WORKSHEET for Evidence-Based Review of Science for Veterinary CPCR

1. Basic Demographics

Worksheet author(s)

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[redacted]

2. Clinical question:

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

3. Conflict of interest specific to this question:

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet?

- No conflict of interest -

4. Search strategy (including electronic databases searched):

1) Medline via Pub Med
2) CAB abstracts 1990 to present

4a. Databases

Medline via Pub Med

1) Cardiopulmonary resuscitation
2) Hypocalcemia
3) Hypercalcemia
4) Calcium
5) Hypokalemia
6) Hyperkalemia
7) Potassium

1 and 2: 10 relevant hits out of 17
1 and 3: 0 relevant hits out of 3
1 and 4: 60 relevant hits out of 209
1 and 5: 9 relevant hits out of 22
1 and 6: 30 relevant hits out of 71
1 and 7: 27 relevant hits out of 112

CAB abstracts 1990 to present

1) Cardiopulmonary resuscitation
2) Hypocalcemia
3) Hypercalcemia

4) Calcium
5) Hypokalemia
6) Hyperkalemia
7) Potassium

1 and 2: 0 relevant hits out of 1
1 and 3: 0 relevant hits out of 1
1 and 4: 1 relevant hits out of 3
1 and 5: 0 relevant hits out of 0
1 and 6: 0 relevant hits out of 0
1 and 7: 0 relevant hits out of 1

4b. Other sources

None

4c. State inclusion and exclusion criteria for choosing studies and list number of studies excluded per criterion

Inclusion criteria
Human and animal experimental studies, human and animal retrospective studies and human and animal prospective studies involving cardiopulmonary resuscitation (CPR) in which calcium and/or potassium were measured, and the CPR associated abnormalities associated with altered calcium or potassium were evaluated. In addition, to studies in which calcium and/or potassium were measured and if abnormal then corrected and the outcome evaluated.

Exclusion criteria
Review articles and articles involving calcium and potassium abnormalities but not associated with true cardiac arrest (i.e. hyperkalemia causing bradycardia with pulses)

4d. Number of articles/sources meeting criteria for further review:

Twelve

5. Summary of evidence

Evidence Supporting Clinical Question

Good						
Fair						
Poor			• Niemann 1999 E (increased potassium and decreased calcium associated with arrhythmia) (potassium and calcium)			• Youngquist 2010 A (calcium) • Lee 1994 case report, (potasium) • Costa 1993 case report (potassium) • Lin 1993 retrospective case review, (potassium) • Kao 2000 case report (potassium) • Geddes 2006 E (increased potassium associated with arrhythmia) (potassium) • Seidler 2011 E (decreased potassium associated with arrhythmia) (potassium) • Srinivasan 2008 ABCD (calcium)
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Non-target species studies

Evidence Neutral to Clinical question

Good						
Fair						
Poor			• Best (no change in Ca in CPR patients) (calcium) • Bleske (decreased calcium in CPR patients) (calcium)			• Gando (decreased calcium in CPR patients) (calcium)
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Non-target species studies

Evidence Opposing Clinical Question

Good						
Fair						
Poor						
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Non-target species studies

6. REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Calcium

It is shown in some studies that in a CPR patient that blood Calcium (Ca) levels may be decreased and associated with arrhythmias seen in cardiac arrest. Ca administration has been recommended in a CPR setting,[1] particularly if Ca levels are low, which is the focus of this review. Other situations in which Ca should likely be administered include: Ca channel blocker overdose, hyperkalemia, and hypermagnesemia.[2,3,4] Calcium is an important ion because of its role in myocardial excitation contraction coupling. However, Ca may have many harmful effects in a CPR situation, particularly if blood Ca levels are elevated above normal or if intracellular levels are elevated due to hypoxia and ischemia during CPR. Although some studies have shown low blood Ca levels during CPR, Ca levels may be elevated within the cell during a CPR situation due to failure of Ca sequestering mechanisms. [5] Elevated Ca may cause decreased energy production, cellular apoptosis and necrosis, and induce reperfusion injury and inflammation.[4,6,7,8] Evidence that Ca may be harmful is demonstrated by the fact that Ca channel blockers may improve the outcome in some CPR patients.[1,8]

Three studies may support the use of Ca in hypocalcemic patients but the support is weak

One human retrospective study (LOE 6, poor) indicated Ca may be harmful in CPR patient without hypocalcemia but beneficial in patients with hypocalcemia or hyperkalemia. Srinivasan[2] conducted a human retrospectives study in 2008 evaluating the number of in hospital pediatric cardiopulmonary resuscitation patients that were given Ca. (Calcium Use During In-Hospital Pediatric Cardiopulmonary Resuscitation: A Report From the National Registry of Cardiopulmonary Resuscitation). The study included all patients that required CPR including patients with pulses and excluded patients with implanted defibrillators and out of hospital arrest. The primary outcome was survival to hospital discharge. Secondary outcomes included survival of event and neurologic outcome. The study showed that in pediatric patients the use of calcium when adjusted for confounding factors was associated with decreased survival to discharge and unfavorable neurologic outcome. However, in patients with electrolyte abnormalities and toxicological abnormalities (i.e. hyperkalemia, hypocalcemia and Ca channel blocker overdose) Ca administration was not associated with worse event survival or survival to discharge. The study also indicated that Ca use remains prevalent despite guidelines to decrease Ca use. Often Ca was administered in AAHA guideline recommendations (hyperkalemia, Ca channel blocker overdose). However, it was also often administered with asystole and pulseless electrical activity. This may be because both these rhythms have been suspected to benefit from Ca administration in the past, but evidence is minimal and conflicting. The study concluded that Ca is still overused in pediatric CPR and is associated with worse survival to discharge and neurologic outcome, exceptions however, were patients with electrolyte imbalances such as hypocalcemia, toxicological emergencies and possibly postsurgical cardiac patients. It could have been preferred that the study examined specifically hypocalcemic patients compared to non hypocalcemic patients given Ca rather than grouping hypocalcemic patients in an electrolyte imbalance group.

One experimental study in pigs (LOE 6, fair) has indicated calcium may be useful in CPR patients with hypocalcemia. In 2010 Youngquist[9] et al conducted an experimental study in pigs (Hypocalcemia Following Resuscitation from Cardiac Arrest Revisited). Ventricular fibrillation was induced in the pigs electrically and balloon occlusion resulting in ischemia. Pre arrest, during arrest and after blood samples were collected and measurements including ionized Ca, lactate, base excess and pH were evaluated. In the pigs it was found that ionized Ca decreased post CPR and normalized in all groups (electrical and balloon induced fibrillation) after 180 minutes post ROSC. Twelve pigs underwent electrically induced fibrillation and of theses 6 were given Ca chloride 20 minutes after ROSC and 6 were given saline. In the pigs that received Ca, improved cardiac contractility and no effect on diastolic function was noted. However this is an experimental study that did not evaluate survival or neurologic outcome and used the Ca chloride post CPR.

In another study performed by Niemann [10] in 1999 (LOE 3 Poor) (Hyperkalemia and Ionized Hypocalcemia During Cardiac Arrest and Resuscitation: Possible Culprits for Postcountershock Arrhythmias?) ventricular fibrillation was induced in dogs and after 7.5 minutes of fibrillation the dogs were then defibrillated, administered CPR and given epinephrine. Potassium increased and calcium decreased in some of the dogs during CPR. In animals with asystole or pulseless electrical activity it was noted that they had significantly decreased calcium and increased potassium levels compared to baseline values. This was not noted in the dogs that were defibrillated and had rhythms associated with return of spontaneous circulation. The study concluded that increased potassium and decreased calcium may be associated with pulseless electrical activity and asystole post defibrillation. Interesting was that the Ca+ is suspected to be low because of intracellular accumulation and this intracellular accumulation may result in the post defibrillation arrhythmia. Therefore one could easily debate whether calcium administration would be useful as it may further increase intracellular Ca levels despite the low blood Ca.[9] Also it is not clear if potassium or Ca+ or other factors are responsible for the post defibrillation arrhythmia.

The following 3 studies do not support Ca use but document Ca levels in CPR patients

A prospective study by Gando[9] in 1990 (LOE 6 poor)(A comparison of Serum Ionized Calcium in Arterial and Mixed Venous Blood during CPR) was able to show Ca decreased in human patients with prolonged CPR. In addition a trend toward lower Ca levels was seen in nonsurvivors but the difference was not significant from survivors. This may have been due to small number of patients in the study

Another experimental study in dogs that were induced into ventricular fibrillation by Best [11] (LOE 3 poor) (Ionized Calcium During CPR in the Canine Model) did not show decreases in Ca in dogs that underwent cardiac arrest. In addition, Ca administration resulted in increased Ca levels and the calcium did not lead to an effective rhythm. However, another experimental dog study by Blesek[12] (LOE 3 poor) (Hematologic and chemical changes observed during and after cardiac arrest in a canine model--a pilot study) showed decreased Ca levels in dogs during ventricular fibrillation induced CPR.

Potassium

Hyperkalemia is a well known cause of cardiac abnormalities in human and veterinary patients and can lead to cardiac arrest. Hyperkalemia alters cellular membrane potential resulting in bradycardia and eventually asystole. Hyperkalemia may also be associated with electrical mechanical disassociation and is thought to be associated with EMD post-defibrillation.[13] Hyperkalemia may also occur in cardiac arrest due to loss of ATP and therefore Na/K ATPase function and potassium within the interstitial space may be greater than potassium levels in the blood.[13] This further highlights the importance of this electrolyte abnormality in cardiac arrest.

Three case reports and one case review (LOE 6 poor) (Lee, Costa, Kao and Lin) indicated benefits to correcting hyperkalemia with hemodialysis in CPR patients.

These are not true studies, therefore it is difficult to use these articles as evidence but the ability to restore normal heart function only after correcting the hyperkalemia is evidence that correcting hyperkalemia is beneficial in a CPR situation [14,15,16, 17]

Two studies have shown an association with hyperkalemia and refractory CPR arrhythmias or post defibrillation arrhythmias

Geddes[18] et al performed an experimental study in pigs in 2006 (LOE 6 poor) (The Natural Biochemical Changes during Ventricular Fibrillation with Cardiopulmonary Resuscitation and The Onset of Post defibrillation Pulseless Electrical Activity). Ventricular fibrillation was electrically induced in pigs and then CPR was performed and the pigs were defibrillated. After defibrillation it was determined if the pigs were in electrical mechanical disassociation or had a normal rhythm associated with return of spontaneous circulation. The study showed that factors that may be associated with post defibrillation pulseless electrical activity included increased potassium and increased length of ventricular fibrillation. These two may occur together as potassium levels increase during prolonged CPR. Low CO_2 levels were also associated with increased incidence of post defibrillation pulseless electrical activity. One would wonder if the low CO2 was associated with higher tidal volumes or respiratory rates which then resulted in decreased cardiac return and therefore increased ventricular fibrillation duration and increased incidence of post defibrillation pulseless electrical activity. In addition correction of the potassium to determine if normalization of potassium would resolve the arrhythmia was not performed.

The previous mentioned study performed by Niemann[9] in 1999 (Hyperkalemia and Ionized Hypocalcemia During Cardiac Arrest and Resuscitation: Possible Culprits for Postcountershock Arrhythmias?) ventricular fibrillation was induced in dogs (LOE 5 poor) and after 7.5 minutes of fibrillation the dogs were defibrillated, administered CPR and given epinephrine. Potassium increased and calcium decreased in some of the dogs during CPR. In animals with asystole or pulseless electrical activity it was noted that they had significantly decreased calcium and increased potassium levels compared to baseline values. This was not noted in the dogs that were defibrillated and had rhythms associated with return of spontaneous circulation. The study concluded that increased potassium and decreased calcium may be associated with pulseless electrical activity and asystole post defibrillation. However as previously mentioned it is not clear if potassium or Ca or other factors are responsible for the post defibrillation arrhythmia.

One study was found that may support some evidence that hypokalemia may cause arrest rhythms and may occur during CPR therefore correction may be beneficial

Hypokalemia may be associated with arrhythmias resulting in cardiac arrest. A weak association between hypokalemia and cardiac arrest was seen in a human retrospective study performed by Seidler[19] in 2011 (LOE 6 poor) (Distribution of Potassium Levels on Admission for CPR-Severe Hypokalaemia with Dysmorphophobic Eating Disorders). However, this study did not clearly describe if potassium was measured during CPR after beta agonists were administered. This is important, as beta agonists may have falsely lowered potassium levels. However, the degree of hypokalemia (all were severely hypokalemic) noted in these patients may help to support this conclusion. If hypokalemia causes cardiac arrest rhythms, supplementation may be helpful.

7. Conclusion

Calcium

Based on the above studies it is unclear if calcium administration is helpful our harmful in hypocalcemic patients. Although the studies above support Ca use in hypocalcemic patients, both studies cited have a poor level of evidence. One can say that there is a definite need for a study in which outcome is determined after administering Ca versus no Ca in hypocalcemic patients in cardiac arrest. Based on the understanding of Ca physiology indicating the importance of Ca in cardiac function, it appears Ca administration is warranted in documented hypocalcemic patients. In particular, if Ca is severely low and hypocalcemia was documented prior to CPR. However, based on our understanding of Ca pathophysiology one may question the use of calcium in mildly hypocalcemic patients and patients that develop hypocalcemia during CPR. This is because hypocalcemia may only be extracellular and Ca may actually be elevated intracellularly. Increased intracellular calcium has been proposed as a cause of arrhythmias post defibrillation and other harmful processes. The consequences of intracellular increases in Ca during CPR are poorly understood and to add more confusion, some studies have shown a mixed benefit to Ca administration when Ca levels drop during CPR. It is likely best that Ca be administered in hypocalcemic patients that do not respond to conventional CPR therapy. Calcium administration may also be useful in Ca channel blocker overdose or conditions associated with decreased myocardial contractility such as hypermagnesemia and hyperkalemia.[1.] It seems Ca administration should be avoided in canine and feline CPR patients with normal Ca until further studies are conducted.

Potassium

Treatment of hyperkalemia appears to be useful in a CPR situation. However, studies are limited so this conclusion is largely based on our understanding of the consequences of hyperkalemia on cardiac function. Studies examining treating hyperkalemic patients versus not treating hyperkalemic patients in cardiac arrest were not found and would likely be difficult to perform. This is because it is standard of care to treat this abnormality when noted given our well known understanding regarding the relationship between potassium and cardiac function. In addition, it appears that during CPR potassium should be evaluated as it may become elevated during cardiac arrest and result in abnormalities such as post defibrillation pulseless electrical activity.

Hypokalemia may also be associated with cardiac arrest rhythms and if noted treatment appears warranted, but studies and information is very limited. In addition, one should monitor for hyperkalemia, particularly in patients given large amounts of beta agonists, such as epinephrine, during CPR.

8. Acknowledgement
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9. Citation list 2 and 8 were evaluated and identified as relevant calcium articles all other only referenced above in final comments)

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