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RECOVER evidence and knowledge gap analysis on veterinary CPR. Part 4: Advanced life support

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Abstract

Objective – To systematically evaluate the evidence of the effect of advanced life support techniques on outcome in veterinary cardiopulmonary resuscitation (CPR) and to outline knowledge gaps.
Design – Standardized, systematic evaluation of the literature, categorization of relevant articles according to level of evidence and quality, and development of consensus on conclusions for application of the concepts to clinical practice.
Setting – Academia, referral practice, and general practice
Results – Sixteen population, intervention, control group, outcome questions were evaluated to determine if recommendations could be made concerning drug therapy, including vasopressors, vagolytics, corticosteroids, reversal agents, buffer therapy, and correction of electrolyte disturbances. Electrical defibrillation strategies as well as other advanced interventions such as open-chest CPR, impedance threshold devices, and special considerations regarding anesthesia-related cardiopulmonary arrest (CPA) were also investigated.
Conclusions – There is strong evidence supporting the use of standard-dose (0.01 mg/kg) epinephrine in CPR, as well as early electrical defibrillation for animals experiencing CPA due to ventricular fibrillation or pulseless ventricular tachycardia, preferentially using a biphasic defibrillator. For CPA due to certain causes and with the availability of advanced postcardiac arrest support, open chest CPR is preferred. Many knowledge gaps regarding other pharmacologic and advanced therapies were identified, and further studies are recommended to better systematically address these questions.

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Introduction

Advanced life support (ALS) is defined as the aspect of veterinary cardiopulmonary resuscitation (CPR) performed after basic life support (BLS) has been initi-

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Abbreviations

ALS	advanced life support
BLS	basic life support
BP	biphasic
CPA	cardiopulmonary arrest
CPP	coronary perfusion pressure
CPR	cardiopulmonary resuscitation
IT	intratracheal
ITD	impedance threshold device
LOE	level of evidence
MP	monophasic
PEA	pulseless electrical activity
PICO	population, intervention, control group, outcome
RECOVER	Reassessment Campaign on Veterinary Resuscitation

ROSC	return of spontaneous circulation
VF	ventricular fibrillation
VT	ventricular tachycardia

ated. BLS includes intubation, ventilation, and chest compressions, while ALS includes therapy with vasopressors, positive inotropes, anticholinergics, correction of electrolyte disturbances, volume deficits, severe anemia, and prompt defibrillation. If BLS and ALS are performed promptly, initial return of spontaneous circulation (ROSC) rates may be as high as 50% in dogs and cats.[1]

The RECOVER ALS domain was designed to evaluate the scientific evidence for pharmacological therapy, intravascular volume support, and defibrillation techniques that might be employed during CPR in dogs and cats. Many ALS topics have undergone extensive evaluation in experimental animals and in human trials. Subsequently, the ALS domain contains many interventions that may be approached from an evidence-based perspective. Thus, the ALS domain is instrumental in describing the potential importance of pharmaceuticals, defibrillation, and other interventions that might affect the outcome of CPR. ALS recommendations may be controversial, as conclusions of experimental studies are sometimes not borne out in subsequent clinical trials. For example, administration of high-dose epinephrine results in improved outcomes in certain experimental CPR models; however, in clinical trials of people with CPA, these benefits were not noted. Thus, the clinical relevance of a demonstrated physiologic benefit of an intervention during CPR, such as the ability to raise blood pressure, alter myocardial blood flow, or improve tissue oxygenation, can only be adequately determined in formal clinical trials in the target species. While all ALS measures used during CPR have theoretical risks and potential benefits, it is clear that if ROSC is not achieved, death is certain.

Specific clinically relevant questions that were considered in the ALS domain include treatment of asystole, pulseless electrical activity (PEA), and ventricular fibrillation (VF), vaso- and cardioactive medications, as well as supplemental fluids, oxygen, and other treatment for potential electrolyte or acid-base disturbances that are either present at the time of the arrest or develop during prolonged CPR. A large number of ALS domain questions of interest were developed, and those judged most important, including the dosing of epinephrine, technique for defibrillation, and appropriate use of ancillary/supportive techniques, were selected for formal review of the available literature. The key ALS recommendations made in this consensus statement for canine and feline CPR are as follows:

- Standard dose epinephrine (0.01 mg/kg IV) is the preferred dose for CPR;
- Rapid defibrillation is warranted in animals with observed progression to pulseless VT or VF; preferentially using a biphasic (BP) defibrillator;
- Defibrillation should follow a cycle of CPR in unwitnessed pulseless VT or VF;
- Open chest CPR might be considered in select cases with access to postcardiac arrest support;
- Reversal of anesthetic agents and correction of major acid-base and electrolyte disturbances is advisable.

This report is focused on 16 ALS questions specific to the population, intervention, control group, and outcome (PICO question) with a summary of the evidence and the conclusions on treatment recommendations.

Vasopressors and Vagolytic Therapy

The most widely employed pharmacological therapies for veterinary CPA are vasopressors and vagolytic agents.[2] A crucial aspect of restoring myocardial function is improving coronary perfusion pressure (CPP), defined as the difference between diastolic (ie, decompressive) aortic and right atrial pressure. Vasopressors are crucial in increasing aortic pressures by increasing peripheral vascular resistance and directing more of the intravascular volume to the central circulation, although debate exists as to the appropriate vasopressor and dose. The inotropic and chronotropic effects of some vasopressors (catecholamines) are likely less crucial, and may be harmful when treating CPA due to increased myocardial oxygen demand, exacerbating myocardial ischemia, and predisposing to arrhythmias once ROSC is achieved.[3] Vagolytic therapy, specifically atropine, has been proposed in specific cases to counteract high vagal tone that may result in bradycardia or sinus arrest. Three PICO questions involving the use of vasopressors and vagolytic therapy were investigated.

Epinephrine dose and timing (ALS01)

PICO Question

In dogs and cats with cardiac arrest (P), does the use of any specific alternative dosing regimen for epinephrine (I), compared with standard recommendations (0.01 mg/kg IV q 3–5 minutes) (C), improve outcome (eg, ROSC, survival to hospital discharge, survival with favorable neurologic outcome) (O)?

Conclusion

While high-dose epinephrine may be associated with higher levels of ROSC, there are exaggerated adrenergic

effects that likely result in more patient harm and do not appear to improve hospital discharge rates. The current recommendation for epinephrine usage in dogs and cats is 0.01 mg/kg IV; this dose may be repeated every 3–5 minutes.

Summary of the evidence

High-dose epinephrine has been suggested as potentially preferable to low-dose epinephrine. The use of low-dose (0.01 mg/kg) versus high-dose (0.1 mg/kg) epinephrine has been extensively evaluated in experimental models and in people. One study (level of evidence [LOE] 6, poor/supporting) showed that high-dose epinephrine improved survival in prolonged pediatric cardiac arrest in patients that received 2 rounds of low-dose epinephrine.[4] Sixteen articles (LOE 6, good), were neutral/equivocal to the question that high-dose epinephrine improves outcome.[5–18] Two of those articles in nontarget species (pig) LOE 6 good/neutral) found that high-dose epinephrine results in severe tachycardia and hypertension after resuscitation, and did not improve 24-hour survival and neurological outcome.[5,6] Four articles (LOE 6, 2 good/supporting, 1 fair/supporting, and 1 poor/supporting evidence) found that that high-dose epinephrine resulted in worse outcomes.[17,19–21]

Three (LOE 3, good/neutral) studies evaluated this question in small groups of experimental dogs.[13,22,23] In a canine PEA model, after 10-minute arrest time, no difference was found in survival between low-dose epinephrine, low-dose epinephrine plus cardiopulmonary bypass (CPB), or high-dose epinephrine.[13] Another canine study of induced VF cardiac arrest found no difference in ROSC in dogs given high- or low-dose epinephrine either via a central venous catheter or intracardiac route, although the low-dose epinephrine group required a longer resuscitation time.[22] In another canine VF model, which evaluated the use of saline, low- or high-dose epinephrine, or methoxamine (a selective α-1 adrenoceptor agonist), dogs receiving methoxamine were more likely to achieve ROSC, and while high-dose epinephrine was initially associated with improved regional cerebral blood flow, there was a subsequent decline in global hemodynamics associated with poor survival.[23]

In people, several pediatric trials have directly compared high- and low-dose epinephrine, and a meta-analysis evaluating studies in adults has also been published.[9,20,24] In children, Carpenter and colleagues found that high-dose epinephrine did not improve survival over low-dose epinephrine, and no significant differences were found in ROSC, survival rates or Pediatric Overall Performance Category.[9] A later prospective study (LOE 6, against, good/supporting) included children who had failed to resuscitate after low-dose epinephrine. Patients were randomized to receive either high- or low-dose epinephrine. Patients receiving high-dose epinephrine had a lower rate of survival than those receiving low-dose epinephrine.[24] In the meta-analysis, the pooled odds ratio for ROSC supported the high dose, but a benefit of high-dose epinephrine on survival to hospital discharge was not found The authors also argued that high-dose epinephrine might resuscitate an individual who had already suffered irreversible neurologic injury, which might have significant economic and ethical issues.[20]

Knowledge gaps

There have been no controlled studies of high-dose versus low-dose (standard dose) epinephrine in veterinary patients. Extrapolation of human data and experimental studies in dogs suggests that high-dose epinephrine is not suitable for routine use in veterinary patients during CPR. Controlled clinical trials are warranted to determine the optimal dose of epinephrine during CPR in regards to ROSC, hemodynamics, neurologic postresuscitation effects, and survival to hospital discharge.

Vasopressin versus epinephrine (ALS03)

PICO Question

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

Conclusion

The use of vasopressin (0.8 U/kg IV), with or without epinephrine, is a reasonable intervention during CPR. Several studies have concluded that vasopressin causes no additional harm when compared to epinephrine. There is limited evidence suggesting a *benefit* of vasopressin when compared to epinephrine alone in dogs and cats undergoing CPA, while studies in humans have suggested a possible advantage of vasopressin during resuscitation of certain subgroups of patients, particularly those with asystole, prolonged CPA, or with hypovolemia as cause of CPA. Studies are needed to assess whether vasopressin may have a similar advantage in these populations in veterinary medicine.

Summary of the evidence

Three studies provide information regarding the use of vasopressin in CPR in dogs. The single randomized prospective study by Buckley et al (LOE 1, good/neutral) demonstrated no difference in the primary outcome of ROSC between vasopressin and epinephrine.[25] A small survival advantage at 1 hour was seen in the group receiving epinephrine; however, this was a secondary end point. The study was not powered to assess differences between subgroups of cardiac rhythm, length of CPA, or underlying cause of CPA. A prospective study by Hofmeister (LOE 2, poor/supporting) suggested a survival advantage in dogs receiving vasopressin in comparison to epinephrine.[1] This study was clinically important as it examined a large number of animals in an in-hospital setting (161 dogs and 43 cats). Of dogs undergoing CPR, only 8 received vasopressin, 5 of which survived. The small number of animals receiving vasopressin, along with the observational nature, precludes a recommendation for use of vasopressin based on this single study. A single case report (LOE 5, poor/supporting) documented the use of vasopressin in a dog being successfully resuscitated from CPA.[26]

Two studies, one in humans (LOE 6, fair/supporting)[27] and one in pigs (LOE 6, good/supporting),[28] suggest that vasopressin may be superior to epinephrine alone in hypovolemic cardiac arrest. However, in the human study, the vasopressin group concurrently received fluid resuscitation, while in the pig study no interventions were performed for one full hour after ROSC making it difficult to evaluate the clinical significance of its results.

There are several studies investigating the use of vasopressin in animal models. Wenzel et al (LOE 6, fair/supporting) demonstrated improved ROSC and neurological recovery in pigs with prolonged CPA when vasopressin was used as compared to epinephrine.[29] Stadlbauer et al (LOE 6, fair/supporting) showed similar results when vasopressin was used in combination with epinephrine.[30] Stroumpoulis et al (LOE 6, good/supporting) found improved ROSC and CPPs in a piglet VF model when vasopressin was used in combination with epinephrine compared to epinephrine alone.[31] Two porcine models, one (LOE 6, fair/neutral)[32] and one (LOE 6, good/neutral)[33] demonstrated improvement in hemodynamic parameters, such as CPP, but found no improvement in ROSC or neurological outcome with the use vasopressin. Another study by Chen et al (LOE 6, fair/opposing) demonstrated worsened hemodynamics and ROSC in rabbits when vasopressin was used in lieu of epinephrine.[34] Finally, Lopez-Herce et al (LOE 6, good/neutral) found no benefit with the use of terlipressin over epinephrine in a piglet model.[35]

Despite some initial promise in animal models, evidence in human clinical trials shows mixed results. In out-of-hospital arrest, Callaway at al (LOE 6, good/neutral), Cody et al (LOE 6, poor/neutral), Ducros et al (LOE 6, good/neutral), Gueugniaud et al (LOE 6, good/neutral), and Mukoyama et al (LOE 6, good/neutral) all concluded that vasopressin administration had no impact on ROSC or long-term survival.[14,36–39] Lindner et al (LOE 6, good/neutral) demonstrated a modest improvement in 24-hour survival in a group of patients receiving vasopressin versus epinephrine, but no improvement in ROSC or survival to discharge.[40] Wenzel et al (LOE 6, fair/supporting) demonstrated in a large prospective study that patients who received vasopressin followed by epinephrine as rescue therapy had improved survival as did patients with an initial rhythm of asystole, a finding echoed by Guyette et al (LOE 6, poor/supporting).[41,42] Grmec et al (LOE 6, fair/supporting) showed improvement in 24-hour survival in patients receiving vasopressin, but demonstrated no improvement in overall neurological status.[43] Stiell et al (LOE 6, good/neutral) did not find a benefit with vasopressin use over epinephrine in in-hospital arrest.[44] Mentzelpoulos et al (LOE 6, good/supporting) showed an improvement in ROSC for patients receiving a combination of corticosteroids (MPSS) and vasopressin over a group receiving epinephrine and saline placebo.[45] A single case series of in-hospital arrest, Duncan et al (LOE 6, poor/opposing) demonstrated a worsened outcome with vasopressin in pediatric patients.[46] In a large randomized trial of 727 people with out-of-hospital CPA (LOE 6, good/neutral), there was no difference in survival to discharge to hospital discharge between vasopressin during CPR and those treated with epinephrine, but those treated with vasopressin were more likely to survive to hospital admission.[47]

Two meta-analyses (Aung et al [LOE 6, good/neutral] and Wyer et al [LOE 6, poor/neutral]) conclude that vasopressin has no benefit compared to epinephrine.[48,49] A third meta-analysis, Biondi-Zoccai et al (LOE 6, poor/neutral), determined that vasopressin may have a benefit in animals but this did not translate into a benefit in human clinical trials.[50]

Overall, the evidence from animal models suggests a benefit of vasopressin, but there is no consistent advantage in human clinical trials. Trials that have demonstrated a benefit of vasopressin in human populations, such as Wenzel et al, have done so in subgroup analyses of specific arrest rhythms or with combinations of drugs.[41] However, other similarly well-designed trials,

such as Gueugniaud et al have failed to replicate these results.[14] The evidence from veterinary studies is limited; however, the only prospective veterinary CPR trial investigating this question showed no difference in ROSC between dogs receiving vasopressin or epinephrine.[25]

Knowledge gaps

No research has been undertaken in the clinical setting to investigate the effect of arrest rhythm, duration of CPA, or underlying cause of CPA in relation to vasopressin versus epinephrine use in dogs. Understanding of the effect of drug therapies on subgroups of the population with CPA could help tailor therapies more effectively. No information on vasopressin use in CPR exists in cats.

Atropine use (ALS02)

PICO Question

In dogs and cats in cardiac arrest (asystole, PEA, pulseless ventricular tachycardia [VT] or VF) (P), does the use of atropine (I), compared to standard care without atropine (C), result in improved outcome (eg, ROSC, survival) (O)?

Conclusion

The data supporting the use of atropine during CPR is limited. Most studies used atropine as an additional drug, rather than as a sole intervention. For animals with high vagal tone (eg, vomiting, ileus), and subsequent bradycardia/asystole, the use of atropine is reasonable. For animals that are not suspected to have increased vagal tone, evidence supporting for the routine use of atropine is sparse. There is little evidence that the use of atropine is harmful, but there are no high-quality studies supporting its use in dogs or cats.

Summary of the evidence

The only evidence on the clinical use of atropine in veterinary CPR consists in 2 studies, which provide poor/neutral LOE 2[1] or good/neutral LOE 4[51] evidence. All of the animals received atropine during CPR, so no specific conclusions about the effectiveness of atropine could be drawn. In the most relevant experimental study (LOE 3, fair/neutral), dogs with hypoxia-induced PEA were resuscitated with epinephrine, and given either a placebo or increasing doses of atropine (0.04, 0.1, 0.2, and 0.4 mg/kg).[52] Atropine doses of greater than 0.04 mg/kg were associated with a worse outcome, and the conclusion was that atropine at higher than standard doses should be avoided in CPR. In one canine study (LOE 3, fair/opposing), dogs were asphyxiated until asystole occurred, then were randomized to be revived with saline, calcium, atropine, or methoxamine.[53] No dogs randomized to receive atropine (0.5 mg/animal; body weight 11–25 kg) were successfully resuscitated. In a third canine study (LOE 3, fair/supporting), dogs with PEA were randomized to be resuscitated with epinephrine and either atropine (0.5 mg/animal; mean bodyweight 20 kg) or 5% dextrose in water.[54] Dogs receiving atropine were more likely to have ROSC.

In people, atropine has not been comprehensively evaluated as a stand-alone drug for CPR. One study from 30 years ago (LOE 6, poor/neutral) evaluated a small group of people (n = 21) that experienced out-of-hospital cardiac arrest associated with asystole-bradycardia and found no improvement in survival.[55] Other studies included atropine as component of CPR (LOE 6, fair-poor/neutral) and were largely unable to determine any specific beneficial or detrimental effect of atropine.[56–62]

Knowledge gaps

Atropine's primary action in CPR is as a parasympatholytic. While effective in many cases of bradycardia, atropine's role in the presence of long-standing asystole, VF, or pulseless VT is less clear. Clinical trials designed to evaluate the use of atropine or placebo in conjunction with standardized CPR are needed in the setting of animals both with and without suspected high vagal tone. It may be beneficial to consider further research into causes of cardiac arrest in veterinary patients, as these are likely to differ considerably from their human counterparts, and in many veterinary patients with CPA, there is likely a high index of suspicion for enhanced vagal tone. For example, it may be hypothesized that specific patient cohorts, such as brachycephalic patients, patients with severe gastrointestinal disease, or those with respiratory distress associated cardiac arrest may benefit from anticholinergic drugs.

Other Drug Therapy

Other drugs commonly considered in CPR include antiarrhythmic, glucocorticoids, buffers, and reversal agents such as naloxone. In addition, CPA is commonly associated with electrolyte disturbances, making electrolyte supplementation a potentially useful adjunctive therapy. Six PICO questions regarding these drug therapy options were evaluated.

Antiarrhythmic drug therapy (ALS07)

PICO Question

In dogs and cats with cardiac arrest (asystole, PEA, pulseless VT, and VF) (P), does the use of antiarrhythmic drugs (lidocaine, procainamide, amiodarone, bretylium, magnesium) (I), compared with standard CPR regimen (C), improve outcomes (eg, ROSC, survival) (O)?

Conclusion

There is no compelling evidence that supports the routine use of antiarrhythmic drugs to improve outcome in dogs and cats with cardiac arrest. In pulseless VT and VF, early rapid defibrillation or cardioversion is advised before any drugs are administered. In dogs with shock-resistant pulseless VT or VF, amiodarone may be the best choice, although hypotension and anaphylactic reactions have been described in dogs following intravenous amiodarone administration. There is limited, but conflicting evidence that lidocaine may also be a useful adjunctive therapy for patients with shock-resistant VF, especially when used with BP defibrillators. There is no role for bretylium or magnesium.

Summary of the evidence

A multitude of studies have investigated the effects of antiarrhythmic therapy on outcome in CPR. There are five LOE 6 (1 good, 3 fair, and 1 poor, all supporting) studies that support the use of a specific antiarrhythmic drug during CPR for VF, with amiodarone outperforming lidocaine in 2 studies, and the use of lidocaine for VF associated with increased ROSC in another.[63–65] Nowak et al found that bretylium was better than placebo in patients presenting to an emergency room with CPA due to VF or asystole, and Oshige et al found that combining lidocaine and atropine with epinephrine improved ROSC in comparison to epinephrine alone in a study of out-of-hospital CPA.[59,66] In one LOE 3 (good/supporting) study by Anastasiou-Nana and colleagues, dogs with a myocardial-infarction model of VF had improved ROSC rates with amiodarone.[67]

Six studies (LOE 6, with 4 good and 2 fair evidence) were neutral to an effect of antiarrhythmic therapy, with two studies finding no effect of magnesium (Allegra 2001, Hassan 2002) versus placebo for refractory VF.[68,69] In the early 1980s, 2 human studies evaluated the use of bretylium and lidocaine. The first showed no difference in survival in patients with refractory VF treated with lidocaine or bretylium, although patients in the lidocaine group had higher rates of cessation of VF with electrical defibrillation.[70] The second study showed that neither bretylium nor lidocaine were effective for "chemical" defibrillation of out-of-hospital arrest patients.[71]

Two studies showed worse outcomes with the use of antiarrhythmic drugs during CPR. The first (LOE 3, fair/opposing) found that dogs given oral loading doses of amiodarone demonstrated increased defibrillation thresholds, while those given intravenous amiodarone showed no change in the defibrillation threshold.[72] The second study (LOE 6, poor/opposing) showed that people with refractory VF treated with procainamide received more shocks, required longer to resuscitate, and had lower survival to discharge rates.[73] In addition, there is evidence in dogs (LOE 3, good/opposing) that the use of lidocaine is associated with an increase in the defibrillation threshold in when given early in CPR.[74] Of note, a monophasic defibrillator was used in this study. However, more recent data in pigs (LOE 6, good/neutral) investigating the effects of lidocaine on defibrillation thresholds with monophasic versus BP defibrillators suggested that this phenomenon does not occur when BP defibrillators are used.[75]

An additional confounding factor that is relevant to any discussion of antiarrhythmic therapy is that the time interval from the onset of CPA to the administration of drugs is often far less in experimental settings than in the clinical environment.[76] This is considered a major reason that antiarrhythmic therapies that appear beneficial in experimental animals studies do not translate to clinical successes.

The major conclusion of a recent systematic review on the use of antiarrhythmics in adult cardiac arrest in humans was that amiodarone was the drug most likely to be useful for shock-resistant pulseless VT/VF.[77] Insufficient evidence was identified to support or to refute the use of any other antiarrhythmic drug in this setting.

Knowledge gaps

There are no controlled studies in dogs and cats with spontaneous CPA investigating the use of antiarrhythmics. Amiodarone has not been formally evaluated in cats. Pulseless VT is also poorly characterized in veterinary medicine, and this specific arrhythmia deserves further study. Controlled trials on antiarrhythmic drugs for VT/VF, asystole, and PEA are needed in dogs and cats.

Steroids during CPR (ALS11)

PICO Question

In dogs and cats during cardiac arrest (P), does treatment with corticosteroids alone or in combination with other drugs (I), as opposed to care without corticosteroids

(C), improve outcome (O) (eg, survival or neurologic status)?

Conclusion

There is no clear evidence that corticosteroid administration is beneficial or harmful in the ALS phase of CPR. As studies in other diseases suggest a harmful effect of steroids, it is important to clearly demonstrate a specific benefit before considering routine use of corticosteroids during CPR. At this time, based on the available evidence, routine use of corticosteroids in CPR cannot be recommended.

Summary of the evidence

Seven articles were identified that addressed this question. One study (LOE 6, fair/supporting) using a rat cardiac arrest model found a higher rate of ROSC in rats treated with high-dose hydrocortisone and a trend toward a decreased epinephrine requirements.[78] A prospective observational study in dogs and cats undergoing CPR (LOE 2, poor/supporting) found that animals that received steroids were more likely to survive than those that did not.[1] In 3 studies in people, the evidence supported the use of steroids. In one retrospective study (LOE 6, fair/supporting), 52% of people with PEA were resuscitated when treated with dexamethasone, a higher proportion than previously reported.[79] In another study (LOE 6, poor/supporting) evaluating out-of-hospital arrest in people randomized to receive either hydrocortisone or saline, hydrocortisone use was associated with an increased rate of ROSC, particularly when administered within 6 minutes of arrival to the hospital, although there was no difference in 1- and 7-day survival rates between saline and hydrocortisone.[80] In a final supporting human study (LOE 6, poor/supporting), the authors prospectively evaluated vasopressin and epinephrine with hydrocortisone versus vasopressin alone, with study group survivors receiving additional hydrocortisone daily for 7 days. The group receiving steroids had a higher ROSC and higher survival to discharge.[45]

In a case series (LOE 6, poor/neutral), 5 human patients with PEA were given 100 mg of dexamethasone as a bolus.[81] Two patients survived; however, the influence of dexamethasone on outcome was unclear. One study (LOE 6, fair/opposing) was found that opposed the use of steroids. This prospective, randomized, double-blind study in people found no benefit of field use of dexamethasone in PEA.[82]

Knowledge gaps

The effect of corticosteroid use in veterinary CPR is unclear and controlled trials are needed to further identify the effects on ROSC, survival, and potential deleterious effects on infectious or thrombotic complications. Specifically, the use of corticosteroids in patients with relative adrenal insufficiency deserves special evaluation, as some data suggest improved survival when corticosteroids are used in the Prolonged Life Support phase of CPR. Although relative adrenal insufficiency has been rarely documented in veterinary patients, use of corticosteroids may be indicated in this population, and further studies investigating this potential phenomenon are warranted.

Naloxone for CPA (ALS13)

PICO Question

In dogs and cats with cardiac arrest and suspected narcotic depression (P), does naloxone (I), when compared to effective ventilation without naloxone (C), improve outcome (O)?

Conclusion

There is no clear indication for the use of naloxone in CPR in veterinary patients that have not received a known or suspected overdose of opioids, but in patients that have received opioids before experiencing CPA, administration of naloxone may be beneficial.

Summary of the evidence

Naloxone in CPR has been considered from 2 perspectives: (1) for use in patients with opioid overdose and (2) as a positive inotrope and antiarrhythmic mediated by reversal of endogenous endorphins. Rothstein and colleagues (LOE 3, fair/supporting) demonstrated in a VF model in dogs that naloxone did not affect hemodynamics but may have been useful in the management of PEA after defibrillation.[83] Six LOE 6, poor/supporting studies showed a possible beneficial effect of naloxone in patients with CPA secondary to narcotic overdose. Seal and colleagues (2005) showed administering naloxone in the field in suspected heroin overdose was feasible and effective when administered by partners of heroin users, but there was no control group.[84] Saybolt et al found that 42% of patients with CPA associated with opioid overdose had an improvement in ECG rhythm following naloxone therapy.[85] In a rat asphyxia model not involving the use of narcotics, the animals were equally likely to achieve ROSC with naloxone or epinephrine, and 1 mg/kg naloxone was more effective

than 0.5 mg/kg naloxone or placebo (saline).[86,87] Using a similar rat model, Wang and colleagues found improved ROSC rates, a reduced time to ROSC, and better neurologic outcomes in animals treated with epinephrine and naxolone compared to epinephrine alone.[88,89]

Three studies were neutral to the use of naloxone in CPR. Foley et al (LOE 3, fair/neutral) found that naloxone had no effect on ROSC or associated neurohormonal responses in a canine VF model.[90] In a retrospective study of canine and feline CPR survivors, Waldrop et al (LOE 4, poor/neutral) identified that 3 of 18 animals with a successful outcome in CPR received naloxone to reverse opioids administered as part of an anesthetic protocol.[51] Finally, Gervais et al (LOE 6, poor/neutral) evaluated naloxone in a porcine VF model of cardiac arrest not associated with narcotic administration, and found that high-dose naloxone was not beneficial in improving cerebral or myocardial blood flow during closed chest CPR.[91]

Only one rat study was identified that showed a negative association between naloxone administration and outcome (LOE 6, against/poor). In this VF rat model, animals were treated with pentazocaine (a delta opioid receptor agonist) naloxone followed by pentazocaine, or saline. Pentazocaine-treated rats survived longer than those administered placebo or pretreated with naloxone, suggesting blockade of delta receptors could be harmful.[92]

Knowledge gaps

A controlled trial of naloxone in cardiac arrest in veterinary patients is needed, particularly in animals with prior known or suspected opioid administration.

Buffer therapy during ALS (ALS16)

PICO Question

In dogs and cats requiring resuscitation and not responding to CPR (P), does the administration of sodium bicarbonate (I), versus no bicarbonate (C), improve outcome (O)?

Conclusion

The preponderance of evidence advises against the routine administration of sodium bicarbonate as a buffer during CPR to dogs and cats; however, it may be considered in prolonged arrests. Interestingly, in dog studies, there has been less appreciation of a detrimental effect of sodium bicarbonate therapy in CPR than in other species.

Summary of the evidence

CPA is typically associated with the development of an acidemia; this may potentially limit the ability of the vasculature to respond to catecholamines, which exert more predictable vasoconstrictive and other effects at a pH close to 7.4. However, administration of sodium bicarbonate results in an increase in serum osmolarity, alkalemia, and potentially a paradoxical cerebral and metabolic acidosis. Multiple experimental and clinical studies have been conducted to evaluate the value of buffer administration during CPR.

In a rat study, Katz et al (LOE 6, good/supporting) found that animals receiving low-dose carbicarb (an alternative buffer) after 8 minutes of asphyxial cardiac arrest had better rates of ROSC and less neuronal cell death and dysfunction than animals receiving saline or high-dose carbicarb.[93] Liu et al (LOE 6, good/supporting) found that after 5 minutes of nonsupported arrest, piglets treated with buffers during CPR had better cerebral perfusion and less profound cerebral acidosis after ROSC.[94]

In dogs, four studies showed improved outcome with buffers. Bar-Joseph et al (LOE 3, good/supporting) found that after prolonged (10 minutes) untreated VF, dogs receiving CPR in combination with buffers had a higher rate of and shorter interval to ROSC compared to control animals.[95] Leong and colleagues (LOE 3, good/supporting) found that after 10 minutes of untreated VF, higher defibrillation success rates were achieved following 2 minutes of CPR if epinephrine and bicarbonate were administered than in animals immediately defibrillated or animals not administered bicarbonate.[96] In a study using a model of prolonged CPR in dogs by Sanders et al (LOE 3, fair/supporting), concomitant fluid loading and bicarbonate administration resulted in improved survival compared to CPR alone.[97] Finally, in 1995, Vukmir et al (LOE 3, good/supporting) evaluated the effects of bicarbonate after short (5 minutes) and prolonged (15 minutes) duration of untreated VF.[98] Dogs were resuscitated with standard CPR, including defibrillation, high-dose epinephrine (0.1 mg/kg), atropine and lidocaine, and randomized to receive either bicarbonate (1 mmol/kg, followed by titration to effect) or vehicle. ROSC rate, survival to 24 hours, and neurological performance were similar between groups after short duration of untreated cardiac arrest, while buffer therapy exerted a positive effect on these outcome measures after prolonged duration of cardiac arrest.

Two high-quality, randomized, controlled studies in people have shown variable results, with Dybvik et al (LOE 6, good/neutral) showing no improvement in rate of ROSC or survival to hospital discharge associated with the use of buffers.[99] Vukmir (LOE 6, good/supporting)

showed a trend toward improved survival with bicarbonate administration in prolonged arrest.[100]

Six studies in the target species (dog) found the use of buffers was associated with a worse outcome. Berenyi et al (LOE 3, good/opposing) showed that excessive bicarbonate therapy in CPR in dogs might result in high blood pH (up to 7.8) and a dissociation between arterial and CSF pH, which might contribute to post-CPR cerebral depression.[101] Guerci et al (LOE 3, fair/opposing) evaluated bicarbonate in a VF model in dogs following 18 minutes of fibrillation and found no improvement with treatment compared to placebo.[102] Bleske et al in three studies (LOE 3, good/opposing) established negative effect of buffers. In the first study, different dosages and modes of sodium bicarbonate therapy were investigated, and it was confirmed that alkalosis developed in response to bicarbonate therapy.[103] In the second study evaluating an early bolus of low-dose sodium bicarbonate during VF, the investigators found that it was still associated with the development of an alkalosis.[104] Finally, the efficacy of epinephrine as a vasopressor when used in combination with bicarbonate therapy was evaluated in a VF model in dogs.[105] After 3 minutes of VF, dogs were randomized to 2 groups, and treated with sodium bicarbonate (3 mmol/kg) or saline (3 mL/kg), both in combination with epinephrine (0.1 mg/kg). While dogs treated with $NaHCO_3$ had a higher pH, a difference in the rate of successful resuscitation was not found.

Knowledge gaps

Controlled studies involving the potential utility and outcome following the use of buffers in veterinary patients are advised. Guidelines, either pH based or cardiac arrest duration based may be useful and should be further explored. There is no data quantifying the severity of acid-base abnormalities during clinical cardiac arrest in pets. The utility of sodium bicarbonate in cats has not been investigated.

Electrolyte disturbances (ALS12)

PICO Question

In dogs and cats with cardiac arrest (P), does treatment of electrolyte disturbances (eg, hyper- or hypokalemia, hypo- or hypercalcemia) (I), as opposed to standard care without treatment of electrolyte disturbance (C), result in improved outcome (eg, ROSC, survival) (O)?

Conclusion

Electrolyte disturbances associated with CPA may exist prior to the arrest or may develop during CPR subsequent to metabolic acidosis, drug therapy, or other metabolic derangements. There is no compelling evidence to suggest treatment of mild electrolyte disturbances. Moderate-to-severe hyperkalemia influences myocardial function and should be treated. Severe ionized hypocalcemia may be treated, and calcium therapy is warranted in symptomatic calcium channel blocker overdosage.

Summary of the evidence

Few studies have specifically addressed the role of correction of electrolyte disturbances in CPR. Treatment of hyperkalemia in dialysis patients has been associated with improved survival (LOE 6 poor/supporting) in 3 case reports and 1 review.[106–109] One study in a porcine model (LOE 6, poor/supporting) found that pigs with PEA had higher potassium values after defibrillation.[110] Niemann et al (LOE 3 poor/supporting), using a VF model, showed that dogs with higher potassium had more significant arrhythmias, including PEA and asystole.[111] Hypokalemia may also be associated with cardiac arrest, and when severe hypokalemia is present, treatment may be advised. In a retrospective human study, Seidler et al (LOE 6, poor/supporting) found a weak association between hypokalemia and cardiac arrest.[112] Importantly, hypokalemia may result from endogenous or exogenous β-adrenergic agonists (including epinephrine) so retrospective studies without clear delineation of the time of sampling may be problematic.

No studies investigating treatment of hypocalcemia during CPR were identified. Niemann et al (LOE 5, poor/supporting) in a canine VF model documented progressive hypocalcemia in those animals that could not be resuscitated with 10 minutes of ALS interventions, suggesting that hypocalcemia may be associated with more refractory CPA.[111] However, intracellular calcium levels do not parallel extracellular calcium levels, and excessive intracellular calcium may be detrimental.

Knowledge gaps

Therapies targeting correction of electrolyte disturbances during CPR have not been well studied. There is evidence that hyperkalemia and hypocalcaemia may accompany prolonged CPA, and observational studies in dogs and cats are needed. Moreover, investigation of the utility of treatment of these disturbances is needed. While markedly elevated serum potassium that is documented prearrest should be treated, it is unclear at what level therapy is warranted.

Calcium for cardiac arrest (ALS14)

PICO Question

In dogs and cats with cardiac arrest (asystole, PEA, pulseless VT, and VF) (P), does the use of calcium alone or combination with other drugs (I), compared with not using calcium (C), improve outcomes (eg, ROSC, survival) (0)?

Conclusion

The routine use of calcium in veterinary CPR is not warranted. In animals with known severe hypocalcemia, or in those with calcium channel blocker overdose, calcium administration may be warranted. In animals with preexisting severe hyperkalemia, calcium administration is indicated and may be life saving by improving cardiac function.

Summary of the evidence

Calcium is vital in cellular communication (signaling) as well as muscle contraction in skeletal, cardiac, and smooth muscles. Adequate calcium concentrations are required for cardiac contractility. Additionally, there is a clear relationship between low ionized calcium levels and a poor outcome in CPR. However, high exogenous calcium is also associated with impaired neurological outcome and perpetuation of myocardial damage.[113]

Intra-arrest calcium administration was specifically evaluated in 9 articles related to CPR. There were no studies found that supported the routine use of calcium in CPR. Three studies were found that were neutral to the question. Stueven and colleagues (LOE 6, good/neutral) evaluated the effectiveness of calcium chloride in refractory PEA; while there was an increased rate of ROSC in individuals who received calcium, no difference in survival was found.[114] Harrison et al (LOE 6, poor/neutral) found that in out-of-hospital arrest, some patients with PEA responded to calcium supplementation, including three long-term survivors.[115] Gando et al (LOE 6, poor/neutral) found that changes in ionized calcium concentrations were seen in CPR, but there was no improvement in survival associated with correction of the ionized calcium concentration.[116]

Six articles were identified that provided evidence against the recommendation to use calcium in CPR. One LOE 3 (fair/opposing) article evaluated CaCl in a canine VF model and found that it alone was ineffective compared to epinephrine or BLS.[117] Meuret et al (LOE 3, fair/opposing) also evaluated epinephrine versus calcium and epinephrine combined in a canine asphyxial arrest model; in the calcium only group, fewer dogs achieved ROSC, and cardiac function was severely impaired.[118] In people, 3 studies (LOE 6, opposing, poor [1], good [2]) evaluated the use of calcium in cardiac arrest and found no survival benefit.[119–121] In addition, a more recent human study (LOE 6, good/opposing) found no benefit to the use of calcium in CPR.[122]

Knowledge gaps

No controlled trials have been done in veterinary patients investigating the use of calcium in CPR, although the routine administration of calcium during veterinary CPR is not recommended and the perceived need for a study is low. In animals with hypocalcemia or hyperkalemia, investigations of the ionized calcium or potassium concentration at which calcium therapy would be advised are warranted.

Defibrillation

Electrical defibrillation is without question the most effective therapy for sudden cardiac death due to VF in people. Widespread implementation of by-stander-operated electrical defibrillators has been associated with marked improvement in survival. In a hospital setting, current guidelines in human medicine recommend that "shockable" rhythms (VF and pulseless VT) be promptly treated with electrical defibrillation. Three PICO questions investigating optimal electrical defibrillation technique, timing of electrical defibrillation, and defibrillation dosing were investigated.

Defibrillation technique (ALS05)

PICO Question

In dogs and cats with cardiac arrest due to VF or pulseless VT (P), does the use of a defibrillator, or any specific defibrillation strategy (I), compared with no defibrillation (C), improve outcomes (eg, restoration of pulse generating rhythm, ROSC, survival (O)?

Conclusion

The use of prompt electrical defibrillation is associated with a markedly higher rate of ROSC and survival than no defibrillation, and thus electrical defibrillation is a treatment of choice for VF. BP defibrillation is preferable to monophasic defibrillation. There is less evidence concerning stacked versus single shocks for defibrillation, although most evidence points toward prompt resumption of cardiac compressions, and that a single shock is preferable.

Summary of the evidence

When comparing monophasic (MP) versus BP defibrillation, 13 studies were found in support of the use of BP defibrillation. The most compelling studies include an article by Leng (LOE 3, good/supporting), which evaluated resuscitation after prolonged VF in dogs using either monophasic or BP defibrillation.[123] Dogs defibrillated with BP devices required lower doses and achieved ROSC more rapidly. Additionally, Lee and colleagues (LOE 3, fair/supporting), evaluated defibrillation of experimentally induced VF in toy breed dogs.[124] All dogs were successfully defibrillated with either MP or BP countershocks, but animals in the BP group required less energy for defibrillation and had less evidence of myocardial dysfunction postdefibrillation. Additionally, a single case report (LOE 4, good/supporting) documented successful defibrillation of a dog with BP defibrillation after monophasic defibrillation failed.[125] Morrison et al (LOE 6, good/supporting) investigated out-of-hospital arrest in people treated with either BP or MP defibrillation, and identified a higher rate of termination of VF with BP defibrillation, although there was no difference in ROSC or survival to discharge.[126] Also in people, Schneider et al (LOE 6, fair/neutral) randomized 115 people with CPA due to VF to receive either defibrillation using an automated external defibrillator at either 150 J with a BP defibrillator or 200–360 J with a MP defibrillator.[127] BP defibrillation was associated with a higher rate of defibrillation and ROSC and superior neurological functional status in long-term survivors than with MP defibrillation. Koster et al (LOE 6, good/supporting) evaluated 120 patients with out-of-hospital VF and found that BP defibrillation was associated with a higher rate of return of organized rhythm, which was defined as two or more QRS complexes less than 5 seconds apart within 60 seconds of defibrillation.[128] Van Alem et al (LOE 6, good/supporting) evaluated BP versus MP defibrillation in out-of-hospital arrest and found a higher ROSC rate with BP than MP although the study was not powered to evaluate long-term outcome.[129]

Numerous studies compared MP to BP defibrillation in swine models of VF. Walker et al (LOE 6, good/supporting) compared 6 defibrillation waveforms in a VF model and identified that BP defibrillation was preferable, and in animals with low thoracic impedance, BP was nearly 100% successful.[130] Niemann et al (LOE 6, good/supporting) found that defibrillation was more successful with BP and there was less evidence of ST segment changes after ROSC with BP.[131] Zhang et al (LOE 6, good/supporting) evaluated the success of MP versus BP defibrillation in a model of LV dysfunction and identified better success with BP defibrillation.[132] Tang et al (LOE 6, good/supporting) found that pigs were more successfully defibrillated with BP than MP defibrillation at lower energies and had less myocardial damage.[133,134]

In summary, no studies were identified demonstrating that BP was inferior to MP for termination of VF, although several showed no difference between the technologies.

When considering the use of a single shock with an immediate return to chest compressions versus repeated or stacked shocks for VF, there is no evidence available in dogs or cats. While stacked shocks have been recommended historically, newer evidence suggests that chest compressions between single shocks may be more important. A single shock compared to stacked shocks will minimize interruption of chest compressions, reduce myocardial ischemia, and increase defibrillation success. The most compelling evidence supporting one shock is from a pig study by Tang et al (LOE 6, good/supporting), which showed improved survival with a 1 shock protocol compared to stacked shocks, although there was no difference in myocardial dysfunction or neurological status in survivors of either single or stacked shocks.[135] Additionally, 2 studies in people evaluated single versus stacked shocks. Bobrow et al (LOE 6, fair/supporting) showed improved survival with minimally interrupted CPR and a single shock, while Rea et al (LOE 6, poor/supporting) found increased survival with a single shock, as well as improved neurological outcomes.[136,137]

Knowledge gaps

While most of the evidence strongly supports the use of BP versus monophasic defibrillation, no clinical studies in dogs have evaluated BP versus MP. Additionally, the efficacy of BP and MP defibrillation has not been evaluated in cats. Given the lack of clinical evidence, prospective trials evaluating the relative effectiveness of single versus stacked shocks are warranted.

Timing of electrical defibrillation (ALS08)

PICO Question

In dogs and cats with cardiac arrest due to VF (P), does the use of CPR before defibrillation (I) as opposed to defibrillation first (C) improve outcome (O)?

Conclusion

Immediate defibrillation is warranted if the duration of VF is 4 minutes or less, as during this electrical phase of cardiac arrest, less ischemia is present and prompt defibrillation is more likely to be successful. In arrests

believed to have lasted longer then 4 minutes, one cycle of CPR before defibrillation may help replenish energy substrates and increase the likelihood of successful defibrillation.

Summary of the evidence

Evolving concepts in CPR support the three-phase model of CPA. The first phase, lasting approximately 4 minutes and termed the electrical phase, is characterized by minimal ischemia. The second phase, the circulatory phase, occurs between 4 and 10 minutes after CPA, and is associated with energy depletion and potentially reversible cellular damage. After 10 minutes of no circulation, the metabolic phase begins and is characterized by ischemic injury that may require more advanced strategies than conventional BLS and ALS to reinstate cellular function.[138–140] Of importance, in people, VF is a more common primary arrest rhythm than in veterinary patients. However, the question of whether to promptly defibrillate or to provide CPR first has been extensively investigated in experimental studies and in human clinical trials.

There are 3 relevant studies in dogs. Niemann et al (LOE 3, good/supporting) evaluated a model of prolonged untreated VF (7.5 minutes) in dogs and compared immediate countershock versus CPR + epinephrine (0.08 mg/kg) before shock.[141] They found a 3-fold increase in the number of successfully resuscitated dogs if 1 cycle of CPR was provided before a countershock. Wang and colleagues (LOE 3, good/neutral) evaluated immediate defibrillation versus immediate chest compression in a 4-minute canine model of VF and concluded that there was no difference in rate of ROSC and 24-hour survival (LOE 3, good, neutral).[142] Finally, Yakaitis et al (LOE 3, good/opposing) concluded that the energy requirements for defibrillation were proportional to the duration of fibrillation, and immediate defibrillation was preferable if the VF interval was less than 3 minutes (LOE 3, good/opposing).[143] Spearpoint et al (LOE 6, fair/opposing) and Skogvoll et al (LOE 6, poor/opposing) found that early defibrillation was associated with improved survival in humans.[144,145]

Conversely, Berg et al (LOE 6, good/supporting) identified in a porcine model of VF that after 8 minutes of VF, stacked countershocks were more likely effective if delivered after 90 seconds of CPR.[146]

There are two compelling meta-analyses of human out-of-hospital arrest. Meier (LOE 6, good/neutral) evaluated 4 trials involving 1503 patients, and found no difference in ROSC or hospital discharge between early defibrillation and chest compressions followed by defibrillation.[147] However, subgroup analysis provided some evidence that chest compressions before defibrillation in individuals suspected to have longer duration VF were beneficial. Simpson et al (LOE 6, good/neutral) evaluated 3 trials involving 658 patients and again found no clear benefit from early defibrillation compared with chest compressions first, and concluded that either was acceptable.[148]

Knowledge gaps

In clinical cases of CPA, the actual duration of VF is rarely known. Dogs and cats less frequently have VF as the first identified rhythm associated with CPA, and thus the direct application of a recommendation for immediate defibrillation is less clear. A randomized trial of immediate countershock compared with CPR followed by countershock in dogs and/or cats is needed.

Escalating versus fixed defibrillation energy (ALS15)

PICO Question

In dogs and cats with cardiac arrest (P), does the use of an escalating defibrillation energy protocol (I), compared with a fixed energy protocol (C), improve outcomes (eg, ROSC) (O)?

Conclusion

Excessively high defibrillation energy may be associated with increased myocardial damage. However, failure to successfully defibrillate is inevitably associated with death. For monophasic defibrillators, increasing energy doses are associated with increased defibrillation success in animals in which defibrillation at a lower dose failed. Thus, it is reasonable to consider an escalating dosage protocol for defibrillation. For BP defibrillators, the evidence is less clear, but an escalating protocol could be considered as well.

Summary of the evidence

Thirty articles were identified that explored this question in people and in animals. Seven articles were found that provided LOE 6 supporting evidence, with 3 articles identified that had good/supporting evidence for the question. The first article by Clark et al in a porcine model found that successful defibrillation at 200 J was likely with both BP and monophasic defibrillation, but at lower doses, BP defibrillation was more successful.[149] Niemann et al (2004) evaluated a swine model of dose escalation in ischemic VF, and found that more animals were successfully defibrillated using an escalating protocol (200-300-360 J) than with a fixed (150 J) protocol.[150] Stiell et al (2007) in a human clinical trial identified that in patients being treated with BP defibrillation and failure

of the initial shock, an escalating dose was more likely to be successful than a fixed dose.[151]

An additional 23 studies were identified that showed no risk or benefit from the use of escalating defibrillation energy protocols. In the target species (dog), 6 studies were neutral that escalating energy was beneficial to outcome. These included Flaker et al (1990, LOE 3, poor/neutral) who evaluated if multiple shocks adversely affected the outcome of later shocks in a canine model of VF.[152] Specifically in this model, it was identified that while higher shocks are effective earlier in defibrillation, multiple low energy shocks may create a "sensitizing" effect and permit later more effect shocks at lower doses. Additionally, Walcott et al (LOE 3, fair/neutral) evaluated BP external defibrillation in dogs associated with ischemic versus nonischemia-induced VF.[153] This study did not specifically address dose escalation, but found that increasing doses were required to successfully defibrillate ischemic VF in contrast to nonischemic VF. In an animal model of spontaneous VT in German shepherd dogs, Gelzer et al (LOE 3, fair/neutral) found that a greater number of shocks was required to successful defibrillate a GSD in contrast to beagle and that multiple shocks were more likely to successfully defibrillate a dog if a single shock failed.[154] In 1998, Walcott et al (LOE 3, fair/neutral) found that the defibrillation threshold increased over time for monophasic defibrillation, but remained unchanged for BP defibrillation.[155] Leng et al (LOE 3, good/neutral) found increasing defibrillation thresholds for both monophasic and BP waveforms over time, and confirmed that early defibrillation was more likely successful than late defibrillation.[123] Finally, in 1989, Murakawa et al (LOE 3, good/neutral) found that an initial unsuccessful low energy (subthreshold) shock does not decrease the energy requirement for later shocks using an implantable defibrillator.[156]

Knowledge gaps

Reports of successful defibrillation in veterinary patients are rare. Clinical guidelines for monophasic and BP defibrillation are reported, but data are lacking relative to the success of specific doses of energy to successfully defibrillate veterinary patients and whether an escalating defibrillation dose is more effective than a fixed defibrillation dose.

Other ALS Topics

The ALS domain was also charged with investigating other advanced interventions targeted at improving outcomes from CPR, as well as special circumstances surrounding CPR. Four PICO questions were analyzed, evaluating open chest CPR, intratracheal (IT) administration of drugs, impedance threshold devices (ITDs), and cardiopulmonary arrest associated with anesthesia.

Open chest CPR (ALS06)

PICO Question

In dogs and cats with cardiac arrest (P), does the use of open-chest CPR in certain situations (I), compared with closed-chest (standard) CPR (C), improve outcome (eg, ROSC, survival to discharge) (O)?

Conclusion

Open-chest CPR is more effective than closed-chest CPR in restoring ROSC and promoting a good outcome in canine models of VF. In practice, open-chest CPR requires significant resources, is a procedure that requires a skillful veterinary team, and demands advanced postcardiac arrest supportive care. In cases of significant intrathoracic disease, such as tension pneumothorax or pericardial effusion, it may be advisable to promptly perform open-chest CPR. Defibrillation should be readily available.

Summary of the evidence

The vast majority of the available experimental evidence is supportive that open-chest CPR results in improved outcomes, including ROSC, survival, and neurological function. There are 6 compelling experimental studies in dogs. Sanders et al (LOE 3, good/supporting) compared dogs receiving open-chest CPR to those receiving closed-chest CPR after 15 minutes of closed-chest CPR in a VF model.[157] All dogs were defibrillated at 19 minutes. Eighty percent of the dogs in the open-chest group, but none in the closed-chest group, achieved ROSC. Kern et al (LOE 3, good/supporting) in another canine VF model found that open-chest CPR significantly improved outcome when begun after 15 minutes of closed-chest CPR.[158] In a canine myocardial infarct model, DeBehnke et al (LOE 3, good/supporting) compared resuscitation with either closed-chest CPR, open-chest CPR, or CPB.[159] Open-chest CPR or CPB resulted in higher rates of ROSC than closed-chest CPR. Benson et al (LOE 3, good/supporting) found improved survival and improved neurological outcome in dogs randomized to receive open-chest CPR compared to those that received closed-chest.[160] In people, Hachimi-Idrissi et al (LOE 6, good/supporting) reviewed 33 cases of open-chest CPR performed for out-of-hospital arrest that had failed to respond to closed-chest CPR. ROSC was achieved in 13 patients, with 2 long-term survivors, 1 with no neurological abnormalities, and 1 with mild impairment.[161]

Two canine studies were identified that were neutral to this PICO question. Badylak et al (LOE 3, fair/neutral) demonstrated in a canine VF model that even though increased pathological damage was associated with chest wall trauma in open-chest CPR, brain lesions were less severe.[162] Chrissos et al (LOE 3, good/neutral) showed that in dogs with preexisting mitral regurgitation, direct cardiac massage was associated with an increased regurgitant fraction.[163]

Sheikh and Brogan (LOE 6, good/opposing) found no survivors among 15 children subject to open-chest CPR after traumatic cardiac arrest and 20 minutes or more of CPR in the field and concluded that open-chest CPR was an expensive and futile procedure.[164]

Knowledge gaps

The practical applications and successes of open-chest CPR in veterinary patients remain unknown. While in human medicine, resuscitative thoracotomy is warranted in some specific cases of thoracic trauma with arrest in the emergency room, the use of open-chest CPR for cardiac arrest from nontraumatic causes, or from long-standing out-of-hospital arrest is far less clear. In veterinary practice, a controlled clinical trial exploring the use of open-chest CPR in specific circumstances is warranted. Moreover, the time at which administration of open-chest CPR should be initiated needs to be delineated.

Intravenous versus intratracheal drug administration (ALS09)

PICO Question

In dogs and cats with cardiac arrest (P), does the use of tracheal drug delivery (I), compared to intravenous drug delivery (C), worsen patient outcome (eg, ROSC, survival to hospital discharge (O)?

Conclusion

Faced with the lack of venous or intraosseous access, intratracheal (IT) administration of epinephrine, atropine, and vasopressin may be considered. If IT is chosen, a 10-fold increase in the dosage of epinephrine (ie, high-dose epinephrine) should be used, and the drug should be delivered via a catheter to the level of carina or ideally farther distal into the bronchial tree. The drug should be diluted in sterile water, although saline is a reasonable alternative if sterile water is not promptly available.

Summary of the evidence

Studies investigating IT drugs have focused primarily on out-of-hospital cardiac arrest scenarios, where venous access may be absent. In a veterinary review of 204 animals receiving CPR (LOE 2, poor/neutral), only 24 received IT medications, and these were largely followed by IV administration of resuscitative medications, so no comment on the efficacy of IT medications could be made.[1]

One retrospective study (LOE 6, fair/opposing) found a similar outcome in people with out-of-hospital cardiac arrest who received no medication and those who received IT medication.[165] In another retrospective cohort study in humans with sudden cardiac arrest (LOE 6, good/opposing), IV administration of drugs was associated with higher rate of ROSC (27% versus 15%), survival to hospital admission (20% versus 9%), and survival to discharge (5% versus 0%) compared to IT administration.[166] In human neonates, prompt IV access is advised. One retrospective study (LOE 6, fair/neutral) comparing the same dose of epinephrine IV and IT documented better outcomes with IV administration, although the authors suggested that a higher IT dose may have been more effective.[167] Four LOE 3 (2 good/supporting, 2 fair/supporting) studies in dogs identified a favorable physiological response to the administration of IT or intrabronchial (IB) delivery of vasopressin, atropine, or epinephrine in anesthetized dogs.[168–171]

In a piglet model of VF (LOE 6, poor/opposing), low-dose IT epinephrine (0.01 mg/kg) negatively affected outcome compared to the same dose given IV.[172]

There is conflicting evidence regarding the best location in the respiratory tree to directly deliver the drug(s), and the type and volume of the drug diluent to be used. Good evidence exists (LOE 3 god/supporting) that in medium-sized dogs (9.5-15.7 kg), IT administration of high-dose epinephrine (0.1 mg/kg) diluted with 5 mL of 0.9% saline optimizes drug delivery while minimizing the effects on oxygenation and ventilation.[170] However, another study (LOE 3, good/supporting) suggested that sterile water was a better diluent than saline, and that the diluted solution should be administered with a long catheter at or beyond the level of the carina.[173]

Knowledge gaps

While it is clearly established that IT medications are promptly absorbed during anesthesia, it is far less clear if the same absorption occurs during CPR. Human studies show no adult survivors of IT-only CPR, and in infants IT CPR is recommended only as a short-term solution until the placement of an IV catheter. A study comparing

IT versus no medication (eg, BLS alone) would likely be unethical to perform in veterinary patients or people. All studies in dogs to date have been in animals weighing between 8 and 20 kg. The optimal volume of diluent for very small breed dogs, larger breed dogs, and cats is unknown. Experimental studies will be required to address the effectiveness and optimization of IT delivery of drugs in models of cardiac arrest.

ITDs (ALS10)

PICO Question

In intubated dogs and cats with cardiac arrest (P), does the use of an ITD (I), as opposed to routine CPR without an impedance device (C), improve outcome (O)?

Conclusion

Porcine models showed promising improvement in both hemodynamic variables and survival using the ITD. Initial studies in people generally were supportive of use of the ITD; however, no survival benefit was found in the largest human clinical trial to date. In small dogs and cats (<10 kg), size limitations preclude the use of currently available ITDs due to the requirement for chest wall recoil to produce a "cracking pressure" in excess of –12 cm H_2O. The ITD has been used in noncardiac arrest canine models, and appears effective in these scenarios at increasing cardiac output. In dogs >10 kg, the use of an ITD may be considered, although this is based on studies in nontarget species or in scenarios that do not include cardiac arrest. Due to theoretical concerns of worsening pulmonary edema with increasingly negative intrathoracic pressure, severe lung disease or existing pulmonary edema should be considered a contraindication to use of the ITD unless future studies establish its safety.

Summary of the evidence

Increased negative intrathoracic pressure was associated with enhanced venous return during CPR. In pig models of CPR, the use of an ITD led to markedly improved hemodynamics. Lurie et al (LOE 6, good/supporting) showed an improvement in CPP when ITD was used rather than a sham device during CPR.[174] The same group demonstrated similar findings during active compression decompression CPR (LOE 6, good/supporting).[175] Langhelle et al (LOE 6, good/supporting) found an improvement in myocardial blood flow when the ITD was used with standard, but not active compression-decompression CPR.[176] There is also evidence (LOE 6, fair/supporting) from porcine models that manipulation of intrathoracic pressure by controlling airway pressure can lead to reductions in intracranial pressure, which could theoretically improve cerebral perfusion during CPR.[177] No negative effects of an ITD have been observed in experimental animals.

Several human studies have demonstrated that use of an ITD was associated with a higher ROSC and short-term survival, and some studies have found improvements in long-term survival associated with use of the device. Aufderheide (LOE 6, good/supporting) demonstrated improved short-term survival when the ITD was used versus a sham device.[178] Thigpen et al (LOE 6, fair/supporting) reported a significant improvement in survival following in-hospital cardiac arrest when a CPR bundle including use of the ITD was implemented in a single center.[179] Plaisance at al (LOE 6, good/supporting) demonstrated improved 24-hour survival in patients receiving a combination of active compression-decompression and ITD,[180] a finding echoed by Wolcke et al (LOE 6, fair/supporting).[181] A meta-analysis by Cabrini et al (LOE 6, fair/supporting) concluded that a short-term survival benefit results from the use of the ITD.[182] The largest study of 8718 patients by Aufderheide et al (LOE 6, good/negative), however, demonstrated no difference in ROSC, survival to hospital admission, or survival with acceptable neurological outcome between patients randomized to be resuscitated using an active or sham ITD.[183] Efforts to identify subgroups where ITD might be useful, however, are ongoing.

Use of the ITD in noncardiac arrest models has been investigated in dogs; Shih et al 2010 (LOE 3, fair/supporting) demonstrated improved hemodynamics in dogs experiencing anesthesia induced hypotension using a low cracking pressure ITD, and Vigani et al 2011 (LOE 3, fair/supporting) found significant improvements in hemodynamics when a low cracking pressure ITD was used in a canine model of acute hemorrhagic shock.[184,185]

Knowledge gaps

It is unclear if an ITD might be a useful device in larger (>10 kg) canine cardiac arrest. Improvements in venous return may be useful, and further evaluation in dogs is warranted. Studies investigating subgroups most likely to benefit from an ITD are warranted, and might include dogs with preexisting hypovolemia when increased venous return may be of particular benefit.

Anesthetic-related arrests (ALS18)

PICO Question

In dogs and cats with cardiac arrest under anesthesia (P), do anesthesia-specific CPR recommendations (I),

compared to no such recommendations (standard CPR) (C), result in improved outcomes (survival or ROSC) (O)?

Conclusion

Animals that experience CPA while under general anesthesia should be aggressively resuscitated, as a much higher percentage should be anticipated to survive to discharge compared to the general population. No CPR-specific guidelines exist for anesthetic-associated arrest; however, careful monitoring during anesthesia may permit more rapid recognition and potentially improve outcome. Lipid rescue may be considered in animals with CPA due to local anesthetic drugs or in association with other lipophilic drugs.

Summary of evidence

Two studies in dogs and cats showed an improved likelihood of survival in animals with CPA associated with anesthesia. In a prospective, observational study, Hofmeister et al (LOE 2, poor/supporting) showed a 47% survival to discharge rate in dogs and cats after CPR if the arrest occurred while under anesthesia.[1] In a retrospective study, Waldrop et al (LOE 3, good/supporting) reported over 50% of long-term survivors of CPR had CPR in association with anesthesia.[51]

Studies in humans (LOE 6, good/supporting, fair/supporting) have been directed at preventing anesthetic arrests through more careful monitoring and in pediatrics, better airway management.[186,187] One recent review article described the role of anesthetic associated arrest and the development of the specialty of anesthesiology, including the creation of safer procedures, new agents, and improved monitoring.[188] However, as medicine advances, more patients with multiple, concurrent medical disorders are anesthetized for procedures that might not have been performed even 10 years ago. These advances have lead to increased potential for mortality.

Lipid rescue for CPA associated with local anesthetic toxicity has been described in several case reports. Litz et al (LOE 6, poor/supporting) described a case of CPA secondary to a ropivacaine axillary block that was refractory to 10 minutes of CPR.[189] However, more recent experimental evidence in swine asphyxia arrest models induced with intravenous local anesthetic overdose (LOE 6, fair/opposing) has failed to demonstrate efficacy of IV lipid rescue as an alternative or an adjunct to epinephrine when applying standard ALS protocols.[190] Finally, a study of hypoxic arrest in rabbits (LOE 6, fair/opposing) demonstrated that, in this nondrug-induced arrest model, the use of IV lipid rescue worsened the rate of ROSC.[191]

Knowledge gaps

The specific cause of arrest in animals undergoing CPR is often not known. Anesthesiologists assign risk associated with anesthesia, and while critically ill animals (ASA status IV or V) are considered more likely to arrest while under anesthesia, the etiology of anesthetic-related CPA is less clear in healthy dogs and cats. Further studies to better characterize this etiology in healthy animals might improve outcome and prevent some arrests. The efficacy of IV lipid rescue in dogs and cats that arrest due to the administration of lipophilic drugs has not been investigated, and studies examining this novel intervention are warranted.

Discussion

While studies evaluating the efficacy of ALS procedures in clinical veterinary patients are limited, the bulk of the available evidence supports some specific concepts. Continuation of high-quality BLS with very brief interruptions of chest compressions during ALS efforts is recommended.

Early and prompt defibrillation with a BP defibrillator is considered the therapy of choice for VF or pulseless ventricular tachycardia. Some clinicians express concern about the practicality and safety of having defibrillators in their clinics. It is important to recognize that defibrillators may also be used for assessing ECGs and thus may be multiuse in a practice. Additionally, while defibrillation carries risk to the operator and other personnel, studies in people have shown a very low incidence of harm to rescuers with most of the limited reports describing brief tingling or numbness.[192] Given the poor efficacy of pharmacologic agents for treating VF, acquisition of a defibrillator, especially in clinics performing frequent anesthetic procedures, should be seriously considered. However, defibrillators should be used with caution and only after appropriate training to avoid risk to the rescuers.

The evidence suggests that low-dose epinephrine and vasopressin are first line pharmacologic agents in CPR, providing peripheral vasoconstriction to improve blood flow to heart and brain, and enhancing the chance of ROSC. Other drug therapies in ALS, including atropine, buffer therapy, corticosteroids, antiarrhythmics, and electrolyte solutions have far less evidence of efficacy and remain to be comprehensively evaluated in clinical practice.

Further investigations of interventions in ALS are also warranted, and include a better understanding of what

ALS techniques may be useful. Dogs and cats often arrest naturally from a variety of critical illnesses, and the optimal ALS techniques will likely vary depending on the underlying cause of the arrest and species. Further veterinary clinical research is clearly needed to better characterize these species differences and to generate evidence-based recommendations.

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Appendix

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