Clinical question.

In adult and pediatric patients with cardiac arrest (pre-hospital [OHCA] or in-hospital [IHCA]) (P), does the use of vasopressin or vasopressin + epinephrine (I) compared with standard treatment recommendations (C), improve outcome (eg, ROSC, survival to hospital discharge, or 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: revision /new topic for combined vasopressin+epinephrine

Conflict of interest specific to this question

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

Search strategy (including electronic databases searched).

Search 31/08/2009 MESH and terms in medline, AHA endnote database, Cochrane library
"vasopressin", "epinephrine" “heart arrest” “resuscitation” “ventricular fibrillation”
"Vasopressins“[Mesh] AND "Heart Arrest“[Mesh] 167 hits 61 selected
"Vasopressins“[Mesh] AND "Epinephrine“[Mesh]) AND "Heart Arrest“[Mesh]: 94 hits - 44 selected
"Vasopressins“[Mesh] AND "Epinephrine“[Mesh]) AND "Cardiopulmonary Resuscitation“[Mesh] 95 hits - 49 selected

vasopressin AND cardiac arrest :251 hits – 78 selected
vasopressin OR vasopressin AND epinephrine AND cardiac arrest 162 hits-64 selected
vasopressin AND resuscitation 444 hits – 76 selected
vasopressin AND ventricular fibrillation 151 hits – 49 selected
Hand-search 2
Endnote: (march 2008) 130 hits - 42 selected -
Total of examined abstracts :123
Cochrane Library 1 hit

State inclusion and exclusion criteria

Excluded reviews, non cardio-respiratory arrest situations (brain death, vasodilatory shock, haemorrhage, post-cardiac arrests), comparison vasopressin versus placebo. Single case reports

Two articles were considered as abstracts but not included in the analysis : one in Chinese (Li 1999-28) and one on abstract form only (Lee 2000-S91). However they were considered by Aung 2005-165 and didn’t change the meta-analysis conclusion.

Number of articles/sources meeting criteria for further review:
61 articles reviewed
38 LOE 5, 4 LOE 4; 1 LOE 3; 4 LOE 2; 8 LOE 1 + 2 SR and 3 metaanalyses

Asphyxial cardiac arrest or pediatric cardiac arrest articles 5 LOE 5, 2 LOE 4, 1 LOE 3
### Summary of evidence

#### Evidence Supporting Clinical Question

In adult and pediatric patients with cardiac arrest (pre-hospital [OHCA] or in-hospital [IHCA]) (P), the use of vasopressin or vasopressin + epinephrine (I) compared with standard treatment recommendations (C), improve outcome (eg, ROSC, survival to hospital discharge, or survival with favorable neurologic outcome) (O)?

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#### Level of evidence

| A = Return of spontaneous circulation | C = Survival to hospital discharge | E = Other endpoint |
| B = Survival of event                | D = Intact neurological survival   | Italics = Animal studies |
| * VP compared to Epi                  | # simultaneous VP+EPI compared to Epi | °successive VP/EPI vs EPI |

Pediatric studies (or asphyxia model) | CS corticosteroids | MA Metaanalysis | SR Systematic review |
**Evidence Neutral to Clinical question**

In adult and pediatric patients with cardiac arrest (pre-hospital [OHCA] or in-hospital [IHCA]) (P), the use of vasopressin or vasopressin + epinephrine (I) compared with standard treatment recommendations (C), is neutral towards outcome (eg, ROSC, survival to hospital discharge, or survival with favorable neurologic outcome) (O)?

|------|--------------------------|-----------------------|--------------------|---------------------|------------------------|----------------------|-------------------|-------------------|------------------|------------------|----------------|----------------|------------------|------------------|------------------|------------------|

**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
* VP compared to Epi  
# simultaneous VP+EPI compared to Epi  
° successive VP/EPI vs EPI  

Pediatric studies (or asphyxia model)  
CS corticosteroids  
MA Metaanalysis  
SR Systematic review

**Evidence Opposing Clinical Question**

In adult and pediatric patients with cardiac arrest (pre-hospital [OHCA] or in-hospital [IHCA]) (P), the use of vasopressin or vasopressin + epinephrine (I) compared with standard treatment recommendations (C), does not improve outcome (eg, ROSC, survival to hospital discharge, or survival with favorable neurologic outcome) (O)?

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**Level of evidence**
Asystole, secondary to cardiac arrest is the most frequent presenting rhythm in children and infants. It differs from VF because the progression to ischemia is sudden in VF and gradual but is considerably greater in asphyxia which occurs prior to the onset of arrest, leading to cellular energy store depletion before the onset of cardiac arrest. Adrenaline/Epinephrine is the most commonly recommended drug for asphyxial cardiac arrest and for cardiac arrest in children. The optimal dose is unknown and clinical data have failed to show any survival advantage of high-dose adrenaline (100 μg/kg) compared with the standard dose of 10 μg/kg (Schindler 1996-1473; Carpenter 1997-403; Perondi. 2004-1722).

The very poor survival results of pediatric resuscitation with administration of any dose of epinephrine as first line therapy encouraged the evaluation of alternative vasopressors drugs like vasopressin.

Vasopressin, a major hormone mediating potent vasoconstriction is known to increase blood pressure and systemic vascular resistance and to decrease cardiac output, heart rate, and myocardial contractility. (Cartheuser 1980-668; Frishman 1997-769; Frishman 1998-765).

The level of endogenous vasopressin has been correlated in several studies with short-term resuscitation outcome (Lindner 1992-662; Paradis.1993-261; Ito 2004-55). Endogenous vasopressin plays an important role during CPR, as shown in the study by Krismer et al in pigs after blockade of the V1 receptors (Krismer 20011499). This study (Krismer. 2001-1499) documented reduced coronary blood flow when endogenous vasopressin activity is blocked. Other roles of endogenous vasopressin include down-regulation of endogenous-adrenaline level and increased the left ventricular myocardial blood flow, hence favoring return of spontaneous circulation (ROSC). These effects are amplified by exogenous vasopressin. In an out-of-hospital series of 60 cardiac arrests victims, plasma arginine vasopressin and adrenocorticotropin (ACTH) concentrations were significantly higher and adrenaline and noradrenaline concentrations significantly lower in patients in whom spontaneous circulation was restored than in non-resuscitated patients. No difference was seen for plasma level of endothelin (Lindner 1996-145). However there was no correlation of endogenous vasopressin levels with survival at discharge, a higher cortisol concentration being the only hormone significantly correlated with good outcome (Ito 2004-55).

Administration of vasopressin during resuscitation decreased the level of endogenous catecholamines in animals (Krismer 2001-1499; Wenzel 2000-1096) and humans [Morris 1997-878] but it has not been shown that it results in a decrease of oxygen consumption. Administration of vasopressin also enhances the release of other stress hormones (ACTH, cortisol) ([Kornberger 2000-3517). Interactions between endogenous and exogenous vasopressors and stress hormones are complex; [Lindner 1996a; (Wenzel 2000-1096); Morris 1997-878]. Understanding these complex interactions may help to develop a stress hormone cocktail that may improve the outcome of patients with cardiac arrest.

In the past ten years, several series and RCTs have been published: some of them comparing mainly vasopressin to epinephrine (Wenzel 2004-105; Lindner 1997- Stiell 2001-105; Mukoyama 2009-755) and some comparing combination of vasopressin and epinephrine (successively or simultaneously) to epinephrine alone (Callaway 2006-1316; Mentzenopoulos 2009-15; Guenegniaud 2008-21; Grmec 2006-R13; Grmec 2008-311 Lindner 1996-1061; Mally 2007-R39; Guyette 2004-277; Mann 2002-149; Matok 2007-1161; Morris 1997-878) and as a subgroup of the main study conducted by Wenzel (Wenzel 2004-105).

Four adult studies were performed in the out-of-hospital setting (Gueugniaud 2008-21; Guyette 2004-277; Wenzel 2004-105; Lindner 1997-535), others in the in-hospital setting. The three pediatric studies were performed in-hospital and mainly with children admitted to the pediatric intensive care units (Mann 2002-105; Matok 2007-1161; Duncan 2009-191).

**Vasopressin versus epinephrine**

The LOE 1 adult monocentre RCT of Lindner 1997-535 showed that during in-hospital ventricular fibrillation, administration of vasopressin increased the rate of ROSC and 24 hour survival but not the survival to discharge nor neurological outcome. The study was small with 40 patients enrolled. The Stiell 2001-105 multicentre RCT enrolled 200 patients and showed no superiority of either drug in term of ROSC or survival to discharge. These results were pooled in the meta-analysis of Biondi-Zoccai 2003-221. In this meta-analysis, vasopressin appeared to be equivalent to adrenaline in ROSC and survival to discharge for VF in adult humans. The same meta-analysis pooled also animal studies (31 studies) in a separate analysis. In this animal pooling comparison of vasopressin with epinephrine, vasopressin was
superior to adrenaline for ROSC and in studies with animals in VF but was not significantly superior to adrenaline in the sub-group with non-VF cardiac arrests.

In the RCT of out-of-hospital cardiac arrests by Wenzel and coworkers (Wenzel 2004-105) vasopressin was not superior to epinephrine for all outcomes. However in subgroups analyses, a better survival (but with more disabled patients at hospital discharge) was observed when the presenting rhythm was asystole. In another subgroup analysis, when epinephrine was given after the two doses of one of the study drugs, a better survival at hospital admission and discharge (with the same neurological outcome in the two groups) was observed with combination of vasopressin and adrenaline.

The study of Mukayama 2009-755 studied out-of-hospital cardiac arrest. Patients were randomized to received either vasopressin or epinephrine and never received the other study drug. The patients received their first dose of any drug in the emergency department. No difference in outcome parameters were observed.

The two meta-analyses (Aung 2005-165 and Wyer 2006-86) came to a similar conclusion. In a meta-analysis of the three published RCT (Lindner 1997-535, Stiell 2001-105 and Wenzel 2004-105), both articles concluded that vasopressin was not superior to epinephrine for ROSC, survival at admission (Aung 2005-1765) and for survival at discharge and neurological outcome (Aung 2005-165 and Wyer 2006-86). Their statistical analyses of the three presenting rhythm subgroups (VF, PEA or asystole) showed no evidence of the superiority of vasopressin.

**Vasopressin combined with epinephrine versus epinephrine alone**

In the LOE 1 study of Callaway 2006-1316, a combination of epinephrine and vasopressin given successively showed no benefit for ROSC, hospital admission or survival duration compared to epinephrine plus placebo in an out-of-hospital cardiac arrest (n=325 adult patients).

In the LOE 1 prospective multicenter randomized study of out-of-hospital cardiac arrest by Gueugniaud 2008-21; 2894 adult patients were assigned to receive either epinephrine and vasopressin or 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. No differences for admission survival (primary end point); ROSC, survival to hospital discharge, neurologic outcome and one year survival (secondary outcomes) were observed.

The small LOE 1 study of in-hospital cardiac arrest (Mezelopoulos 2009-15) is the only RCT showing a benefit of administration of combined vasopressin and epinephrine in comparison with epinephrine alone. However corticosteroids were added to the study group in a complicated design and the power of the study is weak.

The systematic review (SR) of Stillberg 2008-380 concluded that a combination of epinephrine + vasopressin was not superior to epinephrine alone in adult cardiac arrest by analyzing the three published studies (Callaway 2006-1316, Wenzel 2004-105, Stiell 2001-105). Only the study of Wenzel showed a slightly increased ROSC and survival to discharge in the vasopressin+epinephrine groups but with an increased number of patients with cognitive impairment. The authors of the SR concluded that use of a combination of epinephrine and vasopressin was not clearly superior to epinephrine alone.

The LOE 2 study of Guyette (Guyette 2004-277) showed better ROSC and greater frequency of pulse on arrival to the ED when vasopressin was associated to epinephrine in out-of-hospital resuscitation, and this was particularly significant when initial rhythm was asystole. Other studies compared epinephrine alone with vasopressin combined with epinephrine and showed better ROSC, better rate of hospital admission but none of these 3 LOE 2 studies showed an improvement of the survival at discharge or neurological outcome (Gmerc 2006-R13, Gmerc 2008-311; Mally 2007-R39)

**Pediatric and asphyxial cardiac arrest**

In the only animal pediatric study of asphyxial cardiac arrest (Voelckel 2000-3777), epinephrine or the combination of epinephrine and vasopressin were equivalent to each other and both were superior to vasopressin alone.

In pediatric pigs with non asphyxial ventricular fibrillation (Voelckel 2002-957) and in a adult porcine model of asphyxia (Mayr 2001-1651), the combination of vasopressin and epinephrine proved to be more effective than epinephrine alone or vasopressin alone. In the rat model of asphyxia (Chen 2007-509; Kono 2002-215) epinephrine and vasopressin were equipotent.

In the LOE 1 meta-analysis of Biondi-Zoccai 2003-22, pooling the animal studies showed that vasopressin was not significantly superior to epinephrine in the sub-group with non-VF cardiac arrests. This may suggest that efficiency of vasopressors may be different in pediatrics compared with adult animal preparations in dysrhythmic versus asphyxial cardiac arrest. Whether these experimental studies can be extrapolated to humans is unknown.

In pediatrics, two small series (LOE 4) were published (Mann 2002-149 and Matok 2007-1161) and showed that combination of epinephrine and vasopressin could be considered as rescue therapy for in-hospital long lasting cardiac arrest and increased the rate of ROSC and survival at discharge as well as good neurological outcome. In toto, 8/11 had ROSC; 6/11 patients survived more than 24 hours and 5 survived at hospital discharge with a good neurological status (or with same status compared to before the event).
Recently (March 2009), the AHA National Registry of Cardio Pulmonary Resuscitation (LOE 3 Duncan 2009-191) reported a cohort of children < 18 years in cardiac arrest from 176 North American hospitals during a 5 year period. Only 5% of patients (64/1293 children) received vasopressin for in-hospital cardiac arrest. 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 (Return of a sustained circulation for >20 minutes was lower in the vasopressin group than in the non vasopressin group: 22 of 64 (34.4%) vasopressin vs. 675 of 1229 (54.9%) no-vasopressin (unadjusted OR 0.43; 95% CI 0.25– 0.73) but no difference in 24 hours or discharge survival (10.9% vasopressin vs.27.4% no vasopressin (adjusted OR 0.56; 95% CI 0.21–1.11).

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

#### In adults

<table>
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In the same design of cardiac arrest, 14 LOE 5 animal studies (Babar 1999-185; Kern 2004-S393; Klouche 2003-93A; Kono 2002-215; Krismer 2000-69; Lindner 1993-427; Nozari 2001-59; Pellis 2003-2716; Popp 2007-137; Strohmenger 1996-65; Studer 2002-201; Voelckel 2001-1587; Voelckel 2000-627; Wenzel 1998-1462) showed equivalent ROSC and other outcomes when vasopressin was used in comparison with epinephrine. Six LOE 5 studies (Chen 2007-509; Voelckel 2000-3777; Kern 2004-S393; Prengel 1996-2014; Prengel 1998-19; Kern 2004-S393) showed disadvantages of ROSC and other outcomes when vasopressin was used in comparison with epinephrine. One LOE 4 (Lindner 1996-1061), 3 LOE 2 (Mally 2007-R39; Gmerc 2006-R13; Gmerc 2008-311) showed better ROSC and 24h survival but no better hospital discharge in the vasopressin groups compared to epinephrine groups. Four LOE 1 (Wenzel 2004-105, Stiell 2001-105; Lindner 1997-535; Mukoyama 2009-755) RCT and two LOE 1 meta-analyses (Biondi-Zoccai 2003-221 including two LOE 1 studies (Linder 1997-535; Stiell 2001-105) and 33 LOE 5 studies (28 included in the present analysis : Achleitner 2000-1067; Babar 1999-185; Klouche 2003-93; Komerberger 1999-3517; Krismer 2001-734; Krismer 2003-223; Lindner 1999-427; Loeckinger 2002-2059; Lurie 2002-187; Mayr 2001-1651; Mulligan 1997-265; Nozari 2001-59; Prengel 1996-2014; Prengel 1996-1241; Prengel 98-19; Schwar 2002-1311; Stadlbauer 2003-699; Strohmenger 1996-1360; Studer 2002-201; Voelckel 2000-627; Voelckel 2002-957; Voelckel 2001-1587; Wenzel 2000-527; Wenzel 1999-1379; Wenzel 1999-486) ; and Wyer 2006-86 (including 5 LOE 1 randomized trials : 3 included in this worksheets Wenzel 2004-105; Stiell 2001-105; Lindner 1997-535and 2 not included : Lee 200-S91 and Li 1999-28 ) showed no advantage of the use of vasopressin alone compared to epinephrine, even in the subgroup of asystole. When vasopressin is combined to epinephrine (either in successive or simultaneous administration) 6 animal studies showed a better ROSC (Little 2006-810; Lurie 2002-187; Mayr 2001-1651; Stadlbauer 2003-1743; Strompoulis 2008-R40; Voelckel 2002-957) 1 LOE 4 study (Lindner 1996-1061), 1 LOE 3 (Morris 1997-878) and 4 LOE 2 (Guyette 2004-2777; Gmerc 2006-R13; Gmerc 2008-311; Mally 2007-R39 ) in adult patients showed a benefit on ROSC and 24 h survival but not on survival at discharge. The LOE 1 (Metzelopoulos 2009-15) showed a benefit on ROSC and survival at discharge but the vasopressin group also received steroids and the group was small. The LOE 1 study of Wenzel (Wenzel 2004-105) showed a benefit on survival at discharge and neurological outcome for the subgroup which receive two doses of vasopressin followed by epinephrine. Five LOE 5 animal studies (Chen 2007-509; Voelckel 2000-3777; Kern 2004-S393; Prengel 1996-2014; Prengel 1998-19;) showed no benefit of the use of combination of drugs. Four RCT LOE 1 (Mukoyama 2009-755; Geugniaud 2008-21; Callaway 2006-1316; Stiell 2001-105) and 2 SR LOE 1 (Sillberg 2008-380 (including Callaway 2006-1316; Wenzel 2004-105; Stiell 2001-105) and Koshman 2005-1687( including Wenzel 2004-105; Stiell 2001-105; Lindner 1997-535 ) showed no benefit of the use of drugs combination. |

#### In children

In pediatric animal models, epinephrine alone or combined with vasopressin was superior to vasopressin alone (2 LOE 5: Voelckel 2000-3777; Voelckel 2002-957). One asphyxial model of CA in adult swine showed that combination of epinephrine and vasopressin was better than vasopressin or epinephrine alone (LOE 5: Mayr 2001-1651). In rat model of asphyxial CA, no difference could be observed (2 LOE 5: Chen 2007-509; Kono 2002-215). No studies compared
vasopressin to epinephrine in children.
Two LOE 4 pediatric small series (Mann 2002-149; Matok 2007-1161) showed an advantage on survival with good neurological outcome at discharge for in-hospital cardiac arrest when vasopressin was used as rescue drug. One large multicentre cohort (LOE 3: Duncan 2009-R39) showed worse ROSC and equivalent but dismal survival at discharge when vasopressin was given in pediatric cardiac arrest (in 98.6% of the cases vasopressin was given in combination with epinephrine) compared to the group receiving epinephrine alone.

From published articles in adults, children and animals no significant benefit is observed from the use of vasopressin alone or in combination with epinephrine nor in asphyxial, or non asphyxial cardiac arrest, nor in VF or non VF cardiac arrest.

Acknowledgements:

References used in the discussion but not listed in the citation list nor in the grid


Citation List


LOE 5 supporting (vasopressin vs Epinephrine)
Animal study of cardiac arrest (VF) treated with repeated doses of vasopressin versus epinephrine. Vasopressin increased frequency and amplitude of VF. Rate of ROSC was increased with Vasopressin compared to epinephrine.


LOE 1 neutral (vasopressin vs epinephrine)
This SR analyses 5 RCTs (Wenzel 2004-105, Lindner 1997-535, Stiell 2001-105, Lee 2000-S91 and Li 1999-28) and showed no advantage of vasopressin over epinephrine even in subgroups (VF, PEA and asystole) analysis. Pooled relative risk of death before hospital discharge, vasopressin compared to epinephrine, across the 3 fully reported trials of 0.99 (95% CI 0.95 to 1.02). When the trials by Li 1999-28 and Lee 2000-S91 et al were included, the relative risk was 0.96 (95% CI 0.87 to 1.05). Pooled relative risk of death or neurologic impairment for vasopressin compared to epinephrine, was 1.0 (95% CI 0.94 to 1.07).
No difference observed between subgroups defined by presenting risk.


LOE 5: neutral (vasopressin vs epinephrine)
This animal study of VF reported an increased coronary perfusion with Vasopressin compared to Epi but no better ROSC.


LOE 1 Neutral (vasopressin vs epinephrine)
This systematic review of adult studies failed to show any benefit of the use of vasopressin compared to adrenaline in human trials although animal studies were in favor of vasopressin. Only two existing human studies with opposite results
(one being conducted in the out-of-hospital setting –Lindner 1997 and the other in the hospital Stiell 2001) limited the accuracy of the SR.


LOE 1: neutral (epinephrine + vasopressin versus epinephrine + placebo)
Prospective randomized human study of non traumatic cardiac arrest with 325 adult subjects receiving epinephrine (one or more than one dose) and randomized to receive either vasopressin or placebo after the first epinephrine dose. No benefit observed for ROSC, hospital admission and survival duration.


LOE 5 opposing (vasopressin vs epinephrine)
Animal model of asphyxial cardiac arrest. Epinephrine was superior to vasopressin for ROSC and CPP


LOE 3 (neutral) (vasopressin + epinephrine vs epinephrine)
In a multicentre study 64 children in cardiorespiratory arrest received vasopressin. 98.4% received also epinephrine during resuscitation efforts. The majority of children were hospitalized in a PICU. Duration of arrest was significantly longer in the vasopressin group than in the no vasopressin group. ROSC was lower in the vasopressin group (34.4%) than in no vasopressin group (54.9%). 24h-survival was lower in the vasopressin group (22%) than in the no vasopressin group 39.9% (OR 0.52 95% CI 0.27-1.11). However children in the vasopressin group had much longer arrest than no vasopressin group with 11% having arrest less than 15 minutes compared with 35% of nonvasopressin arrests. Seven (11%) children survived to hospital discharge and 6 of them had favorable neurologic outcome.


LOE 2 Supporting (vasopressin and successive vasopressin + epinephrine vs. epinephrine)
Small study of 109 nontraumatic cardiac arrest patients showing weak better results of ROSC and in 24 h survival but a non significant improvement of the survival at discharge in the Vasopressin groups (either with or without epinephrine) compared to epinephrine alone.


LOE 2 supporting / neutral (vasopressin vs epinephrine)
This is a very small study of 31 trauma patients resuscitated for cardiopulmonary arrest (PEA only) after trauma. The patients were randomized to receive either one dose of 1 mg of epinephrine or one dose of 40 IU of vasopressin followed by epinephrine every 3 minutes in both groups. ROSC and 24 h survival were statistically better in the vasopressin group than in the epinephrine group but discharge from hospital was not different in both groups (vasopressin 31% vs epinephrine % p=0.13)


LOE 1 neutral (successive epi+vasopressin versus epinephrine+ placebo)
Large prospective multicenter randomized study of out-of-hospital cardiac arrest. Study comprised 2894 adult patients which were assigned to receive 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. No difference on admission survival (primary end point); ROSC, survival to hospital discharge, neurologic outcome and one year survival (secondary outcomes).


**LOE 2 supporting (successive vasopressin+epinephrine vs epinephrine)**
Small cohort study of 298 cardiac arrest adult patients. Combination of successively given epinephrine and vasopressin increases the likelihood of ROSC and pulse on arrival at hospital. Non randomised study, allocation made by physician on the scene.


**LOE5 Supporting (vasopressin vs epinephrine+ continuous infusion epinephrine)**
Animal study of VF showed better ROSC and better CPP and Cerebral blood flow with vasopressin and epi.


**LOE 5 neutral (vasopressin vs epinephrine)**
Animal study of VF treated by vasopressin vs epi. No difference in 24-hour outcome. Postresuscitation left ventricular function was worse after vasopressin compared with epinephrine however antagonism of vasopressin during post resuscitation period did not improve survival.


**LOE 5 neutral (vasopressin vs epinephrine vs placebo vs alpha-MNE)**
Vasopressin and adrenaline decreased significantly and equally cardiac functions (cardiac index, lusitropic function, myocardial contractility) in the post-resuscitation period. This effect was due to vasoconstriction, which was less pronounced using an α2-agonist like α-methylnorepinephrine that inhibits the release of endogenous catecholamines and increases the release of nitric oxide. This study emphasizes that vasopressin does not favor optimal post-resuscitation myocardial function. In this study no difference in ROSC for vasopressin and epinephrine was observed.


**LOE 5 neutral (vasopressin vs epinephrine)**
This rat study showed that in an asphyxial arrest model, vasopressin was as potent as adrenaline although no advantage was seen.
Asphyxial models in adult animal are close to pediatric models. Indeed, asphyxia results in greater acidosis, hypoxia and hypercarbia affecting myocardial metabolism more than in VF models


**LOE 5 supporting (vasopressin vs epinephrine)**
Animal study of VF. Swine received either epinephrine or vasopressin after 7 min of cardiac arrest. No differences in CoPP and endothelin-1 release were seen between the two drugs. Epinephrine group animals received more DC-shocks than vasopressin group animals. The rate of ROSC was higher in the vasopressin group than in the epinephrine group as was the ACTH secretion.


**LOE 1 neutral (vasopressin vs epinephrine)**
This SR analysed the three RCT published at the time (Wenzel 2004, Stiell 1997 and Lindner 2001) and concluded that no drug was superior to the other and could be considered as the first-line drug in adult cardiac arrest.


LOE 5 supporting (vasopressin vs epinephrine)
Animal model of VF. Pigs receiving vasopressin had higher incidence of ROSC and higher medullary and cortical adrenal gland blood flow than pigs receiving epi.


LOE 5 supporting (vasopressin vs epinephrine vs placebo)
Animal study of VF after epidural anesthesia (vs placebo). This model of cardiac arrest differs from models of cardiac arrest encountered in out-of-hospital settings. More severe acidosis was seen in adrenaline treated animals than in vasopressin treated animals.


LOE 5 neutral (vasopressin vs epinephrine vs placebo)
Animal study of VF in hypothermia. No difference in ROSC nor in coronary perfusion pressure.


LOE 1 neutral (vasopressin vs epinephrine)
Small prospective randomized study of VF in out-of-hospital setting. Despite a higher rate of hospital admission and of 24h survival, survival at discharge and neurological outcome were similar in both groups.


LOE4 supporting
Series of 8 adults in refractory VF. Eight/8 had a ROSC and 3 intact neurological survival at discharge after rescue dose of vasopressin.


LOE 5 supporting (vasopressin vs epinephrine)
Vasopressin increased CPP and myocardial blood flow more than epinephrine in pigs with VF.


LOE 5 supporting (vasopressin vs epinephrine)
Animal study of pigs in VF which received either epinephrine or vasopressin. Myocardial blood flow, coronary venous CO2 and pH were better in the vasopressin group reflecting a better organ perfusion. No difference in ROSC between the groups.


LOE 5 supporting (vasopressin vs epinephrine vs combination vasopressin+epinephrine)
In PEA vasopressin alone or in combination with epinephrine increased the CoPP and the rate of ROSC.

LOE 5 supporting (vasopressin vs epinephrine)
Animal model of VF: administration of vasopressin in his model of cardiac arrest improved pulmonary gas exchange in the postresuscitation phase.


LOE 5 supporting (epinephrine vs combination vasopressin+epinephrine +nitroglycerine)
Animal model of VF: Combination of vasopressin+epi+nitroglycerine was superior to epinephrine for left ventricular and cerebral blood flow and ROSC.


LOE2 supporting (vasopressin and successive vasopressin+epinephrine vs epinephrine)
This cohort study compared successive vasopressin + epinephrine with epinephrine alone in 598 adult patients in cardiac arrest. Combination of Vasopressin+epinephrine was superior to epinephrine only for ROSC, 24h survival rate and neurologic outcome


LOE 4 supporting
Case series of 4 children and 6 episodes of cardiac arrest with 24 h survival of 50% and hospital discharge of ¼ children after administration of vasopressin in long lasting cardiac arrest


LOE 4 supporting (terlipressin)
Case series of seven children (eight episodes of cardiac arrest) which received terlipressin after epinephrine. ROSC 6/8; survival at discharge 4/7, intact neurological survival 4/7.


LOE 5 neutral (vasopressin vs epis vs vasopressin+epinephrine vs placebo)
In a bupivacaine-induced VF, vasopressin, epinephrine and combined vasopressin+epinephrine had a similar ROSC rate and were superior to placebo.


LOE5 supporting (combined epi+vasopressin vs epinephrine or vasopressin alone)
In an animal study, asphyxia cardiac arrest was treated either by epinephrine or vasopressin alone or combined vasopressin + epi. Combination of vasopressin + epinephrine increased CoPP and resulted in better ROSC than the two drugs alone.


LOE1 supporting (combined vasopressin + epinephrine + steroid vs epinephrine)
Small randomized controlled trial (not multicenter) human trial in in-hospital cardiac arrest(n-100). Patients who received combined drugs associated with steroids had higher rate of ROSC and higher rate of survival to hospital discharge.

LOE 5 neutral (epinephrine vs epinephrine + vasopressin)
In this animal study of VF, swines received successive doses of epinephrine or alternated doses of epinephrine and vasopressin. Despite higher CoPP and cerebral blood flow, ROSC was not significantly different in both groups.


LOE 3 supporting (epinephrine + vasopressin)
In this case series of 10 in-hospital adult cardiac arrests, patients served as their own controls and received successively epinephrine then vasopressin. CPP increased more after vasopressin than after epinephrine.

No ROSC was observed.


LOE 1 neutral (vasopressin vs epinephrine):
This monocentre randomized study included 336 patients in cardiopulmonary arrest of cardiogenic origin who received either 1 mg epinephrine (up to a total dose of 4 mg) or 40 IU of vasopressin (up to a total dose of 160IU). Drugs were administered in the emergency department only. No rescue drug was authorized. No difference were seen in ROSC (51 patients in the vasopressin group versus 42 patients in the epinephrine group) nor in 24 h survival, survival to hospital discharge or intact neurological outcome. Administration of vasopressin did not affect any outcome parameter.


LOE 5 neutral (vasopressin + Epi vs vasopressin vs epinephrine
In this porcine model of VF, combination of vasopressin and epinephrine increased coronary perfusion pressure more rapidly and lasted longer than vasopressin or epinephrine administered alone. No difference was seen in the left ventricular blood flow between the three group. Vasopressin alone increased more the cerebral blood flow but combination was superior to epinephrine alone. However no difference on ROSC was observed


LOE5 neutral (vasopressin vs epinephrine)
In this swine model of VF, animal in cardiac arrest received either vasopressin or epinephrine. No difference were seen between groups in term of ROSC, cerebral blood flow or cerebral tissue pH, pCO2 and cerebral oxygen extraction.


LOE 5 neutral (vasopressin vs epinephrine vs epinephrine + alpha1 and beta-adrenergic blockade)
In this swine model of VF, vasopressin and epinephrine were equivalent for ROSC and neurological function Post resuscitation neurological function was improved with epinephrine combined with alpha1 and beta-blockade compared to epinephrine or vasopressin alone.


LOE5 neutral (vasopressin vs epinephrine vs epinephrine + vasopressin vs placebo)
In a swine model of VF, ROSC and seven day survival were identical in the three groups as was the neurological outcome. Results were better in the three treated groups compared to placebo

LOE 5 opposing (vasopressin vs epinephrine vs placebo)
In this animal study of swine in VF, in the postresuscitation period, animals in Vasopressin group had a decrease in renal blood flow that was proportional to the decrease of cardiac index and that was more important than epinephrine group or the placebo group.


LOE 5 opposing (vasopressin vs epinephrine)
In this swine model of VF, vasopressin decreased cardiac index and myocardial contractility more than adrenaline, probably secondary to the greater increase in systemic vascular resistance. The depressant effect of vasopressin on myocardial function was reversible.


LOE 5 supporting (vasopressin vs epinephrine)
In this swine animal model of VF, vasopressin improved more cerebral blood flow and cerebral oxygenation than epinephrine.


LOE 5 supporting (vasopressin vs epinephrine)
In this swine study of animals in VF, animals receiving vasopressin had a greater cerebral blood flow after ROSC than animals receiving epinephrine. No difference in ROSC.


LOE 5 supporting (vasopressin+epinephrine vs epinephrine vs placebo)
In this animal model of VF and long lasting cardiac arrest (18 min without CPR and 4 min of CPR before first attempt of defibrillation) combination of epinephrine and vasopressin given together significantly improves aortic diastolic pressure, ROSC, 5 day survival and neurologic outcome.


LOE 1 neutral (vasopressin vs epinephrine)
Multicentre RCT of 200 adult patients with in-hospital cardiac arrest randomized to received as first drug either vasopressin or epinephrine followed by epinephrine if more than one dose was required for ROSC. No differences were seen in hospital discharge, 1 h survival or neurological outcome (primary outcomes) nor in ROSC. In subgroups analyses, no differences in outcome were seen for VF, asystole or PEA, nor in "younger" patients. Power was low in each subgroup. VF was less frequent (18%) than PEA (41 -54%)


LOE 1 neutral (Epinephrine + vasopressin versus epinephrine)
Systematic review of studies where a combination of epinephrine + vasopressin was compared to epinephrine alone. Three studies (Callaway 2006, Wenzel 2004, Still 2001) were analysed. Only the study of Wenzel showed A better survival to discharge in the vasopressin+epinephrine groups but with an increased number of patients with cognitive impairment. ROSC was also slightly increased. The authors concluded that use of a combination of epinephrine and vasopressin was not clearly superior to epinephrine alone.

**LOE 5 neutral (vasopressin vs epinephrine)**

This swine model of VF receiving vasopressin or epinephrine before defibrillation showed an increased myocardial blood flow and increased VF frequency before defibrillation in both groups.


**LOE 5 supporting (vasopressin + epinephrine vs epinephrine + placebo)**

Swine study of VF (10 min). Animals received either combination of vasopressin + epinephrine or epinephrine + saline placebo. Increased rate of ROSC and improved haemodynamic parameters occurred in the vasopressin+epinephrine group compared to the epinephrine group.

Studer, W., X. Wu, et al. (2002). "Resuscitation from cardiac arrest with adrenaline/epinephrine or vasopressin: effects on intestinal mucosal tonometer pCO(2) during the postresuscitation period in rats." Resuscitation 53: 201-207.

**LOE 5 neutral (vasopressin vs epinephrine)**

In this animal model of rats in VF receiving vasopressin or epinephrine, no significant difference was seen in ROSC. Mesenteric ischemia was however less important in vasopressin rats than in epinephrine rats in the postresuscitation period.


**LOE 5 supporting (vasopressin + epinephrine vs vasopressin vs epinephrine)**

In a pediatric porcine model of long lasting VF (20 min), piglets received either combination of vasopressin+ epinephrine or vasopressin alone or epinephrine alone twice before defibrillation attempt. Combination drugs improved left ventricular blood flow and cerebral blood flow. No significant difference in ROSC were demonstrated in this experiment.


**LOE 5 neutral (vasopressin vs epinephrine)**

In a swine model of hypovolemic shock followed by VF, bone marrow flow and was higher and vascular resistance lower in vasopressin animals compared to epinephrine animals.


**LOE 5 opposing (epinephrine versus epi+vasopressin versus vasopressin alone)**

Pediatric swine model of asphyxia cardiac arrest. Animals received either vasopressin, epinephrine or a combination of vasopressin + epinephrine after 8 min of CA and 8 min of CPR. No difference was seen in the three groups for CoPP and cerebral blood flow; left ventricular blood flow was higher in the vasopressin group than in the two other groups. ROSC was higher in epinephrine > vasopressin alone and not significantly different between epinephrine and epi+vasopressin.


**LOE 5 supporting (vasopressin vs epinephrine vs placebo)**

In a swine model, hypovolemic animals in VF received either vasopressin, epinephrine or placebo. No difference in ROSC between epinephrine and vasopressin groups but better 1h survival, better renal blood flow and less acidosis in vasopressin group compared to epinephrine group.


**LOE 1 neutral (vasopressin vs epinephrine)**
Large good conducted RCT of 1186 cardiac arrest adult patients showing no benefit of vasopressin vs epi. Subgroup analysis showed a better survival at discharge (but more disabled patients) in the asystole group. In subgroup analysis of the refractory cardiac arrest patients, vasopressin followed by epinephrine was better than epinephrine alone (LOE 1 supporting).


LOE 5 supporting (vasopressin vs epinephrine vs placebo)
In an animal model of VF (4 min) + 3 min CPR, drugs (vasopressin or epinephrine or placebo) were administered every min. Defibrillation occurred at 22 min of the start of the CA. Aortic diastolic pressure was higher in vasopressin group than in epinephrine or placebo groups. ROSC and 24 h survival with full neurological recovery was achieved only in Vasopressin pigs.


LOE 5 supporting (vasopressin vs epinephrine)
In an animal model of VF (4 min) drugs (vasopressin or epinephrine or placebo) were administered every 5 min after 3 or 8 min of CPR. Defibrillation occurred at 22 min of the start of the CA. Coronary perfusion pressure was higher in both vasopressin groups when compared with corresponding epinephrine groups. ROSC and 1 h survival were achieved only in the two Vasopressin groups.


LOE 5 supporting (vasopressin vs epinephrine)
In this animal model of PEA after 15 min + 3 min CPR, pigs received either vasopressin or epi. Left myocardial and cerebral blood flows and ROSC were higher in the vasopressin group than in the epinephrine group.


LOE 5 neutral (vasopressin vs vasopressin+epinephrine)
In an animal model of cardiac arrest (15 min of VF followed by 2 min of PEA and 3 min of CPR), pigs received either epinephrine or combination of vasopressin + epinephrine. No difference were seen in ROSC nor in coronary and cerebral perfusion pressure and left ventricular myocardial blood flow. Only cerebral blood flow was increased by vasopressin alone compared to the combination of drugs.


LOE 1 Neutral
SR analyzing 5 RCT (Wenzel 2004-105; Stiell 2001-105; Lindner 1997-535; Lee 2000-S91 (abstract), LI1999-28 (Chinese language)) and one good meta-analysis (Aung 2005-17). No benefit of Vasopressin versus epinephrine in patient with non-traumatic cardiac arrest. Despite a trend towards benefit of vasopressin over epinephrine shown in asystole sub-groups, the SR does not demonstrate consistency in this analysis nor benefit in the total analysis. outcome of predischarge mortality, vasopressin compared to epinephrine, was 0.91 (95% CI 0.52 to 1.57). In all analyses, the CI around the pooled effect included values favoring epinephrine. For the revised composite outcome of death or major disability, the pooled odds ratio, vasopressin compared to epinephrine, is 1.32, 95% CI 0.82 to 2.14.