Cardiopulmonary arrest (CPA) is relatively common in some patient populations and is associated with significant mortality.

Experimental information indicates that vasopressin may offer some benefit over epinephrine in the management of CPA, particularly in patients with prolonged arrest.

The positive effects of vasopressin in cardiopulmonary resuscitation are due to extracerebral vasoconstriction and its ability to avoid the myocardial hypoxia and tachycardia that occur with the use of epinephrine.

Further clinical research must be conducted to evaluate vasopressin’s role in the management of veterinary patients in CPA.
One pharmacologic agent currently under investigation and showing some promise is vasopressin, which is also known as antidiuretic hormone. Since the publication of a 1996 human study demonstrating dramatically increased levels of vasopressin in post-CPA/CPCR patients, much attention has been focused on its use as a pressor agent to improve myocardial and cerebral blood flow in CPCR while avoiding several of the negative effects of epinephrine. A large, multicenter trial is currently underway to evaluate its use in human medicine. Although early clinical trials have produced conflicting results, vasopressin is listed as an alternative to epinephrine in the American Heart Association (AHA) 2000 Advanced Cardiovascular Life Support guidelines for first-line pressor in defibrillation–refractory ventricular fibrillation and pulseless ventricular tachycardia. Vasopressin is not approved for use in pediatric patients or those with pulseless electrical activity (formerly known as electromechanical dissociation). In the Advanced Cardiovascular Life Support ratings, which provide information regarding the evidence supporting or refuting the use of a particular drug or technique in CPCR, vasopressin was assigned an AHA intervention rating of “Class IIb” (acceptable; fair to good evidence provides support). In contrast, epinephrine is listed as “Class Indeterminate” due to the paucity of clinical evidence supporting its use in CPA. However, a recent prospective study failed to find any advantage of using vasopressin over epinephrine for in-hospital patients in CPA. Although most studies of vasopressin in CPCR have used animal models, no veterinary clinical studies have been performed with respect to vasopressin’s role in CPCR to date.

<table>
<thead>
<tr>
<th>Rating</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Class I</td>
<td>Definitely recommended; supported by excellent evidence; has proven efficacy and effectiveness</td>
</tr>
<tr>
<td>Class IIA</td>
<td>Acceptable and useful; good/very good evidence provides support</td>
</tr>
<tr>
<td>Class IIB</td>
<td>Acceptable and useful; fair to good evidence provides support</td>
</tr>
<tr>
<td>Class III</td>
<td>Not acceptable; not useful; may be harmful</td>
</tr>
<tr>
<td>Class indeterminate</td>
<td>Available evidence insufficient to support a final class decision; results promising but additional confirmation is needed; evidence shows no harm but no benefit either</td>
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**Table 1. AHA Ratings for Advanced Cardiovascular Life Support Interventions**

**EPINEPHRINE USE IN CPCR**

For decades, the pharmacologic mainstay of CPCR has been epinephrine, largely for its α-adrenergic effects of vasoconstriction and increased cerebral and coronary perfusion. However, concurrent β-adrenergic stimulation causes several undesirable effects, notably increased chronotropy, arrhythmogenicity, increased myocardial oxygen demand, and decreased subendocardial perfusion. Additionally, epinephrine is associated with post-CPCR myocardial dysfunction and lactate production. In cases of prolonged CPCR, the adren-ergic pressor response is blunted in the presence of severe acidosis, thereby limiting the usefulness of epinephrine.

Recent studies have either failed to show any advantage of using epinephrine over saline placebo or demonstrated adverse outcomes. Additionally, no benefit has been shown with the administration of a high dose (10 mg) versus a low dose (1 mg) of epinephrine.

**PHARMACOLOGY OF VASOPRESSIN**

Vasopressin is a peptide hormone produced in the supraoptic nuclei adjacent to the pituitary gland and is secreted by the posterior pituitary (or neurohypophysis) in response to increased plasma osmolality or decreased intravascular volume. Osmoreceptors in the hypothalamus and baroreceptors in the carotid body and atria detect changes in plasma osmolality and blood pressure, respectively, and cause the release or sequestration of vasopressin and other regulatory hormones. Its half-life in animals with intact circulation is 10 to 20 minutes, which is longer than that of epinephrine. The synthetic analogue of vasopressin, 1-deamino-8-D-arginine vasopressin, has minimal pressor effects and is not appropriate for use in CPCR. Vasopressin can be administered by IV, intratracheal, or intraosseous routes when used in CPCR.

Vasopressin exerts its pressor effects through stimulation of vasopressin-specific V1 receptors found in vascular smooth muscle, causing intense, nonadrenergic vasoconstriction. V1 receptors are cell membrane–bound and coupled to intracellular second messengers, such as adenylyl cyclase, phospholipase A, and protein kinase A. Vasopressin preferentially constricts arterioles in extracerebral tissues, with relatively less constriction in renal and coronary blood vessels, and may actually dilate the cerebral vasculature, thereby improving cerebral perfusion.

Its antidiuretic effects are due to increased permeability of the renal collecting duct cell membrane to water in the presence of vasopressin (via V2 receptor-mediated stimulation), causing water to move down its concentration gradient and be reabsorbed.
are present in the medullary portion of the kidney. In the absence of vasopressin (such as in central diabetes insipidus), the collecting duct system is almost impermeable to water. 

**VASOPRESSIN USE IN CPCR**

Observational studies of post-CPA patients provided the background for initial investigations into the therapeutic use of vasopressin. A 1996 study by Lindner and colleagues involving 60 cases of out-of-hospital CPA showed a positive association between high vasopressin levels post-CPA and return of spontaneous circulation, whereas high levels of endogenous catecholamines were associated with poorer outcomes.

Animal models of CPA have largely been favorable with regards to vasopressin's role in CPCR, particularly after prolonged CPCR. Most studies on vasopressin have been conducted using swine and have reported superior coronary perfusion pressure, cerebral blood flow, and neurologic outcomes when compared with epinephrine. Doses of vasopressin used in animal models have ranged between 0.4 to 0.8 U/kg. In one swine study in which 17 subjects underwent 4 minutes of ventricular fibrillation, 3 minutes of basic life support (chest compressions), and 15 minutes of advanced life support (i.e., drugs, defibrillation), all animals in the vasopressin group (n = 6) had return of spontaneous circulation, whereas all animals in the epinephrine group (n = 6) and saline placebo group (n = 5) did not. All animals in the vasopressin group survived with only mild ataxia; however, all animals in the placebo and epinephrine groups died. Several animals in the vasopressin group needed sedation to allow weaning from mechanical ventilation after CPCR. Survivors underwent magnetic resonance imaging 4 days after resuscitation and no neuropathologic lesions were seen.

Coronary perfusion pressure above 15 mmHg is generally accepted as a good predictor of return of spontaneous circulation. In a swine model of CPA and prolonged CPCR, animals in the vasopressin treatment group were able to maintain a coronary perfusion pressure at or above this level for the duration of the study, whereas those in the epinephrine group were only able to maintain this level transiently after drug administration.

One of the first human clinical studies was a case review involving the use of vasopressin in eight patients undergoing prolonged CPCR for in-hospital CPA and who were refractory to standard doses of epinephrine and defibrillation. After administration of 40 U of vasopressin and defibrillation, return of spontaneous circulation was noted in all patients, three of whom (37.5%) survived to hospital discharge. A larger prospective, randomized study of 40 patients with out-of-hospital CPA comparing vasopressin to epinephrine as the initial pressor demonstrated improved initial survival (70% for vasopressin versus 35% for epinephrine), 24-hour survival (60% versus 20%), and survival to discharge (40% versus 15%) with similar neurologic status on discharge to patients in the epinephrine group.

Different end points, such as return of spontaneous circulation, 1-hour survival, survival to hospital discharge, and level of neurologic function, have been used in many studies, thereby making comparison difficult. In addition, many studies included only small groups of patients or had methodological flaws. In addition, multiple variables, such as drug dose and route of administration, response times of rescuers, and duration of CPA, can affect an individual patient's response to pharmacologic agents during CPCR. A recent randomized, blinded, placebo-controlled study comparing vasopressin to epinephrine in 200 cases of in-hospital CPA did not detect any significant increase in 1-hour survival (39% for vasopressin versus 35% for epinephrine), hospital discharge (12% versus 14%, respectively), or neurologic outcome (36% for vasopressin versus 35% for epinephrine, as assessed by the Mini-Mental State Examination Score). The authors conducting the study disagreed with the recent AHA guidelines' calling for vasopressin as an alternative to epinephrine in CPCR.

When used during CPA, vasopressin causes vasoconstriction of peripheral arterioles and preferential shunting of blood toward the heart and central nervous system. This is a result of differential constriction of skin, skeletal muscle, intestinal blood supply, and possibly cerebral vasodilatation. Unlike epinephrine, vasopressin does not cause increased heart rate or myocardial oxygen consumption. Vasopressin may be of particular benefit when CPCR is prolonged as the response of V1 receptors is intact despite severe metabolic and respiratory acidosis.

As with epinephrine, some side effects can be seen with the administration of vasopressin for CPA, although the frequency of their occurrence is unknown. Acute pulmonary edema has been reported in a human patient after peripheral administration, and intracoronary administration has resulted in myocardial ischemia due to vasoconstriction in dogs in experimental studies. Other uncommon effects include gangrene from peripheral vasoconstriction, allergic reactions, and water retention/toxicosis.

**CONCLUSION**

Although the role of vasopressin in the management of CPA is still highly controversial and under study, preliminary laboratory and clinical investigations seem to indicate that it may offer some benefit over such traditional therapies as epinephrine. Despite severe systemic
vasodilation, vasopressin causes intense peripheral vasoconstriction, which preferentially shunts blood flow to vital structures, such as cerebral and myocardial tissues. Vasopressin causes less chronotropy due to its absence of effect on β receptors, and it does not cause increased myocardial oxygen consumption as is seen with epinephrine. Additionally, vasopressin improves several intermediate variables that correlate with increased survival, such as improved cardiac perfusion pressure, improved cerebral blood flow, and early return of spontaneous circulation. Studies on vasopressin use are currently underway in human medicine that should help shed some light on its role in CPA management, and veterinary clinical studies will be required to elucidate its place in the management of veterinary CPA cases. Until these studies show definite, statistically significant improvement in survival to hospital discharge with acceptable neurologic function in veterinary patients, the use of vasopressin in small animal CPR must be approached with caution, if at all.

REFERENCES

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ARTICLE #4 CE TEST

1. Post-CPA survival in veterinary patients is a. up to 10%. b. 10% to 20%. c. 20% to 25%. d. 25% to 45%.

2. Epinephrine’s negative side effects include a. increased lactate production. b. oliguria. c. induction of arrhythmias. a. b and c.

3. Vasopressin is produced by the __________ and released by the_________. a. adrenals; hypothalamus b. thyroid; carotid body c. supraoptic nuclei; posterior pituitary d. vas recta; glomerulus

4. Vasopressin normally causes a. vasoconstriction. c. mydriasis. b. water retention. d. a and b

5. Vasopressin is less likely to induce_________ as is seen with the use of a. myocardial hypoxia; epinephrine b. vasoconstriction; atropine c. bradycardia; lidocaine d. hypotension; dobutamine

(continues on page 454)
6. Unlike epinephrine, vasopressin still exerts its physiologic effects despite
   a. hyperkalemia.
   b. hypocalcemia.
   c. metabolic acidosis.
   d. hypothermia.

7. Vasopressin is a
   a. diuretic.
   b. catecholamine.
   c. peptide hormone.
   d. secretagogue.

8. The beneficial effects of vasopressin in cardiopulmonary arrest are thought to be ____ of peripheral tissues and ____ of cerebral tissues.
   a. vasodilation; vasodilation
   b. vasoconstriction; vasodilation
   c. vasoconstriction; vasoconstriction
   d. vasodilation; vasoconstriction

9. Vasopressin is also called
   a. von Willebrand's factor.
   b. antidiuretic hormone.
   c. serotonin.
   d. a and b

10. Possible negative effects of vasopressin include
    a. severe peripheral vasoconstriction.
    b. pulmonary edema.
    c. allergic reaction.
    d. all of the above