Evolving Role of Vasopressin in the Treatment of Cardiac Arrest

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Sudden cardiac arrest is a major public heath problem, affecting more than 450,000 individuals annually. Response time and the initiation of cardiopulmonary resuscitation (CPR) remain the most important factors determining successful revival. During resuscitation, sympathomimetics are given to enhance cerebral and coronary perfusion pressures in an attempt to achieve restoration of spontaneous circulation. Epinephrine has been the preferred vasopressor since the inception of advanced cardiac life support, although the lack of definitive evidence regarding its effectiveness has created much controversy surrounding its use, including the optimum dosage. Vasopressin is an alternative vasopressor that, when given at high doses, causes vasoconstriction by directly stimulating smooth muscle V_1 receptors. The 2000 American Heart Association (AHA) guidelines commented that vasopressin is a reasonable first-line vasopressor in patients with ventricular fibrillation or pulseless ventricular tachycardia. Since release of those guidelines, additional human studies support an expanded role for vasopressin, whereas other studies cast doubt regarding its efficacy compared with epinephrine. The AHA recently released revised guidelines for CPR and emergency cardiovascular care. The consensus was that vasopressors should remain a part of pulseless sudden cardiac arrest management, with epinephrine 1 mg every 3–5 minutes being the recommended adrenergic of choice. In these revised guidelines, the role of vasopressin expanded beyond previous recommendations, despite the recommendation being downgraded to class indeterminate. The guidelines comment that one dose of vasopressin 40 U may replace the first or second dose of epinephrine in all pulseless sudden cardiac arrest scenarios, including asystole and pulseless electrical activity. A consistent theme with all vasopressors in sudden cardiac arrest is that additional studies are necessary to clearly document greater efficacy compared with no treatment. Further evaluation is warranted to better assess the role of vasopressin in asystolic sudden cardiac arrest, as well as its use with epinephrine, and to determine its optimal timing of administration and potential synergistic effects.

Key Words: vasopressin, epinephrine, cardiac arrest, cardiopulmonary resuscitation.

(Pharmacotherapy 2006;26(6):828–839)

OUTLINE

In the United States, more than 450,000 individuals experience sudden cardiac arrest

annually, with 60–70% of episodes occurring outside the hospital.[1] Sudden cardiac arrest has various causes, although ischemic heart disease is the most common precipitating event, accounting for 335,000 sudden deaths/year.[2] Most patients with sudden cardiac arrest demonstrate ventricular fibrillation at some point during the arrest, although ventricular fibrillation identified at the initial rhythm occurs in only 40% of individuals experiencing an arrest.[1, 3–5] The remaining observed rhythms tend to be asystole and pulseless electrical activity, although it is likely that those with asystole deteriorate to that rhythm after first experiencing ventricular fibrillation or ventricular tachycardia.[6, 7]

Response time remains the most important factor for determining the outcome of a sudden cardiac arrest. In general, with each minute of treatment delay, the rate of survival decreases 10% in a patient who experiences ventricular fibrillation cardiac arrest.[2] Recent studies reinforce that survival depends heavily on the effectiveness of emergency response and time to defibrillation.[8, 9] Unfortunately, the overall survival for patients with sudden cardiac arrest remains low; patients with ventricular fibrillation as the initial rhythm have a higher survival rate compared with those who have pulseless electrical activity or asystole.[6] Overall, survival to hospital admission after an arrest ranges from 20–30%, with survival to hospital discharge being 3–16%.[10, 11]

The goals of managing sudden cardiac arrest are restoration of spontaneous circulation (ROSC) and minimization of vital organ hypoxemia. Cardiopulmonary resuscitation (CPR) serves as a bridge to maintain vital organ perfusion until ROSC occurs. Unfortunately, the mechanism of myocardial perfusion makes the heart the most difficult organ to perfuse because the pressure of CPR may prevent adequate blood flow in the coronary system. Coronary perfusion occurs during the relaxation phase of the cardiac cycle, allowing the pressure in the aorta created by peripheral resistance to push blood through the coronary arteries. The pressure of the coronary venous system opposes the driving pressure of the aorta. Consequently, coronary blood flow is the result of the difference in pressure between the aorta and the right atrium. This pressure gradient is termed coronary perfusion pressure.[12]

The difficulties of achieving myocardial perfusion have led researchers to focus on coronary perfusion pressure as a critically important variable during sudden cardiac arrest. Animal studies suggest a threshold coronary perfusion pressure must be obtained before ROSC can occur.[13, 14] In a human randomized controlled trial, all patients who achieved ROSC had a coronary perfusion pressure of 15 mm Hg or higher, whereas no patients with a coronary perfusion pressure below 15 mm Hg achieved ROSC.[12] Although achieving a coronary perfusion pressure of 15 mm Hg does not guarantee ROSC, this trial established that a higher coronary perfusion pressure correlates with a better chance of survival.

Epinephrine in the Treatment of Sudden Cardiac Arrest

Sympathomimetic agents are used to enhance cerebral and coronary perfusion pressures during CPR, and epinephrine has been the preferred vasopressor since the inception of advanced cardiac life support (ACLS).[15] Epinephrine is a mixed adrenergic agonist affecting α- and β-receptors. It exerts vasoconstriction by preferentially binding to α-receptors in the peripheral vasculature. This peripheral constriction shunts the blood away from the periphery (e.g., skin, skeletal muscle), moving most of the blood volume to visceral and cerebral regions. The shift in blood volume and increased pressure on the system augments pressure in the aorta, the driving force of coronary perfusion. It appears that both α_1- and α_2-receptors are responsible for epinephrine's effects in CPR. The α_2-receptors are more accessible to circulating catecholamines, and some data suggest that the number of α_1-receptors decreases during ischemia.[16, 17]

In addition to vasoconstriction, epinephrine binds to β-receptors. Binding β_1-receptors enhances the contractile state of the heart, stimulates spontaneous contractions, and increases the vigor and intensity of ventricular fibrillation, perhaps improving defibrillation success.[15] These effects improve the likelihood of achieving ROSC. Conversely, β_1-receptor stimulation is associated with several adverse effects that may decrease the chance of survival

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in the postresuscitation phase. This stimulation may result in more significant myocardial dysfunction after the cardiac arrest owing to increased myocardial workload and a hyperadrenergic state causing tachycardia and hypertension.[18]

The lack of definitive evidence regarding epinephrine's effectiveness has created much controversy surrounding the use of the drug in sudden cardiac arrest, including its optimum dosage. The standard dosage of epinephrine during sudden cardiac arrest is 1 mg every 3–5 minutes.[15] This dosing strategy was derived from animal studies, and as there is a positive dose-response curve with epinephrine, when applied to humans the dosing may be inadequate.[19–22] Hence, subsequent investigations considered the use of weight-based and high-dose epinephrine. One randomized controlled trial compared high-dose and standard-dose epinephrine with placebo in 194 patients.[23] Results of this trial showed beneficial rhythm changes for the 10-mg dose of epinephrine; however, these benefits did not translate into an increase in immediate survival or hospital discharge. Also, no benefit was observed for the standard epinephrine dose of 1 mg.

Many other trials have addressed the ideal dose of epinephrine. Most of these studies compared high-dose epinephrine with the standard dose (1 mg). The largest of these investigations (3327 patients) compared repeated administration of epinephrine 5-mg doses with repeated 1-mg doses.[24] Although the high-dose group had a better ROSC rate than that of the standard-dose group (40.4% vs 36.4%, p=0.02), no difference was noted in survival to hospital discharge (p=0.34).

Another study that used weight-based doses of epinephrine found no difference in ROSC, hospital admission rates, or survival to hospital discharge for high-dose versus standard-dose epinephrine.[25] The ability of high-dose epinephrine to achieve better ROSC without increasing long-term survival lends credence to the hypothesis that excessive β_1-receptor stimulation may have negative effects on survival in the postresuscitation phase.

These study results have prompted researchers to look for alternative vasopressors. Trials comparing epinephrine with norepinephrine, phenylephrine, and the combination of epinephrine and β-receptor antagonists have found no significant difference in survival for any regimen compared with epinephrine alone.[26–28]

Rationale for Vasopressin

In 1992, one group of authors first reported that vasopressin concentrations, along with other stress hormones, were elevated in successfully resuscitated patients.[29] This finding precipitated more than a decade of research devoted to the value of vasopressin in sudden cardiac arrest. According to the 2000 American Heart Association (AHA) guidelines, vasopressin is a reasonable first-line vasopressor in patients with ventricular fibrillation or pulseless ventricular tachycardia.[15]

Vasopressin is an endogenous antidiuretic hormone that, when given at high doses, causes vasoconstriction by directly stimulating smooth muscle V_1 receptors.[30, 31] Subtypes of the V_1 receptor have been identified (V_{1a}, V_{1b}), although the clinical relevance and role of these subtypes require additional investigation.[32] Vasopressin, like epinephrine, causes peripheral vasoconstriction, creating the vital shift in blood volume. Yet, it differs from epinephrine in that it also dilates cerebral blood vessels, creating the possibility of better cerebral perfusion beyond that achieved with epinephrine. Because it has no effect on β_1-receptors, vasopressin has not been associated with the dose-limiting adverse effects of epinephrine, most notably a potential increase in myocardial oxygen consumption and postresuscitation arrhythmias. However, vasopressin is not recommended in conscious patients with ischemic heart disease, as the increased peripheral vascular resistance it causes may provoke angina. In addition to antidiuretic and vasoconstrictive effects, vasopressin produces nausea, intestinal cramps due to smooth muscle constriction, increased mesenteric vascular resistance, bronchial constriction, and uterine contractions in women.[15]

The theoretical advantages of vasopressin compared with epinephrine are based on its longer half-life (10–20 min) and pharmacodynamic differences, which have been studied extensively in animal models. When response time to cardiac arrest is prolonged, especially in the out-of-hospital setting, significant hypoxia and metabolic acidosis may occur. Animal and in vitro studies suggest vasopressin can be useful in this setting, as the efficacy of adrenergic vasopressors (e.g., epinephrine) may be blunted in severe acidosis.[15, 33, 34]

Furthermore, epinephrine's vasoconstrictive properties diminish over time. In one study that compared the effect of a single bolus dose of

vasopressin with a continuous infusion of epinephrine in pigs, the investigators found that the vasopressin group had higher coronary perfusion pressures compared with those of the epinephrine group, corresponding to higher rates of ROSC (12 of 12 pigs in the vasopressin group vs 5 of 12 pigs in the epinephrine group, p=0.005).[35] In addition, continuous infusion of epinephrine provided an initial increase in coronary perfusion pressure that progressively diminished to near prearrest levels 14 minutes after induction of the cardiac arrest. These findings correlate with other data proposing that adrenergic receptors may exert tachyphylaxis during prolonged epinephrine exposure.[15, 36–38]

The relevance of these effects, however, is uncertain given the quick response times observed in contemporary sudden cardiac arrest management. Vasopressin receptor binding is not affected by either mechanism.[39] Hence, vasopressin's mechanism of action represents a nonadrenergic approach, and combination therapy with epinephrine makes theoretical sense.

Vasopressin's effect on ROSC in animal models can be summarized by four representative studies.[40–43] Two of the investigations were in a ventricular fibrillation model of cardiac arrest, another in bupivacaine-induced asystole, and the last in asphyxial cardiac arrest. All four studies compared vasopressin and epinephrine alone with the combination of the two agents. The agents were given at varying weight-based doses approximating both standard- and high-dose treatments. In each of the four studies, the combination treatment provided higher coronary perfusion pressure than either agent alone while achieving ROSC in 100% of the animals tested. The results of coronary perfusion pressure and ROSC were also slightly better for vasopressin alone than for epinephrine alone. Results of other cardiac arrest animal studies support the finding that higher levels of vasopressin improve coronary perfusion pressure and myocardial blood flow.[44–47] In one investigation, the results showed that repeated doses of vasopressin were more effective than epinephrine at maintaining adequate coronary perfusion pressures.[48]

Contradictory results, however, have been published. One study of asphyxial cardiac arrest in an animal model compared high-dose epinephrine with high-dose vasopressin and a combination of high-dose vasopressin with standard-dose epinephrine.[49] The results showed that epinephrine alone was superior to both vasopressin and a combination of the two agents in terms of coronary blood flow and ROSC. Despite vasopressin-treated animals having improvement in myocardial and cerebral blood flow, ROSC was more likely with high-dose epinephrine than with vasopressin. The authors of this study noted that whereas high-dose epinephrine 200 µg/kg produced the best rates of ROSC, it also seemed to change the fibrillation threshold in the postresuscitation phase, requiring additional shocks in four of the six treated animals.

Another animal investigation demonstrated that vasopressin treatment showed improved coronary perfusion pressure but had no effect on neurologic survival.[50] Results of yet another study suggested that the combination of vasopressin and epinephrine versus vasopressin alone significantly decreases cerebral perfusion.[51]

Clinical Trials with Vasopressin

Summary of Human Trials

The first evidence regarding the use of vasopressin to treat human cardiac arrest came from a case series published in 1996.[52] Eight patients refractory to varying doses of epinephrine and defibrillation were given vasopressin 40 U intravenously and then defibrillated. After the administration of vasopressin, all patients achieved ROSC and three patients survived to hospital discharge with intact neurologic function. Based on these results, the authors called for further studies comparing vasopressin with epinephrine.

A subsequent small investigation evaluated the hemodynamic effects of vasopressin compared with epinephrine in patients with prolonged cardiac arrest.[53] The primary outcome of interest was the effect of vasopressin as compared with epinephrine on coronary perfusion pressure. After receiving general resuscitation according to ACLS guidelines, individuals were enrolled in this investigation if they were considered nonsalvageable. Ten patients were evaluated, and a central venous catheter was placed for measurement of coronary perfusion pressure. The coronary perfusion pressure was measured for 5 minutes after the administration of epinephrine 1 mg, then all individuals received vasopressin 1 U/kg followed by an additional 5 minutes of coronary perfusion pressure monitoring. The investigators found that epinephrine did not improve coronary perfusion pressure, whereas coronary perfusion pressure

increased in 4 of 10 patients receiving vasopressin. In those showing a response to vasopressin, the coronary perfusion pressure increased by a mean ± SD of 28.2 ± 16.4 mm Hg. No patients in this investigation achieved ROSC.

Results from the first randomized controlled trial of vasopressin administered to patients for management of out-of-hospital ventricular fibrillation were published in 1997.[54] Management followed the standard treatment at the time, and individuals were considered for enrollment if they remained in ventricular fibrillation despite repeated defibrillation. Forty patients refractory to defibrillation were randomly allocated to intravenous epinephrine 1 mg or intravenous vasopressin 40 U with further defibrillation occurring 60–90 seconds after administration of study drug. For individuals not responding to the initial study drug, conventional ACLS ensued, including subsequent administration of epinephrine. Successful resuscitation was defined as ROSC that persisted to hospital admission and a measurable blood pressure with or without vasopressor administration. Additional end points included survival at 24 hours, survival to hospital discharge, and neurologic outcome (Glasgow Coma Scale score).

The epinephrine and vasopressin groups were evenly matched in terms of total number (20 patients/group), male:female ratio (15:5 vs 14:6), mean age (66 vs 64 yrs), and percentage of patients with witnessed arrest (60% vs 65%). Of note, mean treatment times from start of CPR to administration of study drug were a bit later in those allocated to vasopressin (7.8 vs 8.6 min). Restoration of spontaneous circulation occurred more often in those receiving vasopressin than in those receiving epinephrine (80% vs 55%, p=0.18), which led to a higher rate of successful resuscitation to hospital admission (70% vs 35%, p=0.06). The investigators also found a higher rate of 24-hour survival and survival to hospital discharge; however, only 24-hour survival was statistically higher in those allocated to vasopressin (p=0.02). No significant differences were observed in neurologic outcomes between groups. A major limitation of this study was its small size. In addition, it did not adequately address potential disparities in clinical management after study drug administration or on admission to the hospital. Moreover, the analysis failed to assess the effect that additional doses of epinephrine had on patients in the vasopressin group refractory to initial treatment. The authors were encouraged by these results, but they called for a larger multicenter study to address the potential role of vasopressin in the treatment of cardiac arrest.

Two other trials also suggested potential benefit of vasopressin in the treatment of cardiac arrest.[55–57] In one investigation of 83 patients, vasopressin 0.5 U/kg (low dose) and 1.0 U/kg (high dose) was compared with epinephrine.[55] The investigators noted that vasopressin-treated patients had higher rates of ROSC (60% vs 33%, p value not provided) and survival to hospital discharge (25% vs 10%, p value not provided). The second study, published only as an abstract, suggested a higher rate of ROSC and survival to hospital discharge with vasopressin compared with epinephrine.[56] One should interpret the results of these two studies with caution since the studies' methods cannot be critically assessed.

Based on the above results, the 2000 guidelines from the AHA and the International Liaison Committee on Resuscitation (ILCOR) stated that vasopressin is effective and can be used as an alternative to epinephrine in patients with shock-resistant ventricular fibrillation.[15] Only a single dose was recommended when there was persistent ventricular fibrillation after three defibrillation attempts. The authors of the guidelines acknowledged that the evidence supporting the use of vasopressin in humans, at the time, was limited, and they gave it a class IIb recommendation, meaning the intervention is acceptable but has only fair supporting evidence. In addition to considering data from one randomized controlled study,[54] the authors of the guidelines also considered results of a study not published at that time (subsequently published in 2001[58] and discussed in the following paragraphs). Although the guidelines stated vasopressin might be effective in asystole and pulseless electrical activity, they concluded that there was a lack of sufficient data to support vasopressin in these scenarios.

Because of the positive initial results with vasopressin for the treatment of cardiac arrest, two large randomized trials proceeded. In the first study, which took place in three Canadian university hospitals, the investigators evaluated 1-hour survival, neurologic function, and survival to hospital discharge of patients who had experienced a cardiac arrest.[58] The investigators randomly assigned 200 patients with in-hospital cardiac arrest who required drug therapy to receive vasopressin 40 U or epinephrine 1 mg as the initial vasopressor. If patients failed to achieve ROSC after initial treatment, they

received subsequent injections of epinephrine 1 mg every 3–5 minutes.

The study groups were relatively well matched, with 104 patients allocated to vasopressin and 96 to epinephrine. Of note, more patients in the epinephrine group were in the emergency department or the intensive care unit at the time of arrest. The investigators also provided the initial rhythm disturbance for the vasopressin and epinephrine groups, which included, respectively, pulseless electrical activity (41% and 54%), ventricular fibrillation or tachycardia (23% and 19%), and asystole (34% and 27%). Myocardial ischemia was the most common suspected cause of cardiac arrest. On average, 1.6 minutes elapsed before CPR was begun after arrest, 2.8 minutes to ACLS initiation, and 6.1 minutes until study drug administration.

This investigation found no difference between the vasopressin and epinephrine groups regarding 1-hour survival (39% vs 35%, p=0.66) or hospital discharge (12% vs 14%, p=0.67). Other markers of survival were also similar between the groups, including any return of pulse, pulse after 20 minutes, 24-hour survival, and 30-day survival. Furthermore, when neurologic function was evaluated in those who survived to hospital discharge, neurologic state and quality of life were found to be good, but no difference was observed between the groups. A key difference between this study and the investigation by another group[54] is that the arrest occurred in the hospital. The authors commented that based on the results of this investigation, vasopressin cannot be recommended for routine use for in-hospital cardiac arrest. Correspondingly, they specifically stated that they disagree with the 2000 AHA-ILCOR guidelines recommending its use as an alternative to epinephrine.

An editorial related to this article raised an important issue—epinephrine itself has never been shown to be better than placebo in cardiac resuscitation.[59] Of interest, when the data from this investigation were examined for patients with ventricular fibrillation or tachycardia only, survival at discharge was higher for the epinephrine versus the vasopressin group (33% vs 25%, p value not reported). As with other investigations, this trial failed to asses the effect of refractory patients who received both vasopressin and epinephrine.

The largest trial to date comparing vasopressin and epinephrine was published in 2004.[60] Major aspects of this investigation compared with previous studies include the following: it was for the management of out-of-hospital cardiac arrest; it included patients with ventricular fibrillation or tachycardia, pulseless electrical activity, and asystole; and more than one injection of the study drug was given. Eligible patients who had pulseless electrical activity or asystole underwent randomization immediately, receiving either epinephrine 1 mg intravenously or vasopressin 40 U intravenously. Patients with ventricular fibrillation or tachycardia underwent randomization after the first three attempts of defibrillation failed. If ROSC was not achieved within 3 minutes of the first injection, the patient received a second dose of the same study drug. If ROSC was not achieved after the second dose, the patient was given injections of epinephrine at the discretion of the emergency physician. The primary end point of the investigation was survival to hospital admission, and the secondary end point was survival to hospital discharge.

The study included 1186 patients, 589 assigned to receive vasopressin and 597 assigned to epinephrine. The baseline characteristics were similar between the two treatment groups, including percentage of patients with witnessed arrest, suspected cause, and additional treatments. The initial rhythm for those treated with vasopressin and those treated with epinephrine was typically asystole (44.5% vs 44.6%, respectively) or ventricular fibrillation or tachycardia (37.9% vs 41.7%), whereas pulseless electrical activity was more common in those receiving vasopressin (17.7% vs. 13.7%, p=0.06). The average time to CPR for both groups was 7.9 ± 6.4 minutes with similar times between initiation of basic life support to defibrillation, first injection of study drug, and hospital admission.

The rates of hospital admission between the vasopressin and epinephrine groups, respectively, did not differ significantly among patients with ventricular fibrillation (46.2% vs 43.0%, p=0.48) or pulseless electrical activity (33.7% vs 30.5%, p=0.65). Conversely, vasopressin was associated with higher rates of hospital admission in those with asystole as the initial rhythm (29% vs 20.3%, p=0.02); this also translated to a higher rate of hospital discharge in those receiving vasopressin (4.7% vs 1.5%, p=0.04).

An interesting aspect of the study analysis was that the investigators considered the effects of additional epinephrine doses after the first two doses of study drug were not successful (732 patients). The addition of epinephrine in those initially treated with vasopressin resulted in

higher rates of survival to hospital admission (25.7% vs 16.4%, p=0.002) and hospital discharge (6.2% vs 1.7%, p=0.002) compared with those receiving epinephrine as the initial study drug. No significant differences were noted between the groups in terms of cerebral performance, but a trend toward a poorer neurologic state or coma was noted in those receiving vasopressin who survived to hospital discharge. The investigators concluded that the effects of vasopressin are similar to those of epinephrine for patients with ventricular tachycardia and pulseless electrical activity, but superior in those with asystole. They hypothesized that vasopressin followed by epinephrine may be more effective than using epinephrine alone.

In a corresponding viewpoint, the editorialist commented that these "advances should be translated into a new standard of care without delay."[61] One should balance this enthusiasm with the fact that the greater benefit of vasopressin in asystole was based on a post hoc analysis, and that the overall rate to hospital discharge remained low and associated with poor neurologic outcomes.

Although reasonably well designed, this study has some important limitations. The authors cited variability in the clinical care for the different institutions, lack of dose-response data, and a lower number of patients randomized to treatment than they intended. In addition to these limitations, it is also important to note that although the vasopressin and epinephrine groups were similar in terms of cardiovascular history and baseline characteristics, the data for baseline characteristics were not reported for the subset of patients receiving vasopressin followed by epinephrine. This group of patients had a higher rate of survival but also could have had a better prognosis based on cardiovascular history, baseline characteristics, or both.

One study in humans had as the primary objective to assess the effects of vasopressin and epinephrine in combination.[62] In this retrospective case series, investigators reviewed 298 out-of-hospital cardiac arrests in Pittsburgh from March 2002–March 2003. Patients received epinephrine 1 mg every 3–5 minutes as the initial vasopressor, but 37 individuals also received one dose of vasopressin 40 U, at the discretion of the on-scene physician. Thirty patients did not receive any type of vasopressor, often because ROSC occurred. Subjects receiving vasopressin and epinephrine compared with epinephrine alone were more likely to have ROSC (likelihood ratio [LR] 2.73, 95% confidence interval [CI] 1.24–6.03) and a pulse at hospital arrival (LR 3.85, 95% CI 1.71–8.65). As with the earlier post hoc analysis, this investigation also found combination treatment to have its most profound effect in patients with asystole at presentation. Restoration of spontaneous circulation in asystole was more common in the epinephrine plus vasopressin group (6 [40%] of 15 patients) than in those receiving epinephrine alone (17 [13%] of 127, p=0.008), and this translated into a higher percentage of patients with a pulse at arrival to the emergency department (p=0.004). These data add to the hypothesis of vasopressor synergy, and the authors called for a prospective clinical trial examining this approach.

One must interpret these findings with caution, as the study had several important limitations. In addition to being a retrospective analysis and having disproportionate treatment group sizes, the study did not provide information regarding length of arrest or time to drug administration. Likewise, the addition of vasopressin was based on clinical judgment rather than study protocol, creating the possibility of significant study bias.

The clinical trials mentioned above are summarized in Table 1. As one compares and contrasts these investigations, it is apparent that the studies vary greatly in terms of timing of vasopressin administration, use with epinephrine, and overall study methodology. An important difference among the studies is the location of cardiac arrest (i.e., in vs out of hospital) and associated response times. Response time remains the most important factor determining success; hence, out-of-hospital sudden cardiac arrest differs since management may be delayed. Accordingly, in-hospital investigations have produced better overall rates of survival compared with out-of-hospital investigations; although, the effects of vasopressin and epinephrine have been similar in both settings. These variations and limitations complicate the analysis of the available data and must be considered when one interprets the succeeding meta-analyses.

Meta-Analyses

Two investigations have provided systematic reviews of the available data regarding vasopressin for the treatment of cardiac arrest. The first study provided a systematic review of

Table 1. Selected Human Studies That Evaluated Vasopressin in the Treatment of Cardiac Arrest

Study Design; Country	Setting of Cardiac Arrest	Initial Cardiac Rhythm	Intervention[a]	Outcomes
Case series; Germany (n=8)[52]	In hospital	Unknown; refractory to i.v. epinephrine	Vasopressin 40 U	ROSC in all patients; 3 patients discharged with intact neurologic function
Prospective, United States (n=10)[53]	Unknown	Unknown; patients deemed nonsalvageable after standard ACLS management	CPP monitoring; epinephrine 1 mg, then vasopressin 1 U/kg 5 min later	No improvement of CPP with epinephrine Increases of CPP occurred in 40% of patients receiving vasopressin (mean ± SD increase of 28.2 ± 16.4 mm Hg)
Prospective, randomized, double-blind; Germany (n=40)[54]	Out of hospital	VF resistant to defibrillation	Vasopressin 40 U vs epinephrine 1 mg After initial study drug, standard treatment (epinephrine) ensued	Successful resuscitation to hospital: vasopressin 70% vs epinephrine 35% (p=0.06) Survival at 24 hrs: vasopressin 60% vs epinephrine 20% (p=0.02) Survival to hospital discharge: vasopressin 40% vs epinephrine 15% (p=0.16)
Unknown; China (n=83)[55]	In hospital	Unknown	Vasopressin 0.5 or 1 U/kg vs epinephrine	ROSC: vasopressin 60% vs epinephrine 33% (p=NR) Survival to hospital discharge: vasopressin 25% vs epinephrine 10% (p=NR)
Unknown; unknown (n=10)[56]	Out of hospital	Unknown	Vasopressin 40 U (presumed i.v.)	ROSC: vasopressin 80% vs epinephrine 20% (p=NR) Survival to hospital discharge: vasopressin 60% vs epinephrine 20% (p=NR)
Prospective, randomized, triple-blind; Canada (n=200)[58]	In hospital	VF or VT: 21% PEA: 47.5% Asystole: 30.5% Other: 1%	Vasopressin 40 U vs epinephrine 1 mg Patients not responding to single dose of study drug were given epinephrine as rescue drug	1-hr survival: vasopressin 39% vs epinephrine 35% (p=0.66) Survival to hospital discharge: vasopressin 12% vs epinephrine 14% (p=0.67)
Prospective, randomized, double-blind; Austria, Germany, Switzerland (n=1186)[60]	Out of hospital	VF or VT: 39.8% PEA: 15.7% Asystole: 44.5%	Vasopressin 40 U vs epinephrine 1 mg (up to 2 doses) Additional epinephrine if two study drug injections were unsuccessful	Hospital admission: vasopressin vs epinephrine Overall: 36.3% vs 31.2% (p=0.06) By rhythm: VF: 46.2% vs 43% (p=0.48) PEA: 33.7% vs 30.5% (p=0.65) Asystole: 29% vs 20.3% (p=0.02) Hospital discharge: vasopressin vs epinephrine By rhythm: VF: 17.8% vs 19.2% (p=0.70) PEA: 5.9% vs 8.6% (p=0.47) Asystole: 4.7% vs 1.5% (p=0.04)
Retrospective case series; United States (n=298)[62]	Out of hospital	VF or VT: 26.4% PEA: 17.2% Asystole: 50.5% Undocumented: 5.9%	Epinephrine 1 mg (every 3–5 min) Vasopressin 40 U added at physician discretion	ROSC: epinephrine 25% vs epinephrine plus vasopressin 43% (LR 2.73, 95% CI 1.24–6.03) Survival to emergency department: epinephrine 18% vs epinephrine plus vasopressin 41% (LR 3.85, 95% CI 1.71–8.65)

ROSC = restoration of spontaneous circulation; CPP = continuous perfusion pressure; ACLS = advanced cardiac life support; VF = ventricular fibrillation; VT = ventricular tachycardia; NR = not reported; PEA = pulseless electrical activity; LR = likelihood ratio; CI = confidence interval.
[a]All doses were given intravenously.

randomized trials comparing vasopressin with a control agent.[63] This meta-analysis has limited clinical application as it included only two major human trials and part of its analysis considered animal studies. In human cardiac arrest (240 patients), this pooled analysis suggested vasopressin is equivalent to epinephrine with regard to ROSC (63% vs 59%, p=0.43) and survival to hospital discharge (16% vs 14%, p=0.52). Of note, this meta-analysis did not

include the study published in 2004.[60]

Recently, a second, more comprehensive meta-analysis evaluated the available data from randomized controlled human trials.[57] It included two relatively small investigations and three larger trials, consisting of 1519 patients. Studies were included or excluded based on their methodologic quality as assessed by the scoring system proposed by another group.[64] Three of the trials received the highest score of 5, whereas the others each received a score of 2. Although results showed a trend favoring vasopressin, no statistically significant differences were noted between the treatment groups. Compared with epinephrine, variables favoring vasopressin included higher ROSC rate (risk ratio [RR] 0.81, 95% CI 0.58–1.12), lower rate of death before hospital admission (RR 0.72, 95% CI 0.38–1.39), lower rate of death within 24 hours (RR 0.74, 95% CI 0.38–1.43), and lower occurrence of death before hospital discharge (RR 0.96, 95% CI 0.87–1.05).

After analyzing the entire study group, the investigators performed subgroup analysis based on the initial cardiac rhythm. Compared with epinephrine, no benefit was observed with vasopressin in those with ventricular fibrillation or 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). The authors concluded that the evidence supporting the use of vasopressin does not justify the agent's additional cost. The study goes on to recommend against including vasopressin in future ACLS guidelines. The authors noted important limitations of their study, beginning with the many confounders that affect the results of cardiac arrest trials such as bystander CPR, time to CPR initiation, time to intubation, and time to first ACLS drug. These confounders vary greatly by location of cardiac arrest, and this meta-analysis included both in-hospital and out-of-hospital cardiac arrest. The authors also cited differences between the Anglo-American model (patients transported to the hospital for a higher level of care) and the Franco-German model of emergency care (emergency physician and technology provided at the scene), which they could not account for in their analysis. Furthermore, all trials included epinephrine administered to patients who were refractory to initial vasopressin; however, no analysis for treatment effect in this subgroup was conducted.

The 2005 American Heart Association Guidelines

Recently, the AHA in collaboration with ILCOR released new guidelines for CPR and emergency cardiovascular care.[65] These guidelines differ from the previous recommendations in numerous ways. Most notably, the guidelines emphasize the delivery of high-quality CPR and the importance of minimizing interruptions in chest compressions. To achieve this goal, the guidelines adopted a universal compression:ventilation ratio of 30:2 for all lone rescuers of victims from infancy (excluding newborns) through adulthood.

The guidelines also make specific changes related to the delivery of defibrillation. The use of automated external defibrillators remains an important emphasis for lay rescuers. In a consistent attempt to minimize interruptions in chest compressions, the guidelines diverge from previous recommendations and advise only one shock rather than the three "stacked" shocks for ventricular fibrillation. After the delivery of a single shock, rescuers should immediately give five cycles (about 2 min) of CPR before performing a rhythm check, providing another shock, and/or administering a vasopressor.

The AHA altered recommendations regarding the use of vasopressors in pulseless cardiac arrest as well. The consensus was that vasopressors should remain a part of pulseless sudden cardiac arrest management, although the guidelines emphasize there are no placebo-controlled trials showing that any vasopressor administered during human cardiac arrest increases survival to hospital discharge. In fact, a proposal to remove all recommendations for vasopressors was considered, although not adopted.[66]

As has been the case in every version of the emergency cardiovascular care guidelines, epinephrine remains the recommended adrenergic of choice for pulseless sudden cardiac arrest. Of interest, despite any additional data to suggest the superiority of epinephrine compared with placebo or vasopressin, the recommendation for epinephrine strengthened from class indeterminate (2000 guidelines) to class IIb (2005 guidelines). The role of vasopressin, as an alternative to epinephrine, has expanded beyond the previous guidelines. The updated guidelines comment that one dose of vasopressin 40 U intravenously or intraosseously may be given to replace the first or second dose of epinephrine in all pulseless sudden cardiac arrest scenarios, including asystole and pulseless electrical

activity. Despite the expanded use of vasopressin, an interesting detail is that the recommendation received a class indeterminate grade for all scenarios (research just getting started, continuing area of research, no recommendations until further research), rather than the previous class IIb recommendation for ventricular fibrillation (acceptable, not harmful, and supported by only fair evidence). The role of vasopressor combination treatment is addressed briefly in the guidelines. The authors cite the post hoc analysis from 2004[60] and present the data from the most recent case series conducted in Pittsburgh[62]; however, little discussion is provided regarding the implications of these data on the direction of future research.

Conclusion

Sudden cardiac arrest is a major public heath problem, and despite decades of evaluation and treatment, survival rates remain poor. There are no placebo-controlled trials showing that any vasopressor given routinely increases the rate of survival to hospital discharge. When choosing a vasopressor in pulseless sudden cardiac arrest, epinephrine 1 mg repeated every 3–5 minutes remains the adrenergic agent of choice.

The evidence regarding vasopressin for the treatment of cardiac arrest continues to evolve. Results of preliminary animal studies suggest vasopressin might be effective, and subsequent small human investigations support its use. These studies were validated by larger, randomized trials, but these investigations were not placebo controlled nor did they document greater overall efficacy compared with epinephrine. Moreover, the analysis of vasopressin's effectiveness is confounded by the fact that most vasopressin-treated patients also received epinephrine. Based on available data, the 2005 AHA guidelines for CPR and emergency cardiovascular care state that rescuers may give one dose of vasopressin 40 U to replace the first or second dose of epinephrine in all types of pulseless sudden cardiac arrest, including asystole and pulseless electrical activity.

A consistent theme with all vasopressors in sudden cardiac arrest is that additional studies are needed to clearly document if respective therapies are more effective than no treatment. In the most recent AHA guidelines, no drug for the treatment of pulseless cardiac arrest, including vasopressors, received a recommendation higher than class IIb.

Further investigation is necessary to determine the role of vasopressin in sudden cardiac arrest. These studies should address if the effects of vasopressin differ depending on the first identified rhythm. In addition, it should be determined if vasopressin should be given as the first vasopressor in cardiac arrest or as an alternative in patients unresponsive to epinephrine. A remaining question is if a synergistic effect exists between vasopressin and epinephrine.

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