excluded from analysis. The remaining 47 rabbits were randomized to epinephrine group (n = 24) and vasopressin group (n = 23). Before and after drug administration, CPP in epinephrine group increased significantly (from -4 +/- 4 to 36 +/- 9 mm Hg at peak value, P = .000), whereas CPP in vasopressin group increased only slightly (from 9 +/- 5 to 18 +/- 6 mm Hg at peak value, P = .20). After drug administration, 13 of 24 epinephrine rabbit had ROSC, and only 2 of 23 vasopressin rabbit had ROSC (P < .01). Consequently, we conclude that epinephrine, but not vasopressin, increases survival rates in this adult rabbit asphyxia model.

Comments: LOE 6, Quality: fair, direction: negative for ROSC
In this model of asphyxia induced cardiac arrest, rabbits were randomized to receive either epinephrine or vasopressin. Primary outcome was ROSC with secondary outcome being CPP. CPP and ROSC were significantly higher in the vasopressin group. This is contrast to other studies investigating asphyxia in animal models. There was a 3 minute delay from cardiac arrest to administration of drugs.

7.Cody P, Lauderdale S, Hogan DE, Frantz RR. Comparison of two protocols for pulseless cardiopulmonary arrest: vasopressin combined with epinephrine versus epinephrine alone. Prehosp Disaster Med. 2010 Sep-Oct;25(5):420-3..
INTRODUCTION: Survival from pulseless cardiac arrest typically is dismal. Some suggest that adding vasopressin to epinephrine as a cardiovascular stimulant can improve outcomes. PROBLEM: This study compares survival outcomes using epinephrine verses vasopressin and epinephrine in persons with pulseless cardiac arrest. METHODS: This is a retrospective, cohort evaluation of two resuscitative protocols (P1-epinephrine or P2-vasopressin with epinephrine) in a tiered response, community emergency medical service (EMS) with an approximately 100,000 catchment area. Cases are defined as 18 years or older determined to be in pulseless cardiac arrest. Outcomes were survival to emergency department arrival, to 24 hours, and to hospital discharge. Data were entered into Microsoft Office Excel® and processed using Analyze-it® for continuous and categorical data and Epi-Info® for odds ratios with confidence intervals. RESULTS: There were 204 cases (60.3% males and 39.7% females) who met the inclusion criteria. Thirteen cases received electrical therapy only, and were dropped from analysis, leaving 191 (93.6%) who were included in the study; P1 to 85 (44.5%) and P2 to 106 (55.5%). Younger age was associated with improved survival to discharge home in both protocols, p =

0.003 (95% CI = 0.004-0.010). No difference in survival was noted at the levels of emergency department arrival OR 1.42 (95% CI = 0.73, 2.76) p = 0.26; 24 hour survival OR 0.54 (95% CI = 0.22-1.30) p = 0.133, or discharge home OR = 1.81 (95% CI = 0.49-6.88) p = 0.319. CONCLUSIONS: This study in a community EMS did not demonstrate improved survival with the addition of vasopressin to epinephrine for pulseless cardiac arrest.

Comments: LOE 6, Quality: poor (retrospective with controls), Direction: negative (no benefit)

This is a small retrospective, cohort evaluation in clinical cases examining epinephrine versus vasopressin + epinephrine in out-of-hospital arrest. Outcome variables included: survival to Emergency Department and survival to discharge. There was an insufficient number of survivors to report on neurologic outcome. This study found no benefit in outcomes by adding vasopressin to the cardiac arrest pharmacology profile. The strength of this study is the uniform nature of drug administration with all else consistent between the population groups. The major weakness is the low number of cases, retrospective nature and no discussion to time from collapse to drug administration.

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8. Ducros L, Vicaut E, Soleil C, Le Guen M, Gueye P, Poussant T, Mebazaa A, Payen D, Plaisance P. Effect of the addition of vasopressin or vasopressin plus nitroglycerin to epinephrine on arterial blood pressure during cardiopulmonary resuscitation in humans. J Emerg Med. 2010 Apr 22.

Abstract Background: Infusion of a vasopressor during cardiopulmonary resuscitation (CPR) in humans increases end decompression (diastolic) arterial blood pressure, and consequently increases vital organ perfusion pressure and survival. Several vasoactive drugs have been tested alone or in combination, but their hemodynamic effects have not been investigated clinically in humans. Study Objective: We tested the hypothesis that epinephrine (1 mg) co-administered with vasopressin (40 IU) +/- nitroglycerin (300 mug) results in higher diastolic blood pressure than epinephrine alone. Study Design: A prospective, randomized, double-blinded controlled trial in the prehospital setting. The study included 48 patients with witnessed cardiac arrest. Patients received either epinephrine alone (E alone) or epinephrine plus vasopressin (E+V) or epinephrine plus vasopressin plus nitroglycerin (E+V+N). A femoral arterial catheter was inserted for arterial pressure measurement. Outcome Measures: The primary end point was diastolic blood pressure during CPR, 15 min after the first drug administration (T = 15 min). Results: After exclusions, a total of 44 patients were enrolled. Diastolic blood pressures (mm Hg) at T = 15 min were not statistically different between groups (median [interquartile range]: 20 [10], 15 [6], and 15 [13] for E alone, E+V, and E+V+N, respectively. The rate of return of spontaneous circulation was 63% (n = 10) in the epinephrine group, 43% (n = 6) in the epinephrine plus vasopressin group, and 36% (n = 5) in the triple therapy group (NS). Conclusions: Addition of vasopressin or vasopressin plus nitroglycerin to epinephrine did not increase perfusion blood pressure compared to epinephrine alone in humans in cardiac arrest, suggesting the absence of benefit in using these drug combination(s).

Comments: LOE 6, quality: good, direction negative

Prospective randomized double blinded controlled trial comparing epinephrine, epinephrine + vasopressin, or epinephrine + vasopressin + nitroglycerin in out-of-hospital arrest. The primary outcome measured was diastolic blood pressure 15 minutes after drug administration during CPR. Secondary outcomes measured included ROSC, which showed a trend towards higher ROSC in the epinephrine alone group, although this did not reach statistical significance. Arterial blood pressure tended to also be higher in the epinephrine only group. Time from collapse until drug administration was >20 minutes in all groups.

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9. Duncan JM, Meaney P, Simpson P, Berg RA, Nadkarni V, Schexnayder S; National Registry of CPR Investigators. Vasopressin for in-hospital pediatric cardiac arrest: results from the American Heart Association National Registry of Cardiopulmonary Resuscitation. Pediatr Crit Care Med. 2009 Mar;10(2):191-5

OBJECTIVE: To describe the landscape of vasopressin uses reported to the American Heart Association National Registry of cardiopulmonary resuscitation (CPR) and test the hypothesis that vasopressin use will be associated with improved return of a sustained circulation (ROSC) following in-hospital pediatric cardiac arrest.DESIGN: Multicentered, national registry of in-hospital CPR.SETTING: One hundred seventy-six North American Hospitals reporting to registry from October 1999 to November 2004.PATIENTS: Totally, 1293 consecutive pediatric patients with pulseless cardiac arrest meeting criteria for analysis identified from a registry of all patients resuscitated for cardiac arrest. Inclusion criteria were age <18 years, chest compressions and/or defibrillation, in-hospital location, and documented resuscitation record.INTERVENTIONS: None. MEASUREMENTS AND OUTCOMES: Prearrest, event, cardiopulmonary resuscitation, and postresuscitation variables were collected. Primary outcome variable was ROSC >20 minutes. Secondary survival outcomes included 24 hour, discharge and favorable neurologic survival on hospital discharge. Descriptive, univariate, and multivariable analysis to evaluate the association of vasopressin with survival outcomes were performed.RESULTS: Only 5% of patients received vasopressin in this review. Vasopressin was most often given in a

pediatric hospital (57%) and in and intensive care setting (76.6%). Patients who were given vasopressin had longer arrest duration (median 37 minutes) vs. those who did not (24 minutes) (p = 0.004). In multivariate analysis, vasopressin was associated with worse ROSC but no difference in 24 hours or discharge survival.CONCLUSION: Vasopressin was given infrequently in in-hospital cardiac arrest. It was most likely to be given in an intensive care setting, and in a pediatric hospital. Multivariate analysis shows an association with vasopressin use and worse ROSC.

Comments: LOE 6, quality: poor, direction negative
Retrospective review of human pediatric patients entered into a CPR registry from cardiac arrest occurring in-hospital. Outcomes were defined as ROSC (>20 min), survival (24 hr), hospital discharge and neurologic outcome. Although only a small number of patients received vasopressin, there was a negative correlation with ROSC, but no statistically difference in survival to 24 hours or discharge (although a trend towards worse outcome) Only 1.6% of the 5% of patients administered vasopressin received vasopressin as a sole vasopressor. 98.6% were given a combination of epinephrine and vasopressin.

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10. Grmec S, Mally S. Vasopressin improves outcome in out-of-hospital cardiopulmonary resuscitation of ventricular fibrillation and pulseless ventricular tachycardia: a observational cohort study. Crit Care. 2006 Feb;10(1):R13.

INTRODUCTION: An increasing body of evidence from laboratory and clinical studies suggests that vasopressin may represent a promising alternative vasopressor for use during cardiac arrest and resuscitation. Current guidelines for cardiopulmonary resuscitation recommend the use of adrenaline (epinephrine), with vasopressin considered only as a secondary option because of limited clinical data.METHOD: The present study was conducted in a prehospital setting and included patients with ventricular fibrillation or pulseless ventricular tachycardia undergoing one of three treatments: group I patients received only adrenaline 1 mg every 3 minutes; group II patients received one intravenous dose of arginine vasopressin (40 IU) after three doses of 1 mg epinephrine; and patients in group III received vasopressin 40 IU as first-line therapy. The cause of cardiac arrest (myocardial infarction or other cause) was established for each patient in hospital. RESULTS: A total of 109 patients who suffered nontraumatic cardiac arrest were included in the study. The rates of restoration of spontaneous circulation and subsequent hospital admission were higher in vasopressin-treated groups (23/53 [45%] in group I, 19/31 [61%] in group II and 17/27 [63%] in group III). There were also higher 24-hour survival rates among vasopressin-treated patients ($P < 0.05$), and more vasopressin-treated patients were discharged from hospital (10/51 [20%] in group I, 8/31 [26%] in group II and 7/27 [26%] group III; $P = 0.21$). Especially in the subgroup of patients with myocardial infarction as the underlying cause of cardiac arrest, the hospital discharge rate was significantly higher in vasopressin-treated patients ($P < 0.05$). Among patients who were discharged from hospital, we found no significant differences in neurological status between groups. CONCLUSION: The greater 24-hour survival rate in vasopressin-treated patients suggests that consideration of combined vasopressin and adrenaline is warranted for the treatment of refractory ventricular fibrillation or pulseless ventricular tachycardia. This is especially the case for those patients with myocardial infarction, for whom vasopressin treatment is also associated with a higher hospital discharge rate.

Comments: LOE: 6, Quality: fair, Direction: positive
Prospective observational cohort study of adult humans presenting with cardiac arrest out-of-hospital . Arrest rhythms were limited to fibrillation and pulseless ventricular tachycardia only. Primary outcome measured included ROSC, survival to discharge and neurological recovery. Vasopressin was either administered after 3 doses of epinephrine or was the primary pharmacological agent used. The control was epinephrine alone. Both vasopressin treated groups had improved ROSC and survival to discharge. The authors postulate that vasopressin may have the most pronounced effect on patients with myocardial infarction, not as relevant for veterinary patients.

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11. Grmec S, Strnad M, Cander D, Mally S. A treatment protocol including vasopressin and hydroxyethyl starch solution is associated with increased rate of return of spontaneous circulation in blunt trauma patients with pulseless electrical activity. Int J Emerg Med. 2008 Dec;1(4):311-6.
BACKGROUND: Survival after cardiopulmonary resuscitation (CPR) using standard vasopressor therapy is disappointing. Vasopressin is a potent vasopressor that could become a useful therapeutic alternative in the treatment of cardiac arrest.AIMS: The aim of this prehospital prospective cohort study was to assess the influence of treatment with vasopressin and hydroxyethyl starch solution (HHS) on outcome in resuscitated blunt trauma patients with pulseless electrical activity (PEA) cardiac arrest.METHODS: Two treatment groups of resuscitated trauma patients in cardiac arrest were compared: in the epinephrine group patients received epinephrine 1 mg IV every 3 min only; in the vasopressin group patients first received hypertonic HHS and arginine vasopressin 40 units IV only or followed by epinephrine 1 mg every 3 min until cessation of CPR. Medical trauma care was provided according to

advanced trauma life support (ATLS) guidelines.RESULTS: The study included 31 patients and there were no significant demographic or clinical differences between the treatment groups. Significantly more circulatory restorations [11/13 (85%) vs 3/18 (17%); P < 0.01] and better 24-h survival rates [8/13 (62%) vs 2/18 (11%); P = 0.001] were observed in the vasopressin group. Average mean arterial pressure (100.4 +/- 11.4 mmHg vs 80.3 +/- 12.4 mmHg) and final end-tidal partial pressure of carbon dioxide (PETCO(2)) at admission (4.5 +/- 0.9 kPa vs 2.8 +/- 0.4 kPa) were also higher in the vasopressin group.CONCLUSION: Our results suggest that victims of severe blunt trauma with PEA should be initially treated with vasopressin in combination with HHS volume resuscitation followed by standard resuscitation therapy and other procedures when appropriate. Vasopressin might be potentially lifesaving in blunt trauma cardiac arrest compared to standard treatment with epinephrine

Comments: LOE 6, quality: fair, direction: supportive (for PEA)
Small, prospective cohort study(with retrospective controls) investigating the use of a specific population of cardiac arrest rhythm (PEA) in a specific situation (trauma) out-of-hospital Two groups of patients were compared. Patients in group 1 received epinephrine (retrospective control) Patients in group 2 first received vasopressin in combination with hypertonic hetastarch (4 ml/kg), followed by epinephrine every 3 min. Outcome variables were: ROSC, survival to 24 hours and survival to discharge. Secondary variables included mean arterial pressure. In the vasopressin group, significantly improved ROSC and 24-h survival rates were observed; the survival to discharge showed a trend towards improvement, but was not significant. MAP and PETCO2 at admission to the hospital were also higher in the vasopressin group compared to the epinephrine group. Limitations to this study are the small number of cases and the concurrent colloid administration making it difficult to determine whether the positive outcome was due to vasopressin or due to fluid resuscitation.
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12. Gueugniaud PY, David JS, Chanzy E, Hubert H, Dubien PY, Mauriaucourt P, Bragança C, Billères X, Clotteau-Lambert MP, Fuster P, Thiercelin D, Debaty G, Ricard-Hibon A, Roux P, Espesson C, Querellou E, Ducros L, Ecollan P, Halbout L, Savary D, Guillaumée F, Maupoint R, Capelle P, Bracq C, Dreyfus P, Nouguier P, Gache A, Meurisse C, Boulanger B, Lae C, Metzger J, Raphael V, Beruben A, Wenzel V, Guinhouya C, Vilhelm C, Marret E. Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. N Engl J Med. 2008 Jul 3;359(1):21-30.
BACKGROUND: During the administration of advanced cardiac life support for resuscitation from cardiac arrest, a combination of vasopressin and epinephrine may be more effective than epinephrine or vasopressin alone, but evidence is insufficient to make clinical recommendations.METHODS: In a multicenter study, we randomly assigned adults with out-of-hospital cardiac arrest to receive successive injections of either 1 mg of epinephrine and 40 IU of vasopressin or 1 mg of epinephrine and saline placebo, followed by administration of the same combination of study drugs if spontaneous circulation was not restored and subsequently by additional epinephrine if needed. The primary end point was survival to hospital admission; the secondary end points were return of spontaneous circulation, survival to hospital discharge, good neurologic recovery, and 1-year survival.RESULTS: A total of 1442 patients were assigned to receive a combination of epinephrine and vasopressin, and 1452 to receive epinephrine alone. The treatment groups had similar baseline characteristics except that there were more men in the group receiving combination therapy than in the group receiving epinephrine alone (P=0.03). There were no significant differences between the combination-therapy and the epinephrine-only groups in survival to hospital admission (20.7% vs. 21.3%; relative risk of death, 1.01; 95% confidence interval [CI], 0.97 to 1.05), return of spontaneous circulation (28.6% vs. 29.5%; relative risk, 1.01; 95% CI, 0.97 to 1.06), survival to hospital discharge (1.7% vs. 2.3%; relative risk, 1.01; 95% CI, 1.00 to 1.02), 1-year survival (1.3% vs. 2.1%; relative risk, 1.01; 95% CI, 1.00 to 1.02), or good neurologic recovery at hospital discharge (37.5% vs. 51.5%; relative risk, 1.29; 95% CI, 0.81 to 2.06).CONCLUSIONS: As compared with epinephrine alone, the combination of vasopressin and epinephrine during advanced cardiac life support for out-of-hospital cardiac arrest does not improve outcome. (ClinicalTrials.gov number, NCT00127907.)

Comments: LOE 6, Quality: good, Direction: negative (no benefit)
Large, multicenter prospective, RCT of human adults with out of hospital cardiac arrest comparing epinephrine with combined epinephrine and vasopressin. All arrest rhythms are included, but patients presenting in ventricular fibrillation achieving ROSC with defibrillation alone were excluded (consistent with other studies). Outcomes measured included: ROSC, survival to hospital admission (primary endpoint), survival to discharge, survival to one year and neurologic recovery. The study found no improvement in outcome with combined vasopressin and epinephrine. Of note (and mentioned in subsequent letters to the editor) is the average duration of time before administration of a study drug (21 minutes).
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13. Guyette FX, Guimond GE, Hostler D, Callaway CW. Vasopressin administered with epinephrine is associated with a return of a pulse in out-of-hospital cardiac arrest. Resuscitation. 2004 Dec;63(3):277-82.

OBJECTIVE:Recent data suggest that using vasopressin in combination with epinephrine (adrenaline) may improve treatment of out-of-hospital cardiac arrest. This study examined local experience with the combination of epinephrine and vasopressin administration.METHODS: Data were obtained from an urban, municipal emergency medical service that does not include vasopressin in its formulary. A physician is dispatched to the scene of all cardiac arrest patients treated by this system. Vasopressin could be administered in addition to epinephrine to subjects with out-of-hospital cardiac arrest by the on-scene physician. Demographic information, drug administration and return of pulses were abstracted from patient care records for a 1-year interval. Multivariate logistic regression was used to assess the relationship between vasopressin use and outcomes. RESULTS: During the study period, data were available for 298 subjects receiving epinephrine-only (n=231, 78%), a combination of 40 IU vasopressin and epinephrine (n=37, 12%) or no vasopressor drugs (n=30, 10%). Among patients receiving vasopressor drugs, pulse was restored for 74 subjects (28%), and 56 subjects (21%) had a pulse on arrival at the hospital. Return of pulses was associated with witnessed collapse, bystander CPR, and an initial ECG rhythm of ventricular fibrillation or tachycardia. Subjects receiving vasopressin and epinephrine were more likely to have a return of pulses during the resuscitation (LR: 2.73; 95% CI: 1.24, 6.03) and at hospital arrival (3.85; 1.71, 8.65) than subjects treated with epinephrine alone. CONCLUSIONS: There is an association between using vasopressin in combination with epinephrine and restoration of circulation after out-of-hospital cardiac arrest

Comments LOE: 6, quality: poor (not blinded controls), direction: supports vasopressin
This is a small, retrospective observational study. "Controls" were patients receiving epinephrine alone (n=231) and compared to vasopressin + epinephrine (n=37) versus patients that received no vasopressor agents. Outcomes measured were ROSC and survival to hospital admission (no specific minimum time however). Significantly better outcomes were seen in patients that received both vasopressin and epinephrine with an arrest rhythm of asystole in out of hospital arrest. Major weaknesses to this study are lack of randomization, lack of true controls, lack of blindness, and no study protocol (retrospective).
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14. Hofmeister EH, Brainard BM, Egger CM, Kang S. Prognostic indicators for dogs and cats with cardiopulmonary arrest treated by cardiopulmonary cerebral resuscitation at a university teaching hospital. J Am Vet Med Assoc. 2009 Jul 1;235(1):50-7.
OBJECTIVE: To determine the association among signalment, health status, other clinical variables, and treatments and events during cardiopulmonary cerebral resuscitation (CPCR) with the return of spontaneous circulation (ROSC) for animals with cardiopulmonary arrest (CPA) in a veterinary teaching hospital.DESIGN: Cross-sectional study.ANIMALS: 161 dogs and 43 cats with CPA.PROCEDURES: Data were gathered during a 60-month period on animals that had CPA and underwent CPCR. Logistic regression was used to evaluate effects of multiple predictors for ROSC.RESULTS: 56 (35%) dogs and 19 (44%) cats had successful CPCR. Twelve (6%) animals (9 dogs and 3 cats) were discharged from the hospital. Successfully resuscitated dogs were significantly more likely to have been treated with mannitol, lidocaine, fluids, dopamine, corticosteroids, or vasopressin; had CPA while anesthetized; received chest compressions while positioned in lateral recumbency; and had a suspected cause of CPA other than hemorrhage or anemia, shock, hypoxemia, multiple organ dysfunction syndrome, cerebral trauma, malignant arrhythmia, or an anaphylactoid reaction and were less likely to have been treated with multiple doses of epinephrine, had a longer duration of CPA, or had multiple disease conditions, compared with findings in dogs that were not successfully resuscitated. Successfully resuscitated cats were significantly more likely to have had more people participate in CPCR and less likely to have had shock as the suspected cause of CPA, compared with findings in cats that were not successfully resuscitated.CONCLUSIONS AND CLINICAL RELEVANCE: The prognosis was grave for animals with CPA, except for those that had CPA while anesthetized.

Comments: LOE 5, quality: fair, direction supports vasopressin
This is a recently published large retrospective study of CPR in dogs and cats. The primary outcome measured was ROSC and all occurred in-hospital. Eight dogs were treated were vasopressin and 5 achieved ROSC ; (vasopressin significantly improved the likelihood of ROSC in dog). This study is important as it demonstrates the potential utility of vasopressin in a clinical scenario in veterinary medicine. However, lack of controls or defined protocol for administration for vasopressin makes it difficult to draw additional importance. Not clear whether patients got vasopressin + epinephrine, vasopressin alone and at what point during CPR vasopressin was administered.
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15. Lindner KH, Dirks B, Strohmenger HU, Prengel AW, Lindner IM, Lurie KG. Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. Lancet. 1997 Feb 22;349(9051):535-7.
BACKGROUND: Studies in animals have suggested that intravenous vasopressin is associated with better vital-organ perfusion and resuscitation rates than is epinephrine in the treatment of cardiac arrest. We did a randomised comparison of vasopressin with epinephrine in patients with ventricular fibrillation in out-of-hospital cardiac arrest.METHODS: 40 patients in ventricular fibrillation resistant to electrical defibrillation were prospectively and randomly assigned epinephrine (1 mg intravenously; n = 20) or

vasopressin (40 U intravenously; n = 20) as primary drug therapy for cardiac arrest. The endpoints of this double blind study were successful resuscitation (hospital admission), survival for 24 h, survival to hospital discharge and neurological outcome (Glasgow coma scale). Analyses were by intention to treat. FINDINGS: Seven (35%) patients in the epinephrine group and 14 (70%) in the vasopressin group survived to hospital admission (p = 0.06). At 24 h, four (20%) epinephrine-treated patients and 12 (60%) vasopressin-treated patients were alive (p = 0.02). Three (15%) patients in the epinephrine group and eight (40%) in the vasopressin group survived to hospital discharge (p = 0.16). Neurological outcomes were similar (mean Glasgow coma score at hospital discharge 10.7 [SE 3.8] vs 11.7 [1.6], p = 0.78). INTERPRETATION: In this preliminary study, a significantly larger proportion of patients created with vasopressin than of those treated with epinephrine were resuscitated successfully from out-of-hospital ventricular fibrillation and survived for 24 h. Based upon these findings, larger multicentre studies of vasopressin in the treatment of cardiac arrest are needed.

Comments LOE 6, Quality good, Direction- neutral (no improvement in ROSC, survival to discharge, neurological outcome, but does improve 24 hr survival).
Prospective blinded randomized study comparing vasopressin and epinephrine in out of hospital arrest patients with VF. Outcomes measured were survival to hospital admission, survival to 24 hours, survival to hospital discharge, and overall neurological outcome. There was a significant improvement to survival to hospital to 24 hours and a trend towards improvement in survival to hospital admission and discharge in patients that received vasopressin.

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16. López-Herce J, Fernández B, Urbano J, Mencía S, Solana MJ, del Castillo J, Rodríguez-Núñez A, Bellón JM. Terlipressin versus adrenaline in an infant animal model of asphyxial cardiac arrest. Intensive Care Med. 2010 Jul;36(7):1248-55.
PURPOSE: The objective of this study was to compare the efficacy of terlipressin versus adrenaline in an experimental infant animal model of asphyxial cardiac arrest (ACA). DESIGN: Prospective randomised animal study. SETTING: Laboratory research department of a university hospital. METHODS: Seventy-one, 2-month-old, mechanically ventilated piglets were investigated. ACA was induced by removal of mechanical ventilation. Resuscitation was performed by means of manual external chest compressions and mechanical ventilation (CC + V). After 3 min of CC + V, return of spontaneous circulation (ROSC) was observed in 11 animals. The 60 piglets without ROSC were then randomised to the four study groups: adrenaline standard dose (Asd): 0.01 mg/kg/3 min; adrenaline high dose (Ahd): first dose (0.01 mg/kg) and subsequent doses (0.1 mg/kg/3 min); terlipressin (T): 20 microg/kg/6 min; and adrenaline standard dose plus terlipressin (Asd + T). MEASUREMENTS AND RESULTS: The relationship between haemodynamic (heart rate, blood pressure, ECG rhythm, cardiac index), respiratory (end-tidal CO(2), blood gas analysis) and tissue perfusion (gastric intramucosal pH, central, cerebral and renal saturation) parameters and ROSC was analysed. ROSC was achieved in three piglets treated with Asd (20%), four treated with Ahd (26.7%), one treated with T (6.7%) and seven treated with Asd + T (46.7%) (P = 0.099). ROSC was achieved in 43.1% of animals with pulseless electrical activity, 30.4% with asystole and none with ventricular fibrillation (P = 0.0001).CONCLUSION: In this infant animal model of cardiac arrest, there was a non-significant trend towards better outcome when terlipressin was combined with adrenaline compared with the use of adrenaline or terlipressin alone.

Comments: LOE 6, quality: good, direction negative (not supportive of vasopressin)
Prospective randomized animal study using piglets. Asphyxia cardiac arrest was induced and piglets were randomized into 4 different study groups combining high dose and low dose epinephrine (adrenaline), terlipressin only and low dose epinephrine + terlipressin. Asphyxial cardiac arrest is more similar to cardiac arrest in human children (more respiratory in origin) thus investigating whether vasopressin has a role in respiratory/hypoxia induced arrest. In this model, there was a trend (but did not reach statistical significance) towards better outcome (ROSC) when terlipressin is combined with adrenaline versus either used alone. The authors attempted to simulate a more realistic "clinical" scenario by not administering drugs until >13 minutes after onset of asphyxia. Notably, there was a low rate of ROSC when terlipressin was used alone. Although an animal model study, the delay of 13 minutes may model an out-of-hospital arrest scenario.

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17. Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, Katsios N, Papastylianou A, Gkisioti S, Stathopoulos A, Kollintza A, Stamataki E, Roussos C. Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. Arch Intern Med. 2009 Jan 12;169(1):15-24.
BACKGROUND: Animal data on cardiac arrest showed improved long-term survival with combined vasopressin-epinephrine. In cardiac arrest, cortisol levels are relatively low during and after cardiopulmonary resuscitation. We hypothesized that combined vasopressin-epinephrine and corticosteroid supplementation during and after resuscitation may improve survival in refractory in-hospital cardiac arrest.METHODS: We conducted a single-center, prospective, randomized, double-blind, placebo-controlled, parallel-group trial. We enrolled 100 consecutive patients with cardiac arrest requiring epinephrine according to current resuscitation guidelines. Patients received either vasopressin (20 IU per cardiopulmonary resuscitation cycle) plus epinephrine (1

mg per resuscitation cycle) (study group; n = 48) or isotonic sodium chloride solution placebo plus epinephrine (1 mg per resuscitation cycle) (control group; n = 52) for the first 5 resuscitation cycles after randomization, followed by additional epinephrine if needed. On the first resuscitation cycle, study group patients received methylprednisolone sodium succinate (40 mg) and controls received saline placebo. Postresuscitation shock was treated with stress-dose hydrocortisone sodium succinate (300 mg daily for 7 days maximum, with gradual taper) (27 patients in the study group) or saline placebo (15 patients in the control group). Primary end points were return of spontaneous circulation for 15 minutes or longer and survival to hospital discharge.RESULTS: Study group patients vs controls had more frequent return of spontaneous circulation (39 of 48 patients [81%] vs 27 of 52 [52%]; P = .003) and improved survival to hospital discharge (9 [19%] vs 2 [4%]; P = .02). Study group patients with postresuscitation shock vs corresponding controls had improved survival to hospital discharge (8 of 27 patients [30%] vs 0 of 15 [0%]; P = .02), improved hemodynamics and central venous oxygen saturation, and more organ failure-free days. Adverse events were similar in the 2 groups.CONCLUSION: In this single-center trial, combined vasopressin-epinephrine and methylprednisolone during resuscitation and stress-dose hydrocortisone in postresuscitation shock improved survival in refractory in-hospital cardiac arrest.

Comments: LOE 6, quality: good, direction supportive (v + e + MPSS)

Prospective, double blinded controlled study of human adult patients with cardiac arrest (ventricular fibrillation included) occurring in-hospital. Study group received vasopressin, epinephrine and MPSS as initial drugs with vasopressin and epinephrine (control group received epinephrine and saline). Hydrocortisone was administered to patients who survived initial outcome (ROSC) and were found to be in "post resuscitation shock" (defined as" sustained (>4 hours), new postarrest circulatory failure or postarrest need for at least a 50% increase in any prearrest vasopressor/inotropic support targeted to maintain mean arterial pressure above 70 mm Hg". Primary outcome variables were ROSC (15 minutes) and survival to hospital discharge. Secondary outcome variables were arterial pressure during and 15 to 20 minutes after CPR, intensity of postarrest systemic inflammatory response, number of organ failure–free days until completion of follow-up, and neurologic outcome. It is difficult to determine the significance of this study as there was not a vasopressin alone group (only vasopressin + steroids).

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18. Meybohm P, Cavus E, Dörges V, Steinfath M, Sibbert L, Wenzel V, Scholz J, Bein B. Revised resuscitation guidelines: adrenaline versus adrenaline/vasopressin in a pig model of cardiopulmonary resuscitation--a randomised, controlled trial. Resuscitation. 2007 Nov;75(2):380-8.

BACKGROUND: Synergistic effects of adrenaline (epinephrine) and vasopressin may be beneficial during cardiopulmonary resuscitation. However, it is unknown whether either adrenaline alone or an alternating administration of adrenaline and vasopressin is better for restoring vital organ perfusion following basic life support (BLS) according to the revised algorithm with a compression-to-ventilation (c/v) ratio of 30:2.MATERIAL AND METHODS: After 4min of ventricular fibrillation, and 6min of BLS with a c/v ratio of 30:2, 16 pigs were randomised to receive either 45microg/kg adrenaline, or alternating 45microg/kg adrenaline and 0.4U/kg vasopressin, respectively.RESULTS: Coronary perfusion pressure (mean+/-S.D.) 20 and 25min after cardiac arrest was 7+/-4 and 5+/-3mm Hg after adrenaline, and 25+/-2 and 14+/-3mm Hg after adrenaline/vasopressin ($p<0.001$ and <0.01 versus adrenaline), respectively. Cerebral perfusion pressure was 23+/-7 and 19+/-9mm Hg after adrenaline, and 40+/-10 and 33+/-7mm Hg after adrenaline/vasopressin ($p<0.001$ and <0.01 versus adrenaline), and cerebral blood flow was 30+/-10 and 27+/-11% of baseline after adrenaline, and 65+/-40 and 50+/-31% of baseline after adrenaline/vasopressin ($p<0.05$ versus adrenaline), respectively. Return of spontaneous circulation (ROSC) did not differ significantly between the adrenaline group (0/8) and the adrenaline/vasopressin group (3/8).CONCLUSION: Adrenaline/vasopressin resulted in higher coronary and cerebral perfusion pressures, and cerebral blood flow, while ROSC was comparable.

Comments: LOE 6, quality: fair, evidence: negative (no improvement for ROSC), positive for coronary/cerebral perfusion pressures

Primary outcomes were coronary and cerebral perfusion pressure with a secondary outcome being ROSC. This study was limited to a ventricular fibrillation mode.. Of interest are the improved cerebral and coronary perfusion pressures with vasopressin/epinephrine versus epinephrine alone.

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19. Mukoyama T, Kinoshita K, Nagao K, Tanjoh K. Reduced effectiveness of vasopressin in repeated doses for patients undergoing prolonged cardiopulmonary resuscitation. Resuscitation. 2009 Jul;80(7):755-61.

INTRODUCTION: The efficacy of repeated administration of vasopressin alone during prolonged cardiopulmonary resuscitation (CPR) remains unconfirmed. This study was conducted to estimate the effectiveness of the repeated administration of vasopressin vs. epinephrine for cardiopulmonary arrest (CPA) patients receiving prolonged CPR. METHODS: We conducted a prospective randomized controlled study on patients who experienced out-of-hospital CPA. The patients were randomly assigned to receive a

maximum of four injections of either 40IU of vasopressin (vasopressin group) or 1mg of epinephrine (epinephrine group) immediately after emergency room (ER) admission. Patients who received vasopressors before ER admission or suffered non-cardiogenic CPA were excluded after randomization. RESULTS: In total, 336 patients were enrolled (vasopressin group, n=137; epinephrine group, n=118). No differences were found between these groups (vasopressin group vs. epinephrine group) in the rates of return of spontaneous circulation (ROSC) (28.7% vs. 26.6%), 24-h survival (16.9% vs. 20.3%), or survival to hospital discharge (5.6% vs. 3.8%). In a subgroup analysis by the Fisher's exact test, the rate of ROSC was higher in the vasopressin group than in the epinephrine group, among the patients whose arrests were witnessed (48.1% vs. 27.8%, p=0.010) or who received bystander CPR (68.0% vs. 38.5%, p=0.033). When the independent predictors of ROSC were calculated in the subgroup analysis, however, vasopressin administration (Odds ratio: 0.87-0.28) did not affect the outcome. CONCLUSIONS: This is the first report of a possible vasopressin-alone resuscitation without additional epinephrine. However, repeated injections of either vasopressin or epinephrine during prolonged advanced cardiac life support resulted in comparable survival.

Comments: LOE 6, quality: good, direction: negative (no improvement)
This study investigates the effectiveness of the repeated administration of vasopressin alone (no epinephrine) in prolonged CPR in an out-of-hospital and finds no difference in any outcome measured between epinephrine alone and vasopressin alone. The outcomes measured were: ROSC, 24 hr survival, survival to hospital discharge and neurological outcome. The study claims that with additional subgroup analysis, ROSC was significantly higher in the vasopressin group in those select cases when arrests were witnessed or received bystander CPR. However, the data was not convincing and difficult to put too much weight into these findings.

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20. Schmittinger CA, Astner S, Astner L, Kössler J, Wenzel V. Cardiopulmonary resuscitation with vasopressin in a dog. Vet Anaesth Analg. 2005 Mar;32(2):112-4.
Abstract: That endogenous vasopressin levels in successfully resuscitated human patients were significantly higher than in patients who died pointed to the possible benefit of administering vasopressin during cardiopulmonary resuscitation (CPR). Several CPR studies in pigs showed that vasopressin improved blood flow to vital organs, cerebral oxygen delivery, resuscitability and neurological outcome when compared with epinephrine. In a small clinical study, vasopressin significantly improved short-term survival when compared with epinephrine indicating its potential as an alternative pressor to epinephrine during CPR in human beings. As there was little clinical data available at that time, its recommended use was limited to adult human beings with shock-refractory ventricular fibrillation. In this report, we present the case of a dog in which the successful management of intraoperative asystolic cardiac arrest involved vasopressin. Unexpected cardiac arrest occurred during anaesthesia for the surgical removal of multiple mammary adenocarcinomata in a 11-year-old Yorkshire terrier. Despite an ASA physical status assignation of III, the dog was successfully resuscitated with external chest compressions, intermittent positive pressure ventilation and vasopressin (2 doses of 0.8 IU kg(-1)) and was discharged 3 days later without signs of neurological injury. We believe vasopressin contributed to restoring spontaneous circulation. It may prove increasingly useful in perioperative resuscitation in dogs.

Comments: LOE 5, quality: poor, Direction: positive
This is the only of 2 published reports of using vasopressin in cardiopulmonary resuscitation in a clinical scenario in dogs. The outcomes measured included: ROSC, survival, survival to discharge and neurological outcome. However, it did not discuss how normal neurological function was determined. This arrest occurred under general anesthesia and the arrest rhythm was asystole. 2 doses of vasopressin were administered. No epinephrine was administered. No control (case report).
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21. Stadlbauer KH, Wagner-Berger HG, Wenzel V, Voelckel WG, Krismer AC, Klima G, Rheinberger K, Pechlaner S, Mayr VD, Lindner KH. Survival with full neurologic recovery after prolonged cardiopulmonary resuscitation with a combination of vasopressin and epinephrine in pigs. Anesth Analg. 2003 Jun;96(6):1743-9
We sought to determine the effects of a combination of vasopressin and epinephrine on neurologic recovery in comparison with epinephrine alone and saline placebo alone in an established porcine model of prolonged cardiopulmonary resuscitation (CPR). After 4 min of cardiac arrest, followed by 3 min of basic life support CPR, 17 animals were randomly assigned to receive, every 5 min, either a combination of vasopressin and epinephrine (vasopressin [IU/kg]/epinephrine [_g/kg]: 0.4/45, 0.4/45, and 0.8/45; *n*_6), epinephrine alone (45, 45, and 200_g/ kg; *n*_6), or saline placebo alone (*n*_5). After 22 min of cardiac arrest, including 18 min of CPR, defibrillation was attempted to achieve the return of spontaneous circulation. Aortic diastolic pressure was significantly (*P*_0.01) increased 90 s after each of 3 vasopressin/epinephrine injections versus epinephrine alone versus saline placebo alone (mean_sem: 69_3mmHg versus 45_3mmHg versus 29 _ 2 mm Hg, 63 _ 4 mm Hg versus 27 _3mm Hgversus 23_1mmHg, and 52_4mmHgversus 21_ 3mmHg versus 16_3mmHg, respectively). Spontaneous circulation was restored in six of six vasopressin/

epinephrine pigs, whereas six of six epinephrine and five of five saline placebo pigs died (*P* _ 0.01). Neurologic evaluation 24 h after successful resuscitation revealed only an unsteady gait and was normal 5 days after the experiment in all vasopressin/epinephrine-treated animals. In conclusion, in this porcine model of prolonged CPR, repeated vasopressin/epinephrine administration, but not epinephrine or saline placebo alone, ensured longterm survival with full neurologic recovery.

Comments: LOE 6, Quality fair (controls never made it to outcome), Direction: positive (for neurologic recovery in vasopressin + epinephrine)

This is an animal study investigating vasopressin + epinephrine vs. epinephrine alone vs. placebo in a porcine model of ventricular fibrillation. Primary outcome in this study is neurologic recovery 24 hours post resuscitation. Secondary outcomes were: ROSC and diastolic aortic pressures. (Vasopressin/epinephrine, but not epinephrine alone or saline placebo alone, maintained diastolic aortic pressure at 45 mm Hg during prolonged CPR). The model attempted to simulate out of hospital arrest with 4 minutes of VF followed by 3 minutes of basic and 15 minutes of advanced CLS before defibrillation. The authors propose that improved neurologic outcome in vasopressin treated pigs may be due to the vasodilatory effect of vasopressin on the cerebral vasculature. The only neurologic deficit of all vasopressin-/epinephrine treated animals 24 hours after the return of spontaneous circulation was an unsteady gait. The authors define "long term survival with full neurologic recovery" as 24 hours. A significant limitation to this study ROSC was restored in all vasopressin/epinephrine pigs whereas all other pigs were not able to attain ROSC making comparisons between the different study groups difficult. The authors designs a score for neurological recovery based on clinical assessment only (neurologic deficit score)

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22. Stiell IG, Hébert PC, Wells GA, Vandemheen KL, Tang AS, Higginson LA, Dreyer JF, Clement C, Battram E, Watpool I, Mason S, Klassen T, Weitzman BN. Vasopressin versus epinephrine for in hospital cardiac arrest: a randomised controlled trial. Lancet. 2001 Jul 14;358(9276):105-9.

BACKGROUND: Survival rates for cardiac arrest patients, both in and out of hospital, are poor. Results of a previous study suggest better outcomes for patients treated with vasopressin than for those given epinephrine, in the out-of-hospital setting. Our aim was to compare the effectiveness and safety of these drugs for the treatment of in-patient cardiac arrest. METHODS: We did a triple-blind randomised trial in the emergency departments, critical care units, and wards of three Canadian teaching hospitals. We assigned adults who had cardiac arrest and required drug therapy to receive one dose of vasopressin 40 U or epinephrine 1 mg intravenously, as the initial vasopressor. Patients who failed to respond to the study intervention were given epinephrine as a rescue medication. The primary outcomes were survival to hospital discharge, survival to 1 h, and neurological function. Preplanned subgroup assessments included patients with myocardial ischaemia or infarction, initial cardiac rhythm, and age. FINDINGS: We assigned 104 patients to vasopressin and 96 to epinephrine. For patients receiving vasopressin or epinephrine survival did not differ for hospital discharge (12 [12%] vs 13 [14%], respectively; p50.67; 95% CI for absolute increase in survival 211.8% to 7.8%) or for 1 h survival (40 [39%] vs 34 [35%]; p50.66; 210.9% to 17.0%); survivors had closely similar median mini-mental state examination scores (36 [range 19-38] vs 35 [20-40]; p50.75) and median cerebral performance category scores (1 vs 1). INTERPRETATION: We failed to detect any survival advantage for vasopressin over epinephrine. We cannot recommend the routine use of vasopressin for in hospital cardiac arrest patients, and disagree with American Heart Association guidelines, which recommend vasopressin as alternative therapy for cardiac arrest.

Comments LOE 6, Quality good, Direction: negative (no improvement with vasopressin)

Excellent prospective, randomized blinded trial comparing epinephrine with vasopressin as a first line pharmacological agent in an in-hospital arrest. If ROSC was not achieved with a single dose of the study drug, rescue therapy was provided (epinephrine q 3-5 min). Primary outcome was survival of event. Secondary outcomes were ROSC, survival to hospital discharge and neurological outcome. Excluded were patients with a terminal illness that were not expected to live more than 6 weeks. Subgroups examined included patients with MI and arrest rhythms. The findings found no advantage for vasopressin use over epinephrine.

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23. Stroumpoulis K, Xanthos T, Rokas G, Kitsou V, Papadimitriou D, Serpetinis I, Perrea D, Papadimitriou L, Kouskouni E. Vasopressin and epinephrine in the treatment of cardiac arrest: an experimental study. Crit Care. 2008;12(2):R40.

Epinephrine remains the drug of choice for cardiopulmonary resuscitation. The aim of the present study is to assess whether the combination of vasopressin and epinephrine, given their different mechanisms of action, provides better results than epinephrine alone in cardiopulmonary resuscitation.METHODS: Ventricular fibrillation was induced in 22 Landrace/Large-White piglets, which were left untreated for 8 minutes before attempted resuscitation with precordial compression, mechanical ventilation and

electrical defibrillation. Animals were randomized into 2 groups during cardiopulmonary resuscitation: 11 animals who received saline as placebo (20 ml dilution, bolus) + epinephrine (0.02 mg/kg) (Epi group); and 11 animals who received vasopressin (0.4 IU/kg/20 ml dilution, bolus) + epinephrine (0.02 mg/kg) (Vaso-Epi group). Electrical defibrillation was attempted after 10 minutes of ventricular fibrillation. RESULTS: Ten of 11 animals in the Vaso-Epi group restored spontaneous circulation in comparison to only 4 of 11 in the Epi group ($p = 0.02$). Aortic diastolic pressure, as well as, coronary perfusion pressure were significantly increased ($p < 0.05$) during cardiopulmonary resuscitation in the Vaso-Epi group. CONCLUSION: The administration of vasopressin in combination with epinephrine during cardiopulmonary resuscitation results in a drastic improvement in the hemodynamic parameters necessary for the return of spontaneous circulation.

Comments: LOE 6, quality: good, direction positive (supportive of use of vasopressin)
Prospective randomized animal study using piglets. Cardiac arrest was induced with ventricular fibrillation for 8 minutes prior to administration of drugs and drugs were administered into a peripheral vein (to simulate a human emergency scenario) The primary outcome measured was ROSC with endpoints being defined as ROSC, asystole, or persistent ventricular fibrillation. Successfully resuscitated animals were monitored for 60minutes under anesthesia before being killed. ROSC, aortic diastolic pressure and coronary perfusion pressure were increased in the vaso-epi group compared to epinephrine alone (contrasts other studies).
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24. Voelckel WG, Lurie KG, Lindner KH, Zielinski T, McKnite S, Krismer AC, Wenzel V. Vasopressin improves survival after cardiac arrest in hypovolemic shock. Anesth Analg. 2000 Sep;91(3):627-34

Survival after hypovolemic shock and cardiac arrest is dismal with current therapies. We evaluated the potential benefits of vasopressin versus large-dose epinephrine in hemorrhagic shock and cardiac arrest on vital organ perfusion, and the likelihood of resuscitation. In 18 pigs, 35% of the estimated blood volume was withdrawn over 15 min and ventricular fibrillation was induced 5 min later. After 4 min of cardiac arrest and 4 min of standard cardiopulmonary resuscitation, a bolus dose of either 200 microg/kg epinephrine (n = 7), 0.8 unit/kg vasopressin (n = 7), or saline placebo (n = 4) was administered in a blinded, randomized manner. Defibrillation was attempted 2.5 min after drug administration, and all animals were subsequently observed for 1 h without further intervention. Spontaneous circulation was restored in 7 of 7 vasopressin animals, in 6 of 7 epinephrine pigs, and in 0 of 4 placebo swine. At 5 and 30 min after return of spontaneous circulation, median (minimum and maximum) renal blood flow after epinephrine was 2 (0-31), and 2 (0-48) mL. 100 g(-1). min(-1), respectively; and after vasopressin 96 (12-161), and 44 (16-105) mL. 100 g(-1). min(-1), respectively (P: <.01 between groups). Epinephrine animals developed a profound metabolic acidosis by 15 min after return of spontaneous circulation (mean arterial pH, 7.11 +/- 0.01), and by 60 min all epinephrine-treated animals had died. The vasopressin pigs had (P: = 0.015) less acidosis (pH = 7.26+/-0. 04) at corresponding time points, and all survived > or =55 min (P: < 0. 01). In conclusion, treatment of hypovolemic cardiac arrest with vasopressin, but not with large-dose epinephrine or saline placebo, resulted in sustained vital organ perfusion, less metabolic acidosis, and prolonged survival. Based on these findings, clinical evaluation of vasopressin during hypovolemic cardiac arrest may be warranted. IMPLICATIONS: The chances of surviving cardiac arrest in hemorrhagic shock are considered dismal without adequate fluid replacement. However, treatment of hypovolemic cardiac arrest with vasopressin, but not with large-dose epinephrine or saline placebo, resulted in sustained vital organ perfusion and prolonged survival in an animal model of suspended infusion therapy.

Comments LOE: 6, Quality good, direction: positive (supportive of vasopressin in arrests secondary to hypovolemic shock)

This is an interesting study that used an animal model to assess cardiac arrest secondary to hemorrhagic/hypovolemic shock. (The majority of the other studies in this worksheet used either previously healthy animal models or was performed in people.) In this animal model, vasopressin alone was compared to epinephrine or placebo. The primary outcome was ROSC. Secondary outcomes were survival to an hour. Renal blood flow and coronary blood flow were also evaluated. No interventions were made (no supportive care) from the time of ROSC to the hour time point making it not a realistic model.
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25. Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH; European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study Group. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. N Engl J Med. 2004 Jan 8;350(2):105-13
BACKGROUND: Vasopressin is an alternative to epinephrine for vasopressor therapy during cardiopulmonary resuscitation, but clinical experience with this treatment has been limited. METHODS: We randomly assigned adults who had had an out-of-hospital cardiac arrest to receive two injections of either 40 IU of vasopressin or 1 mg of epinephrine, followed by additional treatment with epinephrine if needed. The primary end point was survival to hospital admission, and the secondary end point was survival to

hospital discharge. RESULTS: A total of 1219 patients underwent randomization; 33 were excluded because of missing study-drug codes. Among the remaining 1186 patients, 589 were assigned to receive vasopressin and 597 to receive epinephrine. The two treatment groups had similar clinical profiles. There were no significant differences in the rates of hospital admission between the vasopressin group and the epinephrine group either among patients with ventricular fibrillation (46.2 percent vs. 43.0 percent, P=0.48) or among those with pulseless electrical activity (33.7 percent vs. 30.5 percent, P=0.65). Among patients with asystole, however, vasopressin use was associated with significantly higher rates of hospital admission (29.0 percent, vs. 20.3 percent in the epinephrine group; P=0.02) and hospital discharge (4.7 percent vs. 1.5 percent, P=0.04). Among 732 patients in whom spontaneous circulation was not restored with the two injections of the study drug, additional treatment with epinephrine resulted in significant improvement in the rates of survival to hospital admission and hospital discharge in the vasopressin group, but not in the epinephrine group (hospital admission rate, 25.7 percent vs. 16.4 percent; P=0.002; hospital discharge rate, 6.2 percent vs. 1.7 percent; P=0.002). Cerebral performance was similar in the two groups. CONCLUSIONS: The effects of vasopressin were similar to those of epinephrine in the management of ventricular fibrillation and pulseless electrical activity, but vasopressin was superior to epinephrine in patients with asystole. Vasopressin followed by epinephrine may be more effective than epinephrine alone in the treatment of refractory cardiac arrest.

Comments: LOE 6, Quality: good, Direction: positive (vasopressin improves outcome in asystole)

This is a well-done double-blinded, prospective, multicenter, randomized, controlled clinical trial investigating vasopressin vs. epinephrine in out-of-hospital arrest. Primary outcome was survival to hospital and the secondary outcome was survival to hospital discharge. Limitations raised by the authors include an important acknowledgment that the clinical care of successfully resuscitated patients in the emergency room, intensive care unit, ward, and rehabilitation facilities may vary among institutions and can't be standardized, but may affect outcome. This large study found that ROSC in patients presenting with asystole (with an extrapolation that asystole is more suggestive of a longer ischemic period) had an improved outcome with vasopressin or vasopressin with additional doses of epinephrine than epinephrine alone. Some challenge statistical analysis with this study- observed treatment effect could vary across groups through random variation and other confounding factors.

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26. Wenzel V, Lindner KH, Krismer AC, Voelckel WG, Schocke MF, Hund W, Witkiewicz M, Miller EA, Klima G, Wissel J, Lingnau W, Aichner FT. Survival with full neurologic recovery and no cerebral pathology after prolonged cardiopulmonary resuscitation with vasopressin in pigs. J Am Coll Cardiol. 2000

OBJECTIVES: We sought to determine the effects of vasopressin and saline placebo in comparison with epinephrine on neurologic recovery and possible cerebral pathology in an established porcine model of prolonged cardiopulmonary resuscitation (CPR). BACKGROUND: It is unknown whether increased cerebral blood flow during CPR with vasopressin is beneficial with regard to neurologic recovery or detrimental owing to complications such as cerebral edema after return of spontaneous circulation. METHODS: After 4 min of cardiac arrest, followed by 3 min of basic life support CPR, 17 animals were randomly assigned to receive every 5 min either vasopressin (0.4, 0.4 and 0.8 U/kg; n = 6), epinephrine (45, 45 and 200 microg/kg; n = 6) or saline placebo (n = 5). The mean value +/- SEM of aortic diastolic pressure was significantly ($p < 0.05$) higher 90 s after each of three vasopressin versus epinephrine versus saline placebo injections (60 +/- 3 vs. 45 +/- 3 vs. 29 +/- 2 mm Hg; 49 +/- 5 vs. 27 +/- 3 vs. 23 +/- 1 mm Hg; and 50 +/- 6 vs. 21 +/- 3 vs. 16 +/- 3 mm Hg, respectively). After 22 min of cardiac arrest, including 18 min of CPR, defibrillation was attempted to achieve return of spontaneous circulation. RESULTS: All the pigs that received epinephrine and saline placebo died, whereas all pigs on vasopressin survived ($p < 0.05$). Neurologic evaluation 24 h after successful resuscitation revealed only an unsteady gait in all vasopressin-treated animals; after 96 h, magnetic resonance imaging revealed no cerebral pathology. CONCLUSIONS: During prolonged CPR, repeated vasopressin administration, but not epinephrine or saline placebo, ensured long-term survival with full neurologic recovery and no cerebral pathology in this porcine CPR model.

Comments LOE 6, quality fair (controls did not survive to outcome assessment), direction positive (vasopressin improves neurologic recovery)

The primary outcome in this porcine model of VF is neurological recovery. Secondary outcomes were ROSC. Neurologic recovery was determined by both a "neurological deficit score in pigs" at 24 and 96 hours (scored used elsewhere) in addition to MRI at 96hours. The study investigated vasopressin versus epinephrine versus saline placebo. All pigs that did not receive vasopressin died whereas all vasopressin pigs survived. Study is similar to that of Stadlbauer (2003) other than combination of drugs used.

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27. Wyer PC, Perera P, Jin Z, Zhou Q, Cook DJ, Walter SD, Guyatt GH. Vasopressin or epinephrine for out-of-hospital cardiac arrest. Ann Emerg Med. 2006 Jul;48(1):86-97.

STUDY OBJECTIVE: The use of vasopressin in patients with cardiac arrest presenting with specific rhythms is controversial. We performed an evidence-based emergency medicine review of evidence comparing vasopressin to epinephrine in structured cardiac arrest protocols. METHODS: We searched MEDLINE, EMBASE, the Cochrane Library, and other databases for randomized trials or systematic reviews comparing vasopressin to epinephrine for adults with cardiac arrest and measuring survival to hospital discharge and neurologic function in survivors. We used standard criteria to appraise the quality of published trials and systematic reviews. We used the random effects model in supplementary analyses to summarize results and to test for significant differences across subgroups of patients presenting with different arrest rhythms .RESULTS: We found 3 high-quality well-reported randomized trials and 1 rigorous meta-analysis. The evidence does not confirm a consistent benefit of vasopressin over epinephrine in increasing survival or improving neurologic outcome in survivors. Subgroup analysis reveals a large difference in effect of vasopressin over epinephrine in cardiac arrest patients with asystole, compared to other arrest rhythms, coming from within-trial comparisons. The difference is not consistent across otherwise similar trials, is not statistically significant, may reflect the application of multiple unplanned subgroup analyses, and is not supported by a plausible biological hypothesis. CONCLUSION: Evidence from randomized trials does not establish a benefit of vasopressin over epinephrine in increasing survival to discharge or improving neurologic outcomes in adult patients with nontraumatic cardiac arrest.

Comments LOE: 6, quality: poor, direction: negative (no benefit)
This large analysis evaluates both metaanalysis (1) and RCT (3) in humans with cardiac arrest. Outcomes included survival to hospital discharge and neurologic function. This study allowed for analysis of pooled data making it a more useful evidence-based review.