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RECOVER evidence and knowledge gap analysis on veterinary CPR. Part 6: Post-cardiac arrest care

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Abstract

Objective – To systematically examine the evidence for interventions after the return of spontaneous circulation (ROSC) on outcomes from veterinary cardiopulmonary resuscitation and to determine important 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 post-cardiac arrest care.
Setting – Academia, referral practice, and general practice.
Results – Fifteen standardized clinical questions important for post-cardiac arrest care were asked and research articles relevant to answering these questions were identified through structured, explicit literature database searches. The majority of these articles report research in species other than dogs or cats or consisted of experimental work in canine cardiac arrest models. Outcome metrics reported in these studies widely varied and ranged from quantification of mechanistic endpoints, such as elaboration of reactive oxygen species, to survival, and functional neurologic outcome.
Conclusions – Despite the near complete absence of clinical veterinary studies, the process allowed the formulation of statements for several postcardiac arrest treatments that were either supportive, such as mild therapeutic hypothermia or controlled reoxygenation, or neutral, such as for mannitol administration or seizure prophylaxis. Evidence grading allowed transparency in regards to the strength of these recommendations. Moreover, numerous knowledge gaps emerged that will allow generation of a road map for progress in veterinary post-cardiac arrest care.

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Keywords: cardiac arrest, cat, CPR, dog, evidence, guidelines

Abbreviations

ALS	advanced life support
BLS	basic life support
CPA	cardiopulmonary arrest
CPP	coronary perfusion pressure
CPR	cardiopulmonary resuscitation
LOE	level of evidence
MTH	mild therapeutic hypothermia
OHCA	out-of-hospital cardiac arrest
PCA	post-cardiac arrest
PEA	pulseless electrical activity
PICO	population, intervention, control group, outcome
RECOVER	Reassessment Campaign on Veterinary Resuscitation
ROS	reactive oxygen species
ROSC	return of spontaneous circulation
$ScvO_2$	central venous oxygen saturation
VF	ventricular fibrillation

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VT ventricular tachycardia

Introduction

A return of spontaneous circulation (ROSC) in a patient that has undergone a cardiopulmonary arrest (CPA) is the first but intermediate goal in resuscitation. The majority of cardiac arrest patients that initially achieve ROSC will not survive to hospital discharge. In humans, between 60% and 70% of sudden cardiac arrest victims and 70% of those suffering from in-hospital cardiac arrest will not survive to hospital discharge despite having achieved ROSC initially.[1,2] In veterinary medicine, reported survival to discharge rates range from 2% to 10% for dogs and cats, despite initial ROSC rates of 35–45%.[3,4] It is the current view that these patients succumb to a lethal post-cardiac arrest (PCA) syndrome that is characterized by a combination of multiorgan failure, cardiogenic shock, anoxic brain injury, and the sequela of preexisting diseases.[5] The discrepancy between rates of ROSC and that of hospital discharge has broadened the focus of attention to include the postresuscitation period in an effort to optimize the opportunity for successful outcomes.[6] The degree of involvement of patients in the PCA syndrome is highly complex and heterogeneous. It is most likely that successful resuscitation to discharge will require a multifaceted therapeutic intervention.

Thus, the clinically relevant questions asked in this RECOVER PCA care domain focused on mitigating the effects of the PCA syndrome. The role of IV fluids, cardiovascular active drugs, and blood pressure management along with hemodynamic optimization strategies with endpoints that allowed the treatment to be titrated to the needs of each patient were investigated. Questions regarding the value of carbon dioxide and oxygen control, as well as mild hypothermia and rewarming rates were addressed. The value of corticosteroids, seizure prophylaxis, hyperosmolar therapy, and metabolic protection was also examined. And lastly, the questions of whether combination therapies to achieve additive or synergistic effects and whether referral center management of the PCA patient provided outcome benefit were asked.

There is a dearth of evidence from which to generate specific recommendations for PCA care in dogs and cats. However, based upon the limited available literature, the key PCA care concepts that emerged from the evidence evaluation are as follows:

- Based upon human studies that suggest hemodynamic optimization protocols during the PCA phase are clinically feasible and potentially useful, in hemodynamically unstable dogs and cats after cardiac arrest, a hemodynamic optimization strategy including fluid therapy adjusted according to criteria customary to veterinary small animal emergency and critical care is reasonable.
- There is good evidence to advocate normoxemia versus hyperoxemia or hypoxemia in the early PCA period.
- The evidence suggests a neurologic benefit of mild hypothermia ($33 \pm 1^{\circ}C$) in the early postresuscitation period, and that fast rewarming after induced or unintended hypothermia may be harmful.
- There is no evidence to support routine administration of corticosteroids, antiseizure prophylaxis, mannitol, or metabolic protectants after cardiac arrest.
- Low-dose corticosteroid treatment of patients with persistent hypotension requiring sympathomimetic support may be considered.
- Hypertonic saline (HS) may be considered in animals that are suspected of having cerebral edema as evidenced by coma or obtundation after cardiac arrest.
- Bundled therapy including hypothermia, hypertension, and normocapnia (compared to normothermia, normotension, and hypocapnia) and thiopental, methylprednisolone, phenytoin, and perhaps antioxidants, may have outcome benefit.
- More comprehensive PCA care in a specialty center with access to more advanced monitoring equipment and supportive care may have an outcome benefit.

Cardiovascular Support

Cardiovascular dysfunction after resuscitation from CPA can be attributed to the underlying precipitating disease, such as hypovolemia or cardiac dysfunction, or the subsequent reperfusion injury. Myocardial stunning and a sepsis-like syndrome with increased vascular permeability and microvascular dysfunction may result from these processes.[7–10] To establish and maintain adequate organ perfusion following ROSC, the use of IV fluids and cardioactive and vasopressor drugs are often employed to support circulation to certain resuscitation endpoints. This section examines the utility of a protocol-driven hemodynamic optimization strategy (PA02), the general use of IV fluids (PA01), and the evidence regarding the use of vasopressors and inotropes (PA03 and PA04).

Goal-directed therapy (PA02)

Population, intervention, control group, outcome (PICO) Question: In dogs and cats with ROSC after cardiac arrest that have cardiovascular dysfunction (hypotension/hypoperfusion) (P), does early hemodynamic

optimization (I), as opposed to standard care (C), improve outcome (O) (eg, survival)?

Conclusion

Human studies suggest that a hemodynamic optimization protocol applied during the PCA phase is clinically feasible and useful. However, a survival benefit could not be clearly established in part because these studies were bundled with other interventions (eg, mild therapeutic hypothermia [MTH]). Interventions included in these protocols were fluid and pressor administration guided by central venous oxygen saturation ($ScvO_2$), blood lactate, and central venous and arterial blood pressure. At this time, the application and benefit of early hemodynamic optimization in dogs and cats specifically, in the post resuscitative period, is unknown.

Summary of the evidence

Two human retrospective studies (LOE 6, good and fair/supporting) demonstrated that arterial hypotension after resuscitation from cardiac arrest was associated with decreased survival and neurologic outcome indicating the importance of the avoidance of hypotension in the PCA period.[11,12] Myocardial stunning (a phenomenon that arises early after global myocardial ischemia in which left and right ventricular ejection fraction decreases and end diastolic pressure increases reversibly) may contribute to the hemodynamic dysfunction. In a swine model (LOE 6, poor/supporting), myocardial stunning was identified early after CPA, was responsive to inotropic agents and resolved over 24–72 hours.[13,14] Adrie et al (LOE 6, fair/supporting) described in people after CPA an immunologic profile similar to sepsis and coined the term "sepsis-like syndrome" to describe PCA disease.[7]

Early goal-directed hemodynamic optimization (EGDHO), a therapeutic algorithm aimed at timely restoration of the balance between oxygen delivery and demand was effective in significantly improving survival rates in humans with severe sepsis and septic shock (LOE 6, good/supporting).[15] A second human study (LOE 6, poor/neutral) examined the feasibility and effect of a comprehensive bundle of care including hemodynamic optimization, antibiotics, tight glycemic control, steroids, activated protein C, and lung-protective ventilation in septic adults. The investigators reported a relative mortality reduction of 31%; however, the change was not significant.[16] A similarly designed study was employed to test an algorithm for titration of PCA hemodynamic therapy (LOE 6, fair/neutral) in adult humans.[17] The study identified a trend toward improved outcome in the treatment group, but the study was not powered sufficiently to definitively show a treatment effect. Another human study (LOE 6, good/neutral) examined a standardized PCA bundle of care that included EGDHO as well as mild therapeutic hypothermia and early revascularization of coronary occlusions.[18] Those treated with the combination therapy were more likely to survive than historic controls (odds ratio = 3.6, $P = 0.001$). However, EGDHO was coadministered with MTH, thus the isolated effect of EGDHO on outcome could not be determined.

As oxygen delivery to the tissues in relation to oxygen demand is a more important reflection of hemodynamic status than blood pressure alone, the monitoring of global perfusion metrics such as $ScvO_2$ and blood lactate may be important in the postresuscitation patient. In an experimental canine study (LOE 3, fair/supporting), $ScvO_2$ measurements were shown to correlate well with a variety of low perfusion states.[19] Lactate has been reported to be associated with poor survival in systemically ill dogs with sepsis (LOE 5, poor/supporting).[20] Two human studies (LOE 6, fair/supporting), demonstrated that lactate level was inversely associated with the likelihood of survival from CPA.[21,22]

Knowledge gaps

While the benefit and feasibility of a bundle of postresuscitation care elements is relatively well supported for humans, no such evidence exists in clinical veterinary medicine. Specific hemodynamic optimization strategies have neither been proven to be effective in human medicine, nor even tested in veterinary medicine. There are insufficient data available to determine optimal hemodynamic endpoints to be targeted post-CPR, and currently recommended values (eg, for arterial blood pressure, $ScvO_2$, lactate) are extrapolated from other disease processes such as sepsis. Validating these values for their specific application to PCA care is important.

Administration of intravenous fluids (PA01)

PICO Question

In dogs and cats with ROSC after cardiac arrest that have cardiovascular dysfunction (hypotension, hypoperfusion) (P), does IV fluid administration (I), compared to no fluids (C), result in improved outcome (O) (survival to discharge, neurologic function)?

Conclusion

There was no research identified that specifically evaluated the administration versus the withholding of IV fluids after ROSC and the PICO question can therefore not be answered. However, there were observational data

provided in humans and experimental studies that a need for fluids exists, even after primary cardiac arrest, and that the type of fluids may have an impact on recovery. In the absence of clinical data available to instruct a fluid therapy strategy specific to the PCA phase in dogs and cats, it appears reasonable to adjust fluid therapy according to criteria customary to veterinary small animal emergency and critical care.

Summary of the evidence

Two human studies (LOE 6, fair/neutral) used fluids in addition to therapeutic hypothermia as part of standardized PCA care protocols.[18,23] Neither study demonstrated any harmful effects resulting from these protocols, and one[18] found significantly improved survival rates with a favorable neurologic outcome. However, since other interventions were coadministered, the contribution of IV fluids cannot be elucidated.

Several small clinical studies in people with out-of-hospital cardiac arrest (OHCA) (LOE 6, fair or poor/neutral) evaluated rapid infusions of large volumes (2–3 L) of ice-cold fluids shortly after ROSC to induce therapeutic hypothermia and found that these volumes were well tolerated.[24–29] Jacobshagen et al (LOE 6, poor/neutral) demonstrated hypoxemia after resuscitation from OHCA, but it was not associated with the large volumes of cold fluids.[30] These studies in combination demonstrated the fluid tolerance of sudden cardiac arrest patients, although they were not designed to identify a benefit of fluid administration, but rather to show efficacy for cooling and safety. PCA hypovolemia despite positive fluid balance in OHCA patients was identified by transthoracic echocardiography in a small clinical observational study.[29] Heradstveit et al (LOE 6, fair/neutral) identified transvascular fluid leakage, decreased colloid osmotic pressure, and low systemic vascular resistance in the postresuscitation phase as reasons for the need for IV fluid administration in PCA patients.[31] In human studies using standardized resuscitation protocols (LOE 6, fair or poor/neutral), large volumes of IV fluids (3-13 L/person) during the first 24 hours after ROSC were required to meet predefined hemodynamic endpoints.[17,18,31] One human study (LOE 6, fair/neutral) showed that a combination of a colloid and hypertonic saline (HS) reduced the required total fluid volume administered during the first 24 hours after ROSC, but did not examine outcomes.[31] Three porcine studies (LOE 6, good and fair/neutral) using a VF CPA model (where VF is ventricular fibrillation), found that hypertonic-hyperoncotic solutions administered shortly after ROSC provided neurologic and cardiac protection compared to normal saline.[32–34]

Two experimental canine studies (LOE 3, poor/neutral) evaluated the efficacy of cardiopulmonary bypass for resuscitation and neurologic recovery and found better survival and increased cerebral blood flow in those animals that had hemodilution and higher blood pressures, indicating that fluid administration and resuscitation endpoints can impact outcomes.[35,36] However, as outlined in PA02, the resuscitation goals and the optimal interventions to achieve them have not been clearly identified in either human or veterinary patients.

Knowledge gaps

Given the heterogeneity of the PCA population in dogs and cats, and the scarcity of research on fluid balance during the PCA period, no universal recommendation on IV fluid therapy can be made. In veterinary PCA patients, observational data are needed to better understand the fluid deficits and requirements in this population.

The utility of cardioactive and vasopressor drugs (PA03)

PICO Question

In dogs and cats with ROSC that are hypotensive (P), does the use of any particular cardioactive drug/vasopressor (I), compared to standard care (C), result in improved outcome (O) (survival to discharge/neurologic function)?

Conclusion

The evidence for the use of cardioactive/vasopressor drugs to treat PCA hypotension is either neutral or supportive for improved survival and neurologic outcome; however, it is insufficient to make definitive conclusions.

Summary of the evidence

In four human studies, either cardioactive drugs were not the sole intervention[17,18] or cardiovascular parameters were the only outcomes investigated.[13,37] In the study by Sunde et al (LOE 6, fair/supporting), inotropic support improved survival in bivariant, but not multivariant analysis.[18] In a small study ($n = 18$) by Gaieski et al (LOE 6, fair/neutral), the simultaneous use of hypothermia and vasoactive agents demonstrated outcome benefit (survival 78% in the treatment group; 50% in the historic control group) but the difference was not significant.[17]

There were 10 experimental studies using rat and swine CPA models (LOE 6, all supporting) that have

identified cardioactive drugs/vasopressors as being beneficial for post-ROSC myocardial function[14,38–44] and visceral perfusion.[45,46] A study by Huang et al. using a rodent VF model of CPA (LOE 6, fair/supporting) also demonstrated a survival benefit of inotrope use over control.[39]

Three human studies (LOE 6) were neutral to the intervention.[13,17,37] They were poorly powered,[17] noncontrolled,[37] or nonrandomized.[13,37]

Knowledge gaps

Definitive evidence of a beneficial effect of cardioactive/vasopressor therapy for PCA hypotension on outcome does not exist, despite association with better outcomes in some studies. The question has not specifically been addressed in dogs and cats.

Cardioactive/vasopressor drugs in to induce mild hypertension (PA04)

PICO Question

In dogs and cats with ROSC (P), does the institution of mild hypertension via the use of any particular cardioactive drug/vasopressor (I), compared to standard care (C), result in improved outcome (O) (survival to discharge neurologic function)?

Conclusion

The evidence suggests that hypertension following ROSC may be associated with better neurologic intact survival; however, the nature of the association (ie, causal versus casual) is not known.

Summary of the evidence

Evidence from one experimental study in dogs (LOE 3, good/supporting)[47] supported indirectly by two additional experimental studies in dogs (LOE 3, fair/supporting)[48,49] indicated that after prolonged untreated CPA, hypertensive reperfusion with a mean arterial pressure (MAP) of greater than 150 mm Hg may be associated with better survival and neurologic outcome.

A clinical study in humans (LOE 3, poor/neutral) retrospectively evaluated MAP in the first minutes after ROSC by dividing patients into a high MAP (>100 mm Hg) or low MAP (≤100 mm Hg) group.[50] Interestingly, what was considered hypertension in this human study was considered normal control in the canine studies. There was no statistically significant difference in neurologic outcomes between groups, but 5 of the 6 patients achieving MAP of at least 150 mm Hg survived with good neurologic status.

In a primate model of global brain ischemia without cardiac arrest (LOE 6, poor/opposing), a repetitively induced increase of the MAP with norepinephrine to 150–190 mm Hg for 3–5 minute periods during the first 48 hours postischemia was associated with a worse neurologic outcome.[51] This would not favor the intervention; however, post hoc analysis revealed if MAP was raised rapidly to normal levels after reperfusion and then maintained at a normal or slightly elevated level, neurological outcome was better than in animals in which MAP was raised slowly or was low for prolonged periods after reperfusion.

In a swine model of OHCA (LOE 6, poor/opposing) examining the effect of norepinephrine-induced hypertension on myocardial oxygen use, 9 of 10 animals achieved a spontaneous hypertension bout immediately after ROSC.[52] Induction of hypertension with norepinephrine for 15 minutes (mean aortic pressure 95 mm Hg versus 73 mm Hg in the control group) significantly increased oxygen use in the myocardium, increasing the risk of myocardial hypoxia.

Increased survival was seen in a rat asphyxial arrest model (LOE 6, poor/supportive) when PCA care included mild hypothermia combined with induced hypertension, compared to controls.[53] There was no benefit in recovery of neurological function in surviving animals, and the effect of hypothermia versus hypertension could not be isolated.

Knowledge gaps

Validating that hypertension in dogs and cats in the PCA period is a causative effector versus positive outcome marker could lead to establishing the timing, duration, and level of hypertension to be targeted.

Support of Ventilation and Oxygenation

Rapid normalization of blood oxygen, carbon dioxide, and pH, and reoxygenation of ischemic tissues is a prime objective of the PCA period. The partial pressure of carbon dioxide in arterial blood ($PaCO_2$) has an important regulatory influence on cerebral blood flow; alveolar minute ventilation regulates $PaCO_2$ and control of it may have survival benefit. In addition, ventilation plays a major role in acid-base homeostasis, impacting numerous cellular and subcellular processes. Arterial oxygenation is a major determinant of oxygen delivery, and assuring normoxemia may have a survival benefit. Oxygen is, however, a major source of reactive oxygen species (ROS) excessive amounts of which could be harmful.[54] In this section, the importance of ventilation (PA06) and

oxygenation (PA08) strategies in the PCA period is examined.

Ventilation in the PCA period (PA06)

PICO Question

In dogs and cats with ROSC after cardiac arrest (P), does normocapnia (± via positive pressure ventilation [PPV]) (I), compared to hyper- or hypocapnia (C), result in improved outcome (O) (survival to discharge and neurologic function)?

Conclusion

There are few studies investigating the effect of carbon dioxide manipulation post-ROSC and the available evidence does not support or refute the benefit of normo-, hypo-, or hypercapnia after ROSC.

Summary of the evidence

Two studies suggest a potential benefit of hypocapnia after ROSC. One study in an experimental cat VF cardiac arrest model (LOE 3, fair/opposing) improvements in cerebrovascular CO_2 responsiveness and decreased intracranial pressures were reported after 3 hours of hyperventilation ($PaCO_2$ of 15–20 mm Hg) compared to normoventilation (40–45 mm Hg); however, EEGs and cerebral blood flow were not different between the groups and neurological function was not examined.[55] In a dog study of prolonged cardiac arrest (LOE 3, poor/opposing), histopathological neuronal damage after ROSC was reduced by maintaining $PaCO_2$ of 15–20 mm Hg compared to normocapnia.[56]

One study in dogs (LOE 3, poor/supporting) and one in humans (LOE 6, fair/supporting) support normocapnia to improve CNS blood flow, neurologic function, and histopathological neuronal damage; however, these studies included multiple simultaneous interventions.[18,49]

The incidence of mortality in patients undergoing PPV after CPA has been described in a human study (LOE 6, poor/neutral)[57] and in a retrospective study in cats (LOE 4, poor/neutral), although the design of these studies does not allow any conclusion regarding the effect of PPV on outcomes.[58] These studies evaluated a population of ventilated patients of which a subgroup was PCA. In the human study, 1.9% of 15,757 cases had been resuscitated from CPA and had a statistically significant increased risk of ICU mortality (odds ratio of 1.45) compared to the overall population. In the feline study, 1 of 9 cats that were ventilated after CPA survived to hospital discharge.

Knowledge gaps

Additional studies are needed to determine if manipulation of carbon dioxide concentrations has therapeutic value in dogs and cats in the PCA period.

Oxygen supplementation post-ROSC (PA08)

PICO Question

In dogs and cats with ROSC after cardiac arrest (P), does the administration of 100% oxygen (I), compared to titration to normoxia (eg to $SpO_2 > 94\%$) (C), result in improved outcome (O) (survival to discharge or neurologic function)?

Conclusion

There is, in both quantity and quality, good evidence to advocate normoxia/normoxemia versus hyperoxia/hypoxemia in the early PCA period.

Summary of the evidence

In a small clinical study including 28 people successfully resuscitated from OHCA and randomized to hyperoxia versus normoxia early post-ROSC (LOE 6, fair/supporting), significantly higher levels of neurospecific enolase, a marker of neuronal injury, were found in subjects treated with 100% oxygen.[59] In an experimental swine study (LOE 6, fair/supportive), animals resuscitated with bypass and controlled, slow reoxygenation from hypoxia to normoxia versus immediate normoxia showed lower weaning rates off bypass, but had lower concentrations of ROS in coronary sinus blood.[60] A study in rats (LOE 6, good/neutral), in which normoxia during and after CPR was compared with hyperoxia showed no effect of treatment group on neuronal cell death, survival, and neurologic outcome.[61] Zwemer et al conducted a study in a canine CPA model (LOE 3, good/neutral) in which two different levels of hypoxic resuscitation were compared with normoxia.[62] Hypoxia resulted in worse neurologic function and lower overall survival rate, while plasma ROS concentrations were elevated in all groups to a similar degree. Overall this study indicated that normoxic reperfusion is preferable over a hypoxic strategy.

Several experimental studies of good quality in dogs (LOE 3, good/supporting) provide strong evidence in support of a normoxic strategy during or soon after reperfusion compared to a hyperoxic approach.[63–69] In addition, the findings in four clinical studies in people (LOE 6, good/supporting or neutral) suggest the superiority of normoxic over hyperoxic reperfusion.[70–73] These studies collectively were comprehensive with respect to

examining endpoints, making for a strong argument for normoxia even in the absence of LOE 1 or 2 studies.

Knowledge gaps

Clinical canine and feline trials are needed to strengthen the conclusion that hyperoxemia during the PCA period is harmful. Surrogate outcome measures, such as ROS determination, would be acceptable metrics for such studies.

Hypothermia after Cardiac Arrest

MTH, the lowering of the patient's core temperature to 32–34°C, is widely used in human patients that remain comatose after ROSC. The widespread clinical application of MTH is in response to the successful use of postarrest therapeutic hypothermia in two landmark trials.[25,74] Two PICO questions (PA10 and PA11) were evaluated to examine the evidence for temperature management in the post-ROSC period in dogs and cats.

Use of hypothermia after cardiac arrest (PA11)

PICO Question

In dogs and cats that remain comatose after resuscitation from cardiac arrest (P), does a specific onset, level, and duration of therapeutic hypothermia (I), compared to normothermia (C), improve outcome (O) (neurologic intact survival)?

Conclusion

The preponderance of evidence from clinical human and experimental canine studies suggest a beneficial effect on neurologic intact survival of mild hypothermia (core temperature of 33 ± 1°C) instituted as soon as possible and maintained for >12 hours.

Summary of the evidence

There are a large number of experimental canine studies examining the benefit of therapeutic hypothermia for disorders other than cardiac arrest care, but these were not used to address this PICO question. Two studies in a canine VF CPA model (LOE 3, good and fair/supporting),[75,76] a study in a rodent asphyxial CPA model (LOE 6, good/supporting),[77] and several human studies (LOE 6, good/supporting)[25,74,78–82] were evaluated, as they most closely resembled the population in question. All of these studies were in support of the intervention with the one dog[75] and rat[77] studies considered to be good evidence. Only one retrospective study in humans (LOE 6, fair/neutral) showed no benefit or harm of MTH in subjects in which the first identified rhythm was asystole or PEA.[83]

Knowledge gaps

Studies addressing the clinical application of MTH in veterinary patients are needed. The safety, practicality, and efficacy of methods of reaching and maintaining target temperatures should be evaluated, allowing for the validation of the onset, level, and duration of optimal hypothermia in dogs and cats.

Rewarming rate after cardiac arrest (PA10)

PICO Question

In dogs and cats with ROSC after cardiac arrest (P), does rewarming at a certain rate (°C/hour) (I), compared to fast rewarming to normal temperature (C), improve outcome (O) (neurologic intact survival)?

Conclusion

Although the evidence is lacking with respect to specific rates of rewarming after accidental or therapeutic hypothermia, slower rewarming rates appear preferred over faster ones in a number of related populations and evaluated endpoints.

Summary of the evidence

While there were no studies in dogs during the PCA period comparing rates of rewarming, the findings of three experimental studies (LOE 3, good/supporting)[84–86] and one dog case report (LOE 5, poor/supporting)[87] suggest slow rewarming is indicated. Additionally, studies on rewarming in rats (LOE 6, good/fair/supporting) provide evidence for the benefit of a slow rewarming rate.[88,89] Findings in experimental models in dogs (LOE 3, good to fair/neutral)[49,90–101] and other species (LOE 6, good to poor/neutral)[102–104] did not provide evidence of a treatment benefit of slow versus fast rewarming; however, no studies were found that documented harm associated with a slow rewarming rate.

Knowledge gaps

Studies directly comparing rewarming rates post-ROSC are lacking, and these techniques need to be evaluated in dogs and cats.

Neuroprotective, Metabolic, and Supportive Strategies

A number of additional supportive strategies have been employed in an attempt to improve outcomes in PCA, including corticosteroids, anticonvulsants, mannitol, and various metabolic protectants. Additionally, in this review, bundled (combination) therapies and the issue of specialty care facilities were evaluated.

Corticosteroid use after ROSC (PA13)

In 1964, R.C. Lillehei published a manuscript that demonstrated improved outcome in hypovolemic and cardiogenic shock with corticosteroid treatment.[105] Early veterinary[106] and human clinical trials[107,108] reported improved survival in sepsis and septic shock; however, subsequent clinical trials failed to substantiate those findings.[109–112] Given the uncertain role of steroids in the management of global ischemic diseases, their use in the PCA period was investigated.

A more focused use of corticosteroids has been described for relative adrenal insufficiency. In 1991, Rothwell reported that patients with adrenal insufficiency and septic shock faired very poorly.[113] Relative adrenal insufficiency has been identified in PCA patients[114] and has been associated with poor outcomes.[115] Early studies[116–119] suggested that low-dose corticosteroid treatment (hydrocortisone) allowed withdrawal of pressors and improved survival from sepsis and hospital discharge rates, but this was not demonstrated in the latest study.[120]

PICO Question

In dogs and cats with ROSC after cardiac arrest (P), does the administration of corticosteroids (I), compared to standard care (C), result in improved outcome (O) (survival to discharge, neurologic outcome)?

Conclusion

There is insufficient evidence to answer the question, and specific recommendations relative to the administration of corticosteroid post-ROSC cannot be made based on the available information.

Summary of the evidence

A comprehensive review of the literature found no clinical studies in dogs or cats that were relevant to the question. One prospective canine laboratory study (LOE 3, poor/neutral) reported that a group that received methylprednisolone (130 mg/kg) had better neurologic, overall performance, and brain histopathologic injury scores than did other groups not receiving methylprednisolone, but this group concurrently received thiopental (30 mg/kg) and phenytoin (15 mg/kg), and so the beneficial effects could not be attributed specifically to the methylprednisolone.[121]

In a prospective rat study (LOE 6, fair/neutral), comparing preasphyxial cardiac arrest placebo and methylprednisolone, and PCA placebo and methylprednisolone, only the PCA methylprednisolone group exhibited return of EEG activity 20 minutes post-ROSC and required no norepinephrine for blood pressure support. Although the mean cytosolic and lysosomal enzyme levels were lower in the postarrest methylprednisolone group compared to the other groups, the differences did not reach statistical significance.[122] Since this was a nonsurvival study, it does not directly address the outcome measures of this PICO question.

Two cohort, retrospective, human clinical studies (LOE 6, fair/neutral) reported no beneficial effects of corticosteroid treatment.[123,124] A prospective, human clinical study (LOE 6, good/neutral) reported that vasopressin and methylprednisolone treatment was associated with a significant improvement in ROSC; however, there was a trend towards a higher incidence of PCA shock (defined as the need for increased vasopressor/inotropic support) in the treatment group.[125] This study is confounded by the concurrent use of vasopressin. In patients experiencing PCA shock, low-dose hydrocortisone infusion resulted in improved hemodynamics and central venous oxygen saturation, more organ failure – free days, and improved survival to hospital discharge. While this study exhibits confounding issues relative to the question, it suggests that corticosteroids, as part of a bundled approach, during resuscitation may improve ROSC and low-dose hydrocortisone therapy post-ROSC may improve survival.

Knowledge gaps

There are no clinical studies in dogs and cats. The studies that are available, relevant to the question, are confounded by concurrent drug therapy, variable dosing, and variation in the types of corticosteroids administered such that it is not possible to ascertain whether corticosteroids alone made for significant improvement in patient outcome. Future studies should address the question directly and criteria that identify patients who might be benefited or harmed by corticosteroid therapy should be developed and validated.

Seizure prophylaxis post-ROSC (PA14)

In humans, seizures and myoclonus occur in 5–15% of adult patients in the PCA period and in 40% of patients

who remain comatose after ROSC.[5] In people, postanoxic myoclonus status epilepticus was associated with poor neurologic outcome.[126]

PICO Question

In dogs and cats with ROSC (P), does seizure prophylaxis (I), compared to standard care (C), result in improved outcome (O) (decreased seizure activity, survival to discharge, neurologic function)?

Conclusion

There are no clinical studies in animals that document the incidence of seizures post-ROSC. The effects of anticonvulsants in experimental models of interest are inconsistent, while use in humans has not demonstrated long-term benefit.

Summary of the evidence

There are two prospective, clinical studies in human adults. Thiopental administration to PCA comatose people (LOE 6, good/neutral) was associated with reduced seizure activity, reduced intracranial pressure and edema formation, reduced brain metabolism, and focal brain damage, but failed to significantly improve 1-year neurologic outcome.[127] The administration of magnesium and/or diazepam (LOE 6, good/neutral) did not change neurologic function in PCA, normotensive, comatose people.[128] The incidence of, or reduction in, seizure activity was not evaluated.

A therapeutic approach (LOE 6, fair/supporting) that bundled control and prevention of seizures with other interventions (therapeutic hypothermia, percutaneous coronary intervention [PCI], control of hemodynamics, blood glucose, and ventilation) was associated with improved discharge rate from the hospital, neurologic outcome, and 1-year survival.[18]

In severe perinatal asphyxia in children (LOE 6, good/supporting), treatment with phenobarbital (40 mg/kg) was associated with a 27% reduction in the incidence of seizures and a significant improvement in neurologic outcome at 3 years of age.[129] In contrast, thiopental (30 mg/kg) in another study of perinatal asphyxia (LOE 6, good/opposing) was not associated with neurologic benefit, but caused significant arterial hypotension.[130] In a feline experimental VF CPA model (LOE 3; good/supporting), thiopental administration (60 mg/kg) significantly reduced the incidence of repetitive, rhythmic bursts of high-frequency electroencephalographic (EEG) activity and improved survival rates.[131] However, among survivors, there was no benefit on neurologic function (neutral).

A bundled therapeutic approach that included seizure prophylaxis (thiopental, phenytoin, methylprednisolone) in an experimental canine cardiac arrest model (LOE 3; fair/supporting) was associated with improved neurologic and overall performance and brain histopathologic damage scores compared to other groups.[121]

Knowledge gaps

The frequency of post-ROSC seizures in dogs and cats needs to be established, as does the efficacy of seizure prophylaxis.

Mannitol and hypertonic saline after cardiac arrest (PA15)

Cerebral edema after cardiac arrest has been described in people, and its occurrence appears to be correlated with poor outcome.[132,133] Cerebral edema may occur with or without intracranial hypertension.[132] Both mannitol and HS have been recommended in dogs and cats if cerebral edema or elevated intracranial hypertension are suspected.[134,135]

PICO Question

In dogs and cats with ROSC after cardiac arrest (P), does the administration of mannitol or HS (I), compared to standard care (C), result in improved outcome (O) (survival to discharge; neurologic function)?

Conclusion

No controlled clinical or experimental trials in any species were identified on the use of mannitol after CPR. A prospective observational veterinary study detected an association between mannitol administration and improved outcome, when the drug was given during CPR. No specific recommendation can be made for or against the routine use of either mannitol or HS after cardiac arrest.

Summary of the evidence

A retrospective veterinary study (LOE 4, fair/neutral) mentions mannitol use during CPR in dogs and cats; however, its effect on outcome was not reported.[4] A prospective observational veterinary study (LOE 2, poor/neutral) reported that intra-arrest mannitol administration was associated with improved survival; however, the study was not designed to determine a causal relationship.[3] HS was reported to improve myocardial blood flow and myocardial perfusion

pressure (LOE 6, poor/supporting)[136,137] and to increase cerebral blood flow (LOE 6, poor/supporting)[138] in a porcine cardiac arrest model. A single small pilot study in people suggested that the combination of HS and hydroxyethyl starch may improve short-term survival (LOE 6, poor/supporting),[139] but this was not confirmed in a subsequent randomized controlled trial (LOE 6, good/neutral).[136] One study in a porcine CPA model reported that HS administration attenuated myocardial and cerebral damage (LOE 6, fair/supporting).[32]

Knowledge gaps

Clinical experience in individual patients suggests that mannitol can be efficacious in the management of deteriorating neurologic status. There have been no controlled clinical or experimental trials in any species regarding the efficacy of mannitol after CPR. There are also no prospective clinical studies in dogs and cats regarding HS; however, experimental evidence in other species suggests a benefit.

Metabolic protection and post-ROSC (PA17)

Survival or death (apoptosis or necrosis) of the organelle, organ, and individual, depends upon the balance between energy production and utilization within individual, and among all, mitochondria. If ATP depletion is mild, cells and organelles are capable of a full recovery once spontaneous circulation has been restored. Progressively more severe magnitudes of ischemia result in mitochondrial apoptosis or necrosis.

Cells and mitochondria are adversely affected by the hypoxia of the CPA and subsequently by reperfusion injury. During the period of hypoxia, mitochondria sequester large amounts of calcium, activating the mitochondrial permeability transition pore (mPTP). Activation of the mPTP occurs early after reperfusion; however, its activation during ischemia is inhibited by the acidosis present during CPA. An intact and impermeable inner mitochondrial membrane is vital to regulation of the accumulation of hydrogen ions in the intermembrane space (generated by the electron transport chain). It is this hydrogen and electrical gradient that drives the ATP synthase (complex V) phosphorylation of ADP to ATP. Activation of the mPTP leads to increases in ROS. These highly unstable oxygen and nitrogen radicals cause lipoperoxidation of all organelle and cell membranes, cause DNA strand breakage, and also activate the mPTP.

DNA damage activates poly-ADP-ribose polymerase (PARP), a family of DNA repair enzymes. While it is important to repair damaged DNA, these enzymes consume a considerable amount of energy at a time when energy production is severely compromised by mitochondrial dysfunction. The goal of metabolic therapeutic strategies is to reduce some or all of the above described injurious processes that occur during the reperfusion process from prolonged CPA.

PICO Question

In dogs and cats with ROSC after cardiac arrest (P), does the use of metabolic protectants (ethyl pyruvate, PARP inhibitors, mitochondrial protectants, antioxidants (I), as opposed to standard care (C), improve outcome (O)?

Conclusion

There are no clinical studies in dogs and cats relative to this PICO question. Experimental studies in dogs, cats, piglets, and rodents are short term survival studies, and therapy is often administered before ROSC. Studies did not address long-term survival in any manner that would equate to "hospital discharge." A heterogeneous group of therapeutic strategies were studied and no single mechanistic target or drug has risen to the top for serious consideration for clinical trials. There have been no clinical studies of metabolic protectants in humans. The evidence, to date, can only be described as suggestive and promising.

Summary of the evidence

Inhibition of the Na^+/H^+ counter exchanger and of membrane sodium channels has been reported to reduce intracellular and mitochondrial calcium overload (LOE 6, good/neutral),[140] to diminish myocardial (LOE 6, good/supporting)[141,142] and neuronal damage, and to improve myocardial (LOE 6, good/supporting),[141–143] (LOE 6, good/neutral)[140] and neuronal function, secondary to ischemia-reperfusion, and to improve ROSC (LOE 6, good/supporting).[143] The proposed mechanism of benefit of limiting intracellular sodium accumulation is via limiting intracellular calcium accumulation. In this regard, inhibition of the release of the neurotransmitter glutamate (LOE 6, fair/neutral)[144,145] or inhibition of the neuronal glutamate receptor[145,146] was also shown to diminish secondary neuronal degeneration after traumatic brain injury or ischemia-reperfusion injury in some but not all (LOE 3, fair/neutral)[147] studies. There were few studies that evaluated calcium channel blockers PCA[145]; one (LOE 6, poor/neutral)[148] reported reduced neuronal degeneration.

There have been several different antioxidants, administered during or after resuscitation, which have been evaluated for their PCA efficacy: alpha-phenyl-tert-butyl-nitrone (PBN) (LOE 6, good/supporting);[149]

nitrite (LOE 6, good/supporting;[150] 21-aminosteroids (LOE 3, fair/supporting);[69,151] methylene blue (LOE 3, fair/neutral).[152] In general, antioxidants are associated with reduced markers of oxidative damage (PBN, Nitrite) (LOE 6, good/supporting), improved mitochondrial function (PBN, Nitrite) (LOE 6, good/supporting), improved cardiovascular function (PBN, Nitrite) (LOE 6, good/supporting), reduced neurologic damage (PBN, Nitrite, [LOE 6, good/supporting] 21-aminosteroids, [LOE 3, fair/supporting] methylene blue, [LOE 3, fair/neutral]), and improved survival (PBN, Nitrite, [LOE 6, good/supporting], 21-aminosteroids [LOE 3, fair/supporting]). Some antioxidant therapies did not provide demonstrable post-CPR outcome benefit (N-acetylcysteine, [LOE 3, fair/neutral],[153] superoxide dismutase/catalase [LOE 3, fair/neutral].[154])

Therapies that block the mPTP, such as hydrogen sulfide[155] and cyclosporine A,[156] were reported to improve survival and neurologic, and myocardial function (LOE 6, good/supporting).[157] A study that combined the free radical scavenger PBN and the mPTP blocker cyclosporine (LOE 6, good/supporting)[158] resulted in more rapid ROSC and improved 24-hour neurological scores in a piglet model of cardiac arrest. The search found no relevant articles regarding the inhibition of PARP enzymes PCA.

A few studies have evaluated preservation of mitochondrial function by providing metabolic substrates such as adenosine[159] or pyruvate.[160] These therapies generally were reported to improve survival (adenosine) (LOE 6, fair/neutral)[159], to enhance myocardial function (pyruvate) (LOE 3, fair/neutral),[160] and to decrease neurological injury (adenosine) (LOE 6, fair/neutral).[159] One study of ethyl pyruvate reported no benefit (LOE 6, fair/neutral).[161]

Knowledge gaps

There is a need to identify whether one or multiple interventions effectively interfere with the cellular and mitochondrial pathologies that lead to organ dysfunction following cardiac arrest. Subsequent clinical trials will be required to determine if these promising intervention(s) are effective and safe in the treatment of complex clinical disease following cardiac arrest.

Bundled therapy post-ROSC (PA19)

It is challenging to ascertain outcome benefit of a single intervention in a complex disease state with a low incidence of survival. Studies are criticized when they incorporate multiple interventions, even if the treatment is demonstrated to be efficacious, because it is unclear which component of the combination therapy provided the benefit. And yet it may well be that individual treatments are ineffective in treating complex disease and that, in fact, complex (bundled) therapy may be necessary. In addition, there is no standard definition of what comprises "a comprehensive care protocol" and how it is different from "standard care" and it is in the context of this amorphous background that we ask this PICO question.

PICO Question

In dogs and cats with ROSC after cardiac arrest (P), does the use of a comprehensive treatment protocol (I), as opposed to standard care (C), improve outcome (eg, survival) (O)?

Conclusion

There are no clinical studies that evaluate this PICO question. Laboratory studies suggest that hypothermia, hypertension, and normocapnia (compared to normothermia, normotension, and hypocapnia) improve neurologic outcome in the PCA period, as described previously in this review. Hemodilution may or may not contribute to these beneficial effects. Combination therapies such as thiopental, methylprednisolone, and phenytoin, and perhaps antioxidants, may enhance neurologic recovery from cardiac arrest.

Summary of the evidence

Mild therapeutic hypothermia (34.2°C compared to 37.6°C), hemodilution (PCV 31% versus 41%), and normocapnia (36 mm Hg versus 30 mm Hg) were associated with significantly better overall performance, reduced neurologic deficit, and histopathologic damage scores 96 hours after ROSC in a canine CPA model (LOE 3, good/supporting).[162] In a previous study from the same laboratory (LOE 3, fair/supporting) norepinephrine-induced hypertension (initially MAP > 200 mm Hg with a sustained MAP > 140 mm Hg compared with a MAP of 100 mm Hg) significantly improved neurologic performance; hypervolemic hemodilution did not further improve outcome.[47] In a follow-up study (LOE 3, fair/neutral), hypothermia was again demonstrated to improve neurologic outcome. Neurologic outcome was further improved with the addition of thiopental and thiopental/methylprednisolone/phenytoin, although only a few of the improvements were significant.[121] In another follow-up study (LOE 3, fair/neutral), the overall performance score, but not the histopathologic damage score nor markers of oxidative damage, were improved with the antioxidant Tempol.[163] Canine patients in one

veterinary study (LOE 2, poor/supporting) were more likely to survive if they were treated with mannitol, lidocaine, fluids, dopamine, corticosteroids, or vasopressin.[3]

A relevant human study (LOE 6, fair/supporting) demonstrated a strong trend toward a treatment benefit of hemodynamic optimization in addition to hypothermia.[17] Several human studies (LOE 6, fair/supporting) demonstrated that failure to adhere to resuscitation guidelines resulted in a significant decrease in survival metrics.[83,164,165]

Knowledge gaps

With regard to this PICO question, there is no established comprehensive PCA treatment protocol that has been shown to be superior. Studies combining interventions believed to be beneficial (followed by those thought but not proven to be effective) to search for additive and even synergistic treatment effects are needed.

Specialty centers and post-ROSC care (PA20)

There is some evidence that intensivist-led human ICUs have better outcomes (Silverman et al., 2011), and although cardiac arrest outcomes in a pediatric intensive care unit were improved with more experience of the primary care nurse, outcomes were not statistically improved by the presence of the senior intensive care unit attending physician (Gaies MG, 2011). With regard to PCA care, the specialist should be adept at cardiopulmonary-cerebral-renal-fluid/electrolyte-metabolic care, in other words, an intensivist. Although perhaps implied, a "specialty center" does not necessary equate to having the services of an intensivist (as indeed, many veterinary hospitals in the United States with this designation do not).

PICO Question

In dogs and cats with ROSC after cardiac arrest (P), does post-CPR care in a specialty center (I), compared to post-CPR care in a nonspecialty center (C), provide better outcomes (O) (eg, survival rates or neurologic outcomes)?

Conclusion

While transfer of post-ROSC patients to a specialty center for care seems quite reasonable, there are no clinical veterinary studies that specifically address this question. The only veterinary study even remotely relevant to this PICO question reported that dogs that survived were more likely to have been treated with multiple drugs and with more people involved.[3] Human studies suggest that PCA patients may have better outcomes when treated in specialty facilities with more PCA treatment experience.

Summary of the evidence

The only veterinary study even remotely relevant to this PICO question (LOE 2, poor/neutral) reported that dogs that survived were more likely to have been treated with mannitol, lidocaine, fluids, dopamine, corticosteroids, or vasopressin and that cats were more likely to survive if they had more people participate in the resuscitation efforts.[3] Several human studies of in-hospital (LOE 6, good/supporting),[166] (LOE 6 fair/supporting)[23,167] and OHCA (LOE 6, fair/supporting)[168,169] that were successfully resuscitated suggest that centers with more experience in post-ROSC care and higher care-giver-to-patient ratio are associated with higher survival rates.

Knowledge gaps

There are no clinical veterinary studies addressing whether referral to a specialty center has outcome benefit.

Discussion

There is a large discrepancy between the number of animals in which ROSC is achieved and the number of animals that are ultimately discharged from the hospital, suggesting that improved PCA therapeutic strategies may improve outcomes.[3,4] Such a conclusion must, however, be tempered by the fact that many cardiac arrests are associated with a lethal underlying disease processes.

Beyond post hoc analyses of case series, there are no veterinary clinical studies evaluating post-ROSC interventions in the dog and cat. There are relatively few experimental (LOE 3) studies in dogs and cats, and few experimental studies in other species such as rats and swine (LOE 6). Taken in total with the modest number of clinical studies in people (LOE 6), these studies provide evidence that can be used to support some veterinary recommendations at this time. They include:

Hypoxemia and hyperoxemia should be avoided; normoxemia is the goal. Mild hypothermia has a positive effect on outcome, but there is no evidence that suggests a specific rewarming rate beyond the notion that rewarming should occur slowly (e.g., less than 1°C/hour).

Although there is no evidence that corticosteroids administered during resuscitation have a survival advantage, there is some suggestion that a relative adrenal insufficiency syndrome exists post-ROSC (in people) and that in such patients corticosteroid replacement therapy may improve survival.

Perhaps surprisingly, there is no consensus on carbon dioxide management in the postresuscitation period. Some studies support maintenance of normocapnia while others support hypocapnia. Hypercapnia should be avoided.

Although intuitively advantageous and somewhat supported by research in people, there is no clear evidence that hemodynamic optimization has survival benefit in dogs and cats. Also lacking is a definition of "hemodynamic optimization." It will be difficult to design and interpret such studies without a clear target. Clearly, the issue must be more precisely defined than "fluids versus no fluids" or "crystalloids versus colloids." Blood pressure might be a starting point for hemodynamic optimization; studies suggest that hypotension and severe hypertension are associated with worse outcomes and that normal to high-normal blood pressures may be associated with better outcomes. But even this conclusion is problematic because the definition of hypo-, versus normo-, versus hypertension varied among the studies. And perhaps this concept is misdirected because "appropriate" blood pressure must be related to intracranial pressure, since cerebral perfusion pressure (the difference between mean arterial pressure and intracranial pressure) is the primary determinant of cerebral perfusion. Studies that evaluate blood pressure without regard to such relationships may be doomed to show "no significant difference." Without this foundation, we are not even close to determining if one drug is superior to another for blood pressure support or hemodynamic optimization.

There is no evidence that prophylactic antiseizure therapy is efficacious in dogs and cats, nor has it even been established that PCA seizures are a problem in these species. There are no experimental or clinical studies in any species that evaluate survival benefit of any metabolic protectant.

Most of this review has focused on the efficacy of single interventions. It may well be that single interventions are not strong enough to overpower the ravages of a CPA. Therefore, the question of bundled therapy, a shotgun approach to many of the suspected problems, may be what is needed. From a mechanistic point of view, it is convenient to demonstrate the efficacy of single therapies, but from a patient point of view, survival with good neurologic function is the only thing that is important. Intuitively, a bundled, comprehensive resuscitation plan should have outcome benefit but there is little evidence to define what that should be.

The last question we asked was whether referral to a specialty center would result in better outcomes in PCA patients, and again found minimal literature to support a recommendation. Experimental animal studies and clinical human trials do suggest that more intensive, goal-directed therapy has survival benefit, but no studies evaluate who might be better at providing that care.

This investigation has identified what we know and do not know about caring for patients who have suffered a CPA and ROSC. The paucity of information creates great opportunity for clinical research. Hypothesis-testing clinical CPR studies in veterinary medicine will be challenging to accomplish given the small numbers of animals with which we deal. Studies are perhaps doable if the objectives are clearly and ethically defined, and cooperative efforts can be organized.

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Appendix

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