

Vasopressin or Epinephrine for Out-of-Hospital Cardiac Arrest

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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. [Ann Emerg Med. 2006;48:86-97.]

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CLINICAL SCENARIO

You are the medical and education director of a regional emergency medical system with basic and advanced life support capabilities. Publicity about a recent trial of vasopressin as an alternative to epinephrine for patients with cardiac arrest leads several members of your training committee to ask when your system is shifting to that alternative. They point out that the American Heart Association guidelines for cardiac resuscitation that you use as the basis for your own advanced life support protocols already list vasopressin as an option. Your paramedic ambulances do not stock vasopressin, nor do your training and recertification programs include it. You decide to examine the evidence favoring vasopressin over epinephrine before making a major revision in your protocols.

The following evidence-based emergency medicine review¹ seeks an answer to the question posed by this scenario.

FORMULATING THE QUESTION

Hospital inpatients receiving cardiac resuscitation might have a prognostic advantage over patients outside of the hospital by virtue of earlier recognition and more rapid initiation of basic and advanced life support interventions. On the other hand, inpatients' prognosis may be adversely affected by their concomitant acute conditions. The magnitude and direction of difference in effect of vasopressin on cardiac arrest outcomes between patients inside and outside of the hospital are unpredictable. We therefore included inpatient studies.

We confined our review to survival to hospital discharge and good neurologic function, outcomes that we believe patients themselves most value. Patients and families might consider admission to an ICU with no increased chance of survival to discharge to constitute an undesirable consequence of a new resuscitation drug. For expediency, resuscitation trialists sometimes define “survival to admission” as their primary outcome measure.^{2,3} Unfortunately, an intervention’s impact on a surrogate outcome such as survival to hospital admission is no guarantee of patient-important benefit.^{4,5} Several studies suggest that survival to ICU admission is not a good surrogate for survival to hospital discharge.^{2,3,6}

We formulated our question as: In patients with cardiac arrest not attributable to trauma or environmental exposures, what is the impact on survival to hospital discharge and survivor neurologic function of vasopressin compared to epinephrine, administered at the first point in a cardiac arrest protocol at which epinephrine would routinely be given?

SEARCHING FOR AND SELECTING THE BEST EVIDENCE

We searched for randomized trials and systematic reviews comparing vasopressin to epinephrine for adults in cardiac arrest. We searched MEDLINE from 1966 to July 2004 and EMBASE from 1980 to January 2004 with the OVID interface, using search terms “vasopressin,” “epinephrine,” “cardiac arrest,” and “heart arrest,” with no language restrictions. We limited our MEDLINE search, but not our other searches, to randomized trials or systematic reviews using epinephrine as the comparison intervention. We included randomized trials or systematic reviews of randomized trials, with no other exclusion criteria. Our search yielded 271 results. We also searched all databases of the Cochrane Library⁷ through 2004 issue 1, Emergency Medical Abstracts (available online at <http://ccme.org>) from 1977 through December 2004,⁸ and online resources including BestBETS (available online at <http://www.bestbets.org>), using the single search term “vasopressin.” These databases yielded a total of 1,036 results. We reviewed the bibliographies of eligible trials and systematic reviews and of selected non-systematic reviews and commentaries for citations of additional eligible articles. Finally, we searched the bibliography of the relevant sections of the 2000 update of the American Heart Association Advanced Cardiac Life Support guideline.⁹

We found 3 trials comparing vasopressin to epinephrine in patients with cardiac arrest, 2 out-of-hospital^{10,11} and 1 limited to inpatients.¹² One published systematic review,¹³ 1 protocol in the Cochrane Database of Systematic Reviews,¹⁴ and 1 “shortcut review,”¹⁵ as well as our bibliographical reference review, revealed no additional trials. We found no placebo-controlled trials or other human randomized trials involving vasopressin for patients with cardiac arrest. The systematic review by Biondi-Zoccai et al¹³ was limited in its reporting, was not restricted to clinical trials, and did not include the most recent and largest randomized trial by Wenzel et al.¹¹ After the

completion of our primary searches and after the initial submission of our review, a second, well-reported, systematic review appeared that used inclusion criteria identical to our own.¹⁶ Aung and Htay¹⁶ identified the same 3 trials identified by our searches, as well as 2 additional clinical trials.^{17,18} We will focus the rest of this review on the Aung and Htay¹⁶ meta-analysis, supplemented by elements of our own analysis that either differ from or go beyond that of Aung and Htay.¹⁶

EXAMINING THE EVIDENCE

Aung and Htay¹⁶ restricted their review to randomized trials comparing vasopressin to epinephrine in patients with cardiac arrest and reporting patient-important outcomes. They independently selected studies for inclusion.

Aung and Htay¹⁶ report a rigorous search of MEDLINE, EMBASE, the Cochrane Library, CINAHL, bibliographies of related articles, registries of conference proceedings, and unpublished trials. They found a statistical test for evidence of studies not identified by their search to be negative. In addition to the 5 trials mentioned previously,^{10–12,17,18} Aung and Htay¹⁶ also report the existence of a trial in progress, the Cardiac Arrest Research Project being conducted by the University of Pittsburgh (available online at <http://newsbureau.upmc.com/emergency/vasopressin04.htm>). This trial compares vasopressin to placebo as an addition to standard therapy including epinephrine and will not be eligible for inclusion in our review.

DESCRIPTION OF THE TRIALS

Table 1 summarizes the key features of the 5 randomized trials identified by Aung and Htay¹⁶ and included in their analysis. Of the 2 trials not identified in our own independent search, one was limited to 10 patients and was published in abstract form only,¹⁷ and the other was published in a Chinese journal.¹⁸ The inclusion of non-English studies and abstracts in systematic reviews is controversial.^{19,20} Exclusion of unpublished studies may lead to underestimation of treatment effect.^{19,21} On the other hand, inclusion of non-English and incompletely reported studies may have little impact on the results of most systematic reviews.^{22,23}

Two members of our own author team fluent in Chinese (QZ and ZJ) reviewed the full text of the study by Li et al.¹⁸ The reports by Lee¹⁷ and Li¹⁸ do not allow full assessment of their study populations, treatment protocols, or the susceptibility to bias, nor do they provide information about the distribution of presenting rhythms between their study groups. We are unclear about the relationship of the results reported by Lee et al¹⁷ to our own target outcomes. Aung and Htay¹⁶ report failed attempts to obtain more information from the authors of these 2 trials. We did not attempt to reproduce their inquiry. The inclusion of these studies in a pooled analysis might distort the estimates in ways that the parsimoniously reported data does not allow an investigator to anticipate or assess.

The 3 fully reported trials encompass a broad range of settings and variability within potentially important parameters,

Table 1. Summarizing the characteristics of 5 randomized trials comparing vasopressin to epinephrine in patients with cardiac arrest.

Study	Patients	Interventions	Comparisons	Outcomes
Wenzel et al, ¹¹ 2004	1,186 European adult patients with out-of-hospital arrest, average age 66 years, 70% men. Excluded terminally ill patients, those successfully defibrillated without drugs or with trauma; 61% arrests attributed to cardiac causes; 40% ventricular fibrillation, 44% asystole; 78% arrests witnessed, average time from arrest to basic life support 7.9 min and to advanced life support 14.9–15.6 min	40 IU vasopressin intravenously either immediately or after 3 attempts at defibrillation Dose repeated in 3 minutes if no return of circulation	1 mg Of epinephrine intravenously after same protocol as for vasopressin	Survival to hospital admission and to discharge, neurologic function by cerebral performance scale ^{24,25}
Stiell et al, ¹² 2001	200 Adult patients with cardiac arrest in Canadian hospitals or emergency wards; 81% inpatients, 50% ward patients, 22% ICU. Average age 70 years, 64% men. Excluded terminally ill patients or those with trauma or exsanguination; 30% of arrests attributed to cardiac causes; 18% ventricular fibrillation, 31% asystole; 81% of arrests witnessed, average time from arrest to basic life support 1.4–1.9 min and to advanced life support 2.5–3.2 min	40 IU Vasopressin intravenously at the point in ACLS protocols that epinephrine first indicated. One dose only	1 mg epinephrine intravenously after same protocol as for vasopressin	Survival to hospital discharge, neurologic function by cerebral performance scale ²⁵ and the Mini-Mental State examination ³⁸
Lindner et al, ¹⁰ 1997	40 Adult European patients with out-of-hospital ventricular fibrillation arrest. Average age 65 years, 72% men. Excluded patients with trauma or terminal illness and patients who received epinephrine by endotracheal tube. Average time from arrest to basic life support 6.1–6.5 min, and to advanced life support 13.9–15.1 min	40 IU Vasopressin intravenously after shocks failed to restore rhythm. One dose only	1 mg Epinephrine intravenously once after shocks failed to restore rhythm	Survival to admission and to hospital discharge, neurologic function by Glasgow Coma Scale score
Lee et al, 2000 ¹⁷	10 Patients in a large university teaching hospital. Other details ambiguous or not reported.	40 Units vasopressin given 0.1 unit/kg/min “as a bolus”	Epinephrine, dose not stated	Return of spontaneous circulation not otherwise described. Neurologic outcome not otherwise described.
Li et al, 1999 ¹⁸	83 Adult Chinese hospital inpatients. Average age 57 years, 67% men. “Average cardiac arrest time” 10 min, not otherwise characterized. Other population details not reported.	0.5 U/kg Vasopressin or 1.0 U/kg vasopressin administered every 10 min	1.0 mg Epinephrine or 5.0 mg epinephrine administered every 5 minutes	Hospital discharge. No neurologic assessment reported.

ACLS, Advanced cardiac life support.

Table 2. Summarizing the assessment for susceptibility to important bias of the 3 fully reported trials.

Criterion	Wenzel et al, ¹¹ 2004	Stiell et al, ¹² 2001	Lindner et al, ¹⁰ 1997
Randomization	Multicenter randomized trial. Randomization blocked in groups of 10 and stratified by center	Multicenter randomized trial. Random distribution of study drugs to crash carts in treatment centers. Stratified by center	Single-center randomized trial. Computer-generated randomization of identical syringes
Concealment	Adequate	Adequate	Adequate
Intention to treat	Yes	74 (27%) Patients were excluded post hoc by means of blinded adjudicated revision of eligibility assessment; 50 were due to cardiac arrest before arrival in hospital. The others were due to protocol violations or ineligibility caused by clinical circumstances	Yes
Baseline comparisons	38% of patients receiving vasopressin presented with ventricular fibrillation versus 41% of patients receiving epinephrine	20% Of patients receiving vasopressin presented with ventricular fibrillation versus 16% of patients receiving epinephrine. Treatment times were somewhat longer in vasopressin group	Well balanced within limits of small number of allocations
Blinding	Blinded with respect to patients, care providers, and data collectors, except for 5 patients whose protocols were broken after hospital admission. Reporting of blinding not explicit for assessors of neurologic outcome or data analysts	Blinded with respect to patients, care providers, and data collectors. Reporting of blinding not explicit for assessors of neurologic outcome or data analysts	Blinded with respect to patients, care providers. Reporting of blinding not explicit for data collectors, assessors of neurologic outcome, or data analysts
Cointerventions	Bystander CPR 19% vasopressin, 18% epinephrine. Time from BLS to ACLS interventions 7.0 min in vasopressin group, 7.7 min in epinephrine group. About 2% more of the vasopressin group received lytics, and 2% fewer received amiodarone and atropine compared to epinephrine group	Time from arrest to study drug 3.2 min vasopressin, 2.5 min epinephrine. No consistent pattern of imbalance in reported drug therapies other than the study drugs	Bystander CPR 20% vasopressin, 25% epinephrine. Time from arrest to study drug 15.1 min vasopressin, 13.9 min epinephrine. Distribution of other cointerventions not reported
Complete follow-up	33 (2.8%) Patients could not be included in analysis because of missing study-drug codes. Additionally, 20 patients, equally divided, were lost to follow-up before hospital discharge, and another 23 patients who survived to discharge were lost to neurologic follow-up.	Complete	Complete

CPR, Cardiopulmonary resuscitation; BLS, basic life support.

such as time from arrest to initiation of advanced life support. For example, in contrast to the patients studied by Wenzel et al¹¹ and Lindner et al,¹⁰ the patients studied by Stiell et al¹² had concomitant acute problems warranting emergency department or hospital admission. Twenty-two percent were in the ICU at arrest.¹² Aung and Htay¹⁶ did not perceive these factors to prohibit pooling of the results of their primary outcomes across the trials, nor do we perceive them to constitute a priori incompatibility of these studies.

The 2 largest trials^{11,12} used a common measure of neurologic outcome, a previously published cerebral performance instrument characterized by clear and discrete gradations of functional recovery, ranging from death to full recovery.²⁴ Other investigators have used this instrument in

cardiac resuscitation research.²⁵ A preliminary report by Nesbitt et al²⁶ indicates that this instrument correlates well with a highly validated measure of health-related quality of life²⁷ but may overestimate the extent of functional recovery in survivors.²⁶

Aung and Htay¹⁶ performed independent assessment of the quality of the trials included in their review, with particular attention to concealment of randomization, blinding, completeness of follow-up, and outcome assessment.¹⁶ They found uniformly high quality in the 3 assessable trials using these criteria,^{10–12} although the blinding of outcome assessment was not explicit in the study by Lindner et al.¹⁰ Aung and Htay¹⁶ report 80% agreement for their independent assessments ($\kappa = .64$).

Secondary Outcome: Death or Severe Neurological Disability

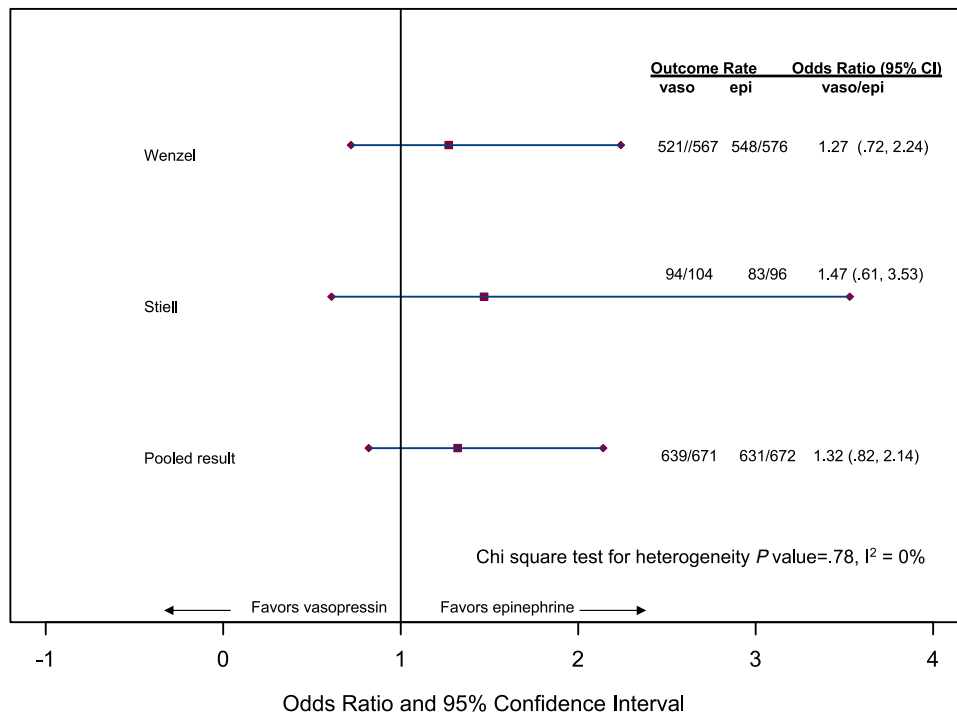


Figure 1. Forest plot of outcome of death or severe disability in the 2 trials using a common measure of neurologic outcome. For each trial, the small square corresponds to the observed odds ratio for predischarge mortality, and the horizontal line defines the 95% CI. An odds ratio of 1, identified by the vertical line, would reflect an identical effect of the 2 drugs. The lowest plot provides the pooled random effects odds ratio and CI. Poor neurologic outcome is defined as a score of 3 or greater on the cerebral performance score.²⁵

Table 2 summarizes our own assessment of the likelihood of bias within the 3 fully reported trials, using criteria similar to those used by Aung and Htay.^{16,28} The loss of 76 patients to complete follow-up (6% of patients randomized) in the Wenzel et al¹¹ study is potentially problematic. If these patients and their outcomes were not randomly distributed between the treatment groups, the results of the trial might be substantially affected.

PRIMARY RESULTS OF THE TRIALS

Aung and Htay¹⁶ chose the random effects model to summarize data from the 5 trials they included.^{29,30} The random effects model usually leads to wider confidence intervals (CIs) around the pooled result than does the fixed effects model and may be considered “more conservative” for this reason.³¹ Aung and Htay¹⁶ used standard methods to assess for statistical heterogeneity between the results of the included studies. They used the I² statistic to provide an estimate of the percentage of the variability between the results of studies being pooled that is due to true differences between the studies, as opposed to variability due to chance alone.^{32,33} When all 5 trials were included, Aung and Htay¹⁶ report a high degree of heterogeneity for the primary outcome of death before hospital discharge.¹⁶ The χ^2 test for heterogeneity yielded a P value of

.09, which is less than the commonly preferred cutoff of .1. I² was 34%, suggesting a substantial portion of variability between the studies to be due to actual differences.

In our own analysis, using odds ratios for the same outcome and including only the 3 fully reported trials, the P value for heterogeneity was .21, and the I² value was 35%. Most of the heterogeneity is due to a trend in the direction of benefit of vasopressin in the study by Lindner et al,¹⁰ a trend not observed in the studies by Wenzel et al¹¹ and Stiell et al.^{12,16} A review of the characteristics of the Lindner et al¹⁰ study, compared to the analogous characteristics of the studies by Wenzel et al¹¹ and Stiell et al,¹² (Table 1) fails to reveal consistent differences that would explain this difference in trend. Under the circumstances, pooling of these 3 studies, as elected by Aung and Htay,¹⁶ may reasonably provide a more generalizable result.³⁴

Aung and Htay¹⁶ report a 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 et al¹⁸ and Lee et al¹⁷ were included, the relative risk was 0.96 (95% CI 0.87 to 1.05). Our own analysis also used the random effects model and preferred odds ratios to risk ratios because of important inconsistencies between the results when risk ratios were used. Such inconsistencies commonly

Table 3. Summary of appraisal of presenting rhythm subgroups in 3 randomized trials comparing vasopressin to epinephrine in patients with cardiac arrest based on criteria proposed for evaluation of subgroup analyses in randomized trials.^{35,36} The hypothesis of a selective benefit of vasopressin over epinephrine in patients resending with asystole fails with respect to several criteria.

Criterion	Conclusion
Was the subgroup difference suggested by comparisons within rather than between studies?	Yes. The effect of vasopressin compared to epinephrine on predischage mortality was reported for the asystole subgroup within 2 of the 3 trials.
Was the magnitude of subgroup difference large?	Yes. The pooled odds ratio of 0.43 for predischage mortality for patients in asystole must be considered a large effect compared to the pooled odds ratio of 1.00 for patients in the ventricular fibrillation subgroup (Figure 3).
Was the subgroup difference consistent across studies?	No. Only 1 trial showed benefit in patients presenting with asystole. One trial showed a trend toward benefit in patients presenting with ventricular fibrillation, a trend that was not observed in the other 2 trials.
Was the subgroup difference statistically significant?	No. The effect of vasopressin compared to epinephrine on predischage mortality in patients with asystole was not statistically different from that in patients with ventricular fibrillation.
Did the trialists plan the subgroup analysis in advance?	Unclear. The only study to report a subgroup effect did not report advance planning of the analysis.
Were many subgroup analyses performed and selectively reported?	Unclear in the Wenzel et al ¹¹ trial. Stiell et al ¹² considered many subgroups.
Is the difference in effect in the subgroup supported by biological hypothesis?	No. A biological hypothesis supporting a selective benefit of vasopressin in patients presenting in asystole or in another rhythm class has not been elaborated in either the trials or other sources reviewed in preparation for our analysis.

occur when outcome rates are extremely high, as in cardiac arrest. Our pooled odds ratio for the outcome of predischage 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.

Aung and Htay¹⁶ analyzed the effect of vasopressin on death before hospital discharge or neurologic impairment. They grouped patients with only moderate disability together with those who died or were in a persistent vegetative states and included the study by Lee et al¹⁷ with those by Stiell et al¹² and Wenzel et al.¹¹ The Lee et al¹⁷ study contributed substantial heterogeneity to this analysis (I^2 of 34%).¹⁶ Aung and Htay¹⁶ report a pooled relative risk of death or neurologic impairment, vasopressin compared to epinephrine, of 1.0 (95% CI 0.94 to 1.07).

A disadvantage of the Aung and Htay¹⁶ approach to assessment of neurologic outcome is that a patient with some residual neurologic deficit but still able to engage in part-time employment is grouped with patients who die or survive with major functional or cognitive impairment. To correct for this disadvantage, including data from the 2 trials that used a common measure of outcome, we classified patients in the 2 worst neurologic outcome categories by the cerebral performance instrument^{24,25} used by Stiell et al¹² and Wenzel et al¹¹ as "poor neurologic outcome." Such patients may have some cognitive function but no independence in activities of daily living. A patient without poor neurologic function by these criteria is at least able to engage in part-time employment in a sheltered environment.²⁵ We believe that this definition of the outcome is more likely to cohere with the values of patients and their families than is that used by Aung and Htay.¹⁶

Using this 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 (Figure 1). We found no important trends with respect to other measures of cognitive function used by Stiell et al¹² and Lindner et al.¹⁰

SUBGROUP ANALYSIS

Wenzel et al¹¹ emphasized an apparent positive effect of vasopressin in decreasing hospital mortality among patients presenting with asystole when advanced life support interventions were initiated. Three trials report data on predischage mortality in subgroups of patients defined by presenting rhythm at initiation of resuscitation.¹⁰⁻¹² Lindner et al's¹⁰ small trial was confined to patients presenting with ventricular dysrhythmias.

Wenzel et al¹¹ also reported apparent benefit of initial vasopressin over initial epinephrine among patients receiving additional doses of epinephrine after the 2 doses of the study drug provided for in the protocol failed to result in return of spontaneous circulation. Such patients are not prospectively identifiable, nor has this effect been reported in other trials.

Aung and Htay¹⁶ detected no statistically significant difference between subgroups defined by presenting rhythm. Their analysis does not, however, exhaust the issue raised by Wenzel et al¹¹ and others. We conducted a systematic subgroup analysis using published validity criteria (Table 3).^{35,36} We confined our consideration of the effect of vasopressin in subgroups to the hypothesis that vasopressin is of benefit in patients with asystole but not in those with ventricular fibrillation. We present the criteria in suggested order of application.

Pre-discharge Mortality--presenting Rhythm Subgroups Reported by Wenzel and Stiell have been pooled and a test for heterogeneity applied

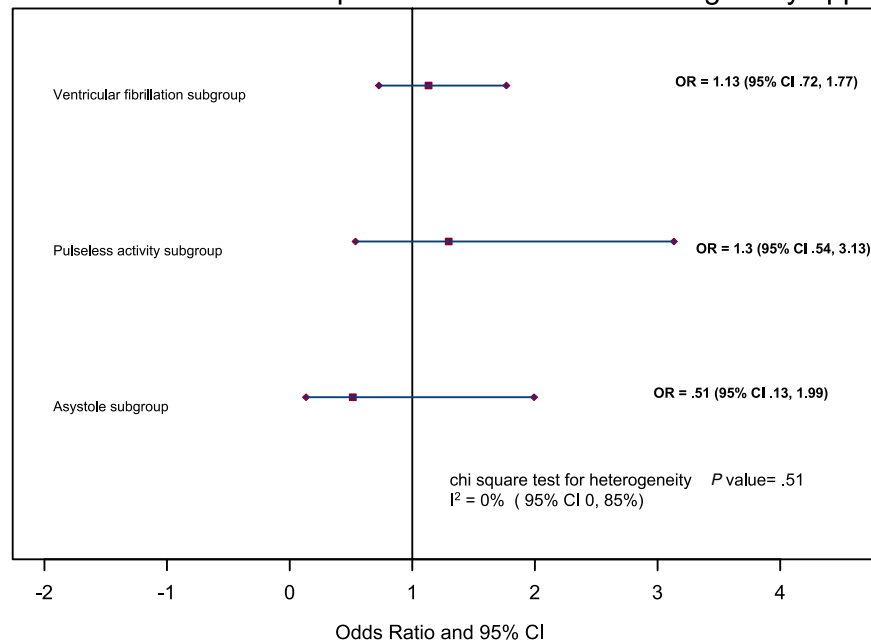


Figure 2. Forest plot illustrating an indirect approach to testing for statistical significance of differences in subgroup effect. See legend to Figure 1 for the explanation of the plot. Subgroup data are pooled across the 2 studies that included patients with all 3 presenting rhythm subtypes. A statistical test for heterogeneity is applied. The *P* value of .51 indicates that the effect of vasopressin compared to epinephrine on mortality within these 3 subgroups is consistent with an underlying effect. The *I*² value of 0 further suggests that all of the observed variation between the subgroups is attributable to chance.

WAS THE SUBGROUP DIFFERENCE SUGGESTED BY COMPARISONS WITHIN RATHER THAN BETWEEN STUDIES?

When investigators conduct independent trials on different subgroups of patients (eg, one trial includes only patients with asystole, another only patients with ventricular fibrillation), apparent differences in effect between the studies may originate from differences in the study populations other than that hypothesized (differences in comorbidity rather than differences in cardiac rhythm) or in aspects of study design (blinding of clinicians or outcome assessors) rather than from differences in response between the subgroups on whom the investigators focus (ventricular fibrillation versus asystole). The apparently greater benefit of vasopressin in patients with asystole reported by Wenzel et al¹¹ is an example of a “within-study” comparison (both Wenzel et al¹¹ and Stiell et al¹² included patients with ventricular fibrillation and asystole), and this strengthens the hypothesis that the difference in effect may be real.

WAS THE MAGNITUDE OF THE SUBGROUP DIFFERENCE LARGE?

The larger the observed difference in effect between subgroups, the less likely it is to have arisen by chance alone. SDW and QZ performed an exact analysis using a logistic regression model to assess the magnitude and precision of

subgroup effects. We believe this method to be more reliable in the setting at hand because exact models are generally preferable, and particularly so when, as here, the data are sparse.

The pooled odds ratio for pre-discharge mortality of patients treated with vasopressin compared to those treated with epinephrine from our exact inference analysis was 0.43 for the asystole subgroups reported by Wenzel et al¹¹ and Stiell et al,¹² contrasting with 1.00 for the ventricular fibrillation subgroups of all 3 trials. This large difference supports the subgroup hypothesis.

WAS THE SUBGROUP DIFFERENCE CONSISTENT ACROSS STUDIES?

Wenzel et al¹¹ observed a trend in the direction favoring vasopressin over epinephrine among patients presenting with asystole and a trend in the opposite direction among patients presenting with ventricular fibrillation (and with pulseless electrical activity). In the trial by Stiell et al,¹² the trends in both asystole and ventricular fibrillation subgroups favored epinephrine. The Lindner et al¹⁰ study of patients with ventricular fibrillation observed a trend in favor of vasopressin. Hence, a consistent pattern of subgroup effects does not emerge from the trials to date.

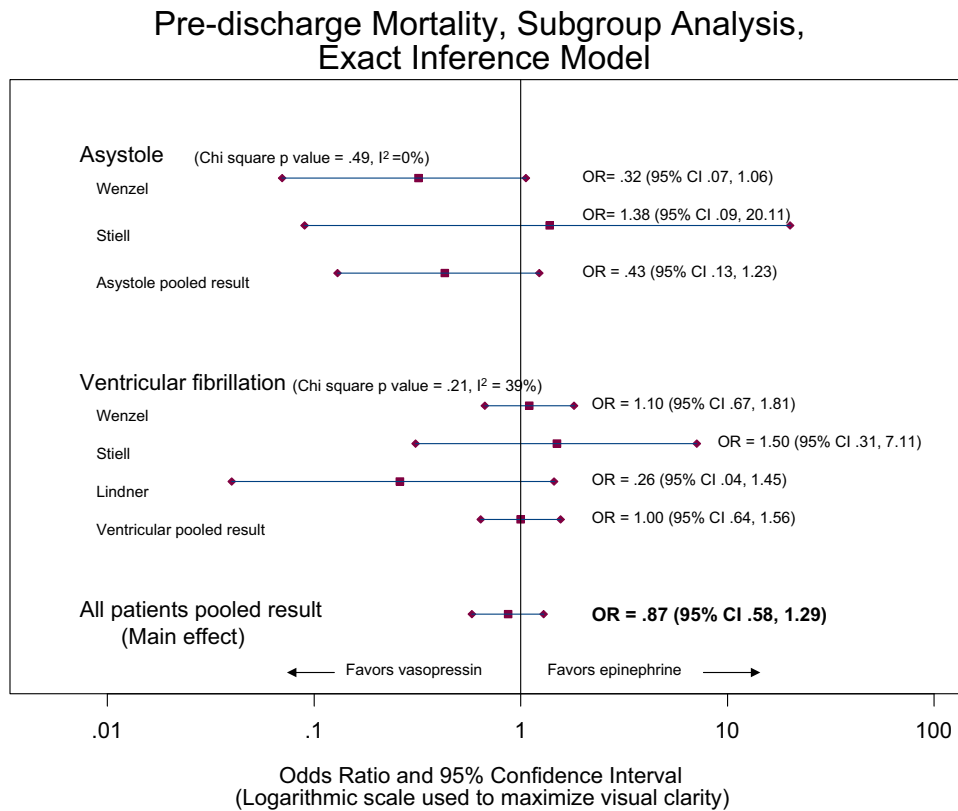


Figure 3. Forest plot illustrating the pooled subgroup effects from the analysis. The analysis uses paired and unpaired data pertaining to the asystole and ventricular fibrillation subgroups from the trials by Wenzel et al,¹¹ Stiell et al,¹² and Lindner et al.¹⁰ See legend to Figure 1 for the explanation of the plot. Odds ratios for the effect on mortality of vasopressin compared to epinephrine are pooled within each subgroup. See text for further explanation.

WAS THE SUBGROUP DIFFERENCE STATISTICALLY SIGNIFICANT?

Investigators and authors sometimes contrast a statistically significant difference between treatment and control in one subgroup (such as those with asystole) with the lack of statistical significance in another subgroup (such as those with other presenting rhythms). This, however, misses the important question, can the difference between the apparent effects in different subgroups (asystole versus ventricular fibrillation) be explained by chance?³⁶

Aung and Htay¹⁶ applied a statistical test for heterogeneity to pooled results in each of the 3 rhythm subgroups. This approach is illustrated in simplified form in Figure 2. In both the Aung and Htay¹⁶ analysis and our own, the tests for significance yield *P* values well above .1 and low values of *I*², indicating that the observed effect of vasopressin compared to epinephrine in patients with asystole is consistent with a hypothesis of a uniform underlying effect across all rhythm subgroups. This falls short of a direct test of the difference in comparative effect of vasopressin between asystole and other rhythm subgroups. Our own analysis illustrates such a direct test.

We started our exact analysis by considering the possibility of an interaction between presenting rhythm subgroup and

treatment effect. When we found no significant interaction, we repeated the analysis without the interaction term and computed exact tests of the subgroup and treatment main effects. The method was applied to all 3 trials (Figure 3)¹⁰⁻¹² and—because this is restricted to within-study comparisons of ventricular fibrillation and asystole subgroups—to the studies by Wenzel et al¹¹ and Stiell et al.¹²

Figure 3 displays the results of our statistical analysis of the subgroup effect. The question we are asking is, can the difference in the odds ratios in the asystole group (0.43) and the ventricular fibrillation group (1.00) be explained by chance? The ratio of these 2 odds ratios is 0.43, and the 95% CI is 0.12 to 1.37. The CI includes 1 and indicates that the difference between the original odds ratios of 0.43 and 1.00 is compatible with chance, ie, it is not statistically significant (*P* = .18).

The odds ratio for mortality for these 2 subgroups from the 3 trials is 0.87 (95% CI 0.58 to 1.29) favoring vasopressin. As a further control for study effect in the exact model, the ratio of odds ratios of effect on mortality of vasopressin in asystole compared to ventricular fibrillation subgroups in the strictly paired analysis is 0.38 (95% CI 0.11 to 1.22; *P* = .12), and the odds ratio for mortality in both subgroups combined is 0.95 (95% CI 0.62 to 1.44), both reflecting trends favoring vasopressin.

In summary, when a direct test of statistical significance is applied, the trend toward a mortality benefit of vasopressin compared to epinephrine in patients with asystole is not significantly different from the comparative effect in patients with ventricular fibrillation.

As summarized in Table 3, the remaining criteria for believability of the subgroup hypothesis about vasopressin compared to epinephrine in patients with asystole were not met.

APPLYING THE EVIDENCE

Returning to our clinical scenario, as the director of emergency medical services and personnel in your region, you must consider a number of issues in deciding whether to upgrade the status of vasopressin in your protocols for patients in cardiac arrest. The recent trial of vasopressin compared to epinephrine received high publicity in the lay press. An editorial accompanying the Wenzel et al¹¹ trial report in the *New England Journal of Medicine* called for unscheduled conventions of the American Heart Association and the American College of Cardiology to incorporate a recommendation of vasopressin for patients presenting in asystole.³⁷ You consequently may be under some pressure to provide the perceived benefits of the new therapy to the region and may even be identified as the cause of any delay.

Changing regional emergency medical services protocols, however, entails considerable effort and expense, whether or not unscheduled meetings and conferences are required. Your regional emergency medical services committee would have to approve the new protocol, and you would have to administer a training update to all relevant care providers. To justify this effort, you need convincing evidence that a patient-important benefit of vasopressin exists.

We have summarized the data from a well-done meta-analysis and from the 3 fully reported randomized trials and have found no overall effect of vasopressin compared to epinephrine in reducing mortality before discharge. After systematically applying 7 published criteria for evaluation of subgroup analyses in randomized trials of effectiveness, we have concluded that the evidence of an important survival benefit of vasopressin over epinephrine for patients with asystole is not compelling. It also remains unclear whether vasopressin compared to epinephrine improves or worsens neurologic outcomes in survivors.

Our review is subject to the limitations inherent in shortcut reviews.¹ However, a well-done meta-analysis and our own independent analysis all suggest that you may reasonably decide not to change cardiac arrest protocols until new evidence becomes available.

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Critically Appraised Topic (CAT):**Does vasopressin in place of epinephrine improve survival to discharge without worsening neurological function in patients with out-of-hospital cardiac arrest?**

Question	In patients with cardiac arrest not attributable to trauma or environmental exposures, what is the impact on survival to hospital discharge and survivor neurological function of vasopressin compared to epinephrine when administered at the first point in a cardiac arrest protocol at which epinephrine would routinely be given?
Reviewed by	Wyer PC, Perera P, Jin Z, Zhou Q, Cook DJ, Walter SD, Guyatt GH
Date	November 1, 2005
Expiration date	November 1 2007
Clinical bottom line	Vasopressin, administered to patients with out-of-hospital or in-hospital cardiac arrest, has no proven survival benefit compared to epinephrine when given at the same point in a structured resuscitation protocol, despite a possible increase in likelihood of hospital admission. A subgroup analysis of data from 3 randomized trials does not reveal a statistically significant benefit of vasopressin in patients presenting with asystole or with other specific arrest rhythms. The trials suggest a possible trend towards worse neurological functional outcomes with vasopressin. Current evidence from randomized trials does not support vasopressin use in victims of cardiac arrest. A well done meta-analysis came to the same conclusion.
Search Strategy	The search for randomized trials enrolling adults with cardiac arrest included MEDLINE, EMBASE, the Cochrane Library from the dates of origin through July of 2004, and Emergency Medical Abstracts from 1977 to December 2004. The MEDLINE search was limited to trials comparing vasopressin to epinephrine. Authors of a recent well done meta-analysis conducted an exhaustive search including registries of conference proceedings and unpublished trials.
Citations	<p>Primary: Meta-analysis Aung K, Htay T. Vasopressin for cardiac arrest. <i>Arch Intern Med.</i> 2005;165:17-24.</p> <p>Secondary: 3 fully reported trials 1. Wenzel V, Krismer AC, Arntz HR, et al. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. <i>N Engl J Med.</i> 2004;350:105-113. 2. Stiell IG, Hebert PC, Wells GA, et al. Vasopressin versus epinephrine for in-hospital cardiac arrest: A randomised controlled trial. <i>Lancet.</i> 2001;358:105-109. 3. Lindner KH, Dirks B, Strohmenger HU, Pregel AW, Lindner IM, Lurie KG. Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. <i>Lancet.</i> 1997;349:535-537.</p>
Primary study characteristics	<p>Study population Adult patients in Canada, Europe and Asia with cardiac arrest in and out of hospital. One study limited to patients with ventricular arrest rhythms. Settings and populations poorly described in 2 Asian studies.</p> <p>Interventions 40 IU vasopressin or 1 mg epinephrine iv either immediately or after 3 attempts at defibrillation in patients with ventricular fibrillation. Dose repeated in 3 minutes if no return of pulse in the largest European study. Study protocol poorly described in 2 Asian studies.</p> <p>Outcome Measures Survival to hospital discharge in all studies. Neurological function by cerebral performance scale in survivors to discharge in 2 studies.</p> <p>Study Design Limited to randomized trials comparing vasopressin to epinephrine in human subjects.</p>
Critical appraisal	The systematic review employed an exhaustive search strategy, included registries of unpublished trials and abstracts and otherwise controlled for publication and selection bias. Quality appraisal and data abstraction were performed independently by 2 reviewers with substantial agreement above chance. Heterogeneity was assessed and was substantial when the 2 Asian studies were included. High quality was observed in 3 fully reported trials and could not be assessed in 2 Asian studies.

Results**Primary and secondary outcomes**

	<i>All trials reporting outcome</i>	<i>Fully reported trials only</i>
Pre-discharge mortality (Aung)	RR+ .96 (.87, 1.05)	RR+ .99 (.95, 1.02)
Death or any disability (Aung) δ	RR+ 1.00 (.94, 1.07)	—
Death or major disability $\delta\delta$	—	OR+ 1.32 (.82, 2.14)

+ Relative risk (RR) or odds ratio (OR) and 95% confidence intervals vasopressin compared to epinephrine. ed to epinephrine. Values of RR or OR <1 favor vasopressin; values of RR or OR >1 favor epinephrine.

δ By cerebral performance score or by estimate of outcome from incompletely reported study.

$\delta\delta$ Data from trials of Wenzel and Stiell using the cerebral performance score. Patients in the lowest 2 categories were considered to have poor neurological outcome and were characterized as dependent on others for activities of daily living and with severe memory disturbance or in a vegetative state.

Subgroup analyses

Evidence supporting the hypothesis of selective benefit of vasopressin over epinephrine in cardiac arrest patients with asystole, compared to other arrest rhythms, includes a large difference in effect size coming from within-trial comparisons. The difference in effect of vasopressin in presenting rhythm subgroups, however, is not consistent across otherwise similar trials, is not statistically significant when appropriate analytical methods are applied, may reflect the application of multiple unplanned subgroup analyses and is not supported by a plausible biological hypothesis.

**2006
Medical Toxicology
Subspecialty
Certification Examination**

The American Board of Emergency Medicine (ABEM), the American Board of Pediatrics (ABP) and the American Board of Preventive Medicine (ABPM) will administer the certification examination in Medical Toxicology on Tuesday, November 14, 2006, in computer-based testing centers located throughout the United States.

Physicians must submit an application to the board through which they are certified. Physicians who are certified by an American Board of Medical Specialties member board other than ABEM, ABP, and ABPM and who fulfill the eligibility criteria may apply to ABEM. Upon successful completion of the examination, certification is awarded by the board through which the physician submitted the application.

The eligibility criteria are available from the three board offices or at www.abem.org, www.abp.org, and www.abprevmed.org.

Application materials will be available for ABEM diplomates on February 1, 2006, and will be accepted with postmark dates through May 1, 2006. ABP and ABPM diplomates should contact their Boards for application cycle information.

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