WORKSHEET for Evidence-Based Review of Science for Veterinary CPCR

1. Basic Demographics

Worksheet author(s)

Elizabeth Rozanski	**Date Submitted for review:** 7/29/2011

[redacted]

2. Clinical question:

In dogs and cats with cardiac arrest (asystole, pulseless electrical activity, pulseless VT and VF) (P), does the use of antiarrhythmic drugs (lidocaine, procainamide, amiodarone, bretylium, magnesium) (I) compared with a standard CPR regimen (C), improve outcomes (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 to report

4. Search strategy (including electronic databases searched):

The search strategy includes PUB MED search primarily, with secondary sources including CAB abstracts, and Google. The goal was to cover the published veterinary and human literature, and to focus on 1) human outcome trials 2) Experimental dog studies. No clinical trials in canine or feline medicine of naturally occurring CPR addressing the question of anti-arrhythmic drugs have been performed.

4a. Databases

-MEDLINE via PUBMED (1950 to Jun 2011)
1. CPR and
2. lidocaine
3. procainamide
4. amiodorone
5. bretylium
6. magnesium

Repeated with Cardiac arrest and resuscitation, no new relevant hits
-CAB (1910 to June 2011)
No other relevant hits when combined CPR and drug and dog (and veterinary) or anti-arrhythmic and CPR; the search was repeated with pulseless electrical activity and asystole as well as VT/VF.

4b. Other sources

-GOOGLE SCHOLAR (performed on July 20, 2011)
Report as for Medline

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

Inclusion criteria

CPR studies (experimental and clinical trials) evaluating lidocaine, procainamide, bretylium, magnesium or amiodarone either alone or in combination with another drug.
Dog and/or cat ideally, but since none existed, human trials as well
Outcome assessed (ROSC, discharge from hospital)

Exclusion criteria

Non-English articles, ex-vivo studies, no outcome assessed, not relevant in study design

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

~ 23, some with overlap; see reference session for particularly useful articles.

5. Summary of evidence

Evidence Supporting Clinical Question (Use of an antiarrhythmic drug is useful in CPR in improving ROSC and/or discharge)

Good			Anastasiou-Nana 1994, A Amiodarone is helpful in resistant VF in dogs with induced MI			*Dorian 2002; a,b Amiodarone is better than lidocaine for VF*
Fair						*Herlitz 1997 a-Lidocaine; Somberg 2002 b-amiodarone is better than lidocaine for VT Nowak 1981 b,c Bretylium is better than placebo*
Poor						*Ohshige 2005 a-lidocaine, atropine, epi is contrast to epi alone*
	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						*Allegra 2001 (Mg vs placebo) Hassan 2002 (Mg vs placebo) Olson 1984(bretylium vs lidocaine) Haynes 1981 (bretylium versus lidocaine)*
Fair						*Kovoor 2005(sotolol vs lidocaine), Weaver 1990(lidocaine vs epi)*
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

Evidence Opposing Clinical Question
(Use of an antiarrhythmic drug is NOT useful in CPR in improving ROSC and/or discharge)

Good						
Fair			Frame 1989 A iv amiodarone was not helpful in dogs with VF			
Poor						*Markel DT (2010) Procainamide did not improve outcome in O-O-H VF*
	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:

Since the provision of CPR has become standard of care, providers have been looking for a pharmacological method to address arrhythmias, including pulseless electrical activity (PEA), asystole and pulseless VT/VF. Many studies have addressed these issues, most commonly in human clinical trials and experimental animal studies. Most commonly, small experimental studies and clinical reports have shown promising results, but later large well-controlled studies have failed to show benefit. Of interest, one recent study documented a significantly shorter time to administration of drugs in experimental studies, than in human medical cases. It is possible that in individual cases, a specific drug therapy is of profound benefit for the specific individual affected with cardiopulmonary arrest. Of equal importance, clinical trials typically compare two drugs, which leaves unanswered if no drug might be better than one of the study drugs.
In dog and cat clinical medicine, the role of drugs in CPR has been very poorly evaluated, with the vast majority of reports retrospective in nature. From the specific drugs discussed, given the currently available information, lidocaine and procainamide are unlikely harmful and may have some benefit. Based on the general use of these drugs in dogs and cats, lidocaine should be used with caution in cats, and probably at a lower dose then is reported for dogs, as they are reported to be sensitive to the neurotoxic effects of the drug. Amiodarone is associated with hypotension, allergic reactions or anaphylaxis in some dogs, however, it is likely the most useful of the IV drugs for CPR, and in shock resistant VF or pulseless VT it may be worth trying. Bretylium is fallen from favor in human medicine but has been incompletely evaluated in veterinary clinical patients and magnesium has similarly been used rarely and without no controlled benefits.

7. Conclusion

DISCLAIMER: Potential possible wording for a Consensus on Science Statement. Final wording will differ due to other input and discussion.

No evidence exists at this time that compellingly supports the routine use of anti-arrhythmic drugs in CPR for improved survival in naturally-occurring CPR in dogs and cats. In dogs and cats with VF or pulseless VT, rapid early defibrillation or cardioversion, before administration of antiarrhythmic drugs, is recommended. For pulseless VT or VF in dogs, amiodarone appears better than the other drug choices and might be considered in shock-resistant VT or VF, despite concerns regarding hypotension and/or allergic-anyphylactic reactions in this species. Little information exists regarding the use of amiodarone in cats during CPR, and the correct dose is also unclear in this species, so little recommendations can be made for the cat.

8. Acknowledgement
The RECOVER team.

9. Citation list
Lidocaine

1) *Herlitz J et al. Lidocaine in out of hospital ventricular fibrillation. Does it improve survival? Resuscitation 1997 33(3) 199-205. This study looked at out of hospital arrest, some of the EMS providers were able to give lidocaine. Patients that received lidocaine were more likely to have ROSC and be admitted to hospital, but no more likely to survive.*
2) *Ohshige K et al. Evaluation of out-of-hospital cardiopulmonary resuscitation with resuscitative drugs: a prospective comparative study in Japan. Resuscitation 2005 66: 53-61. This study was some what hard to interpret, but suggested that giving epinephrine in combination with lidocaine and atropine was better than epinephrine alone for non-traumatic arrests.*
3) *Olson et al. A randomized comparison study of bretylium tosylate and lidocaine in resuscitation of patients from out-of-hospital ventricular fibrillation in a paramedic system. Ann Emerg Med. 1984 Sep;13(9 Pt 2):807-10: Neither were that great, bretylium might be small bit bet*

4) *Haynes et al. Comparison of bretylium tosylate and lidocaine in management of out of hospital ventricular fibrillation: a randomized clinical trial. Am J Cardiol. 1981 Aug;48(2):353-6. Neither worked; no episodes of successful "chemical" defibrillation.*
5) *Kovoor et al. Randomized double-blind trial of sotalol versus lignocaine in out-of-hospital refractory cardiac arrest due to ventricular tachyarrhythmia Intern Med J. 2005 Sep;35(9):518-25; Neither worked, dismal prognosis*
6) *Weaver et al Effect of epinephrine and lidocaine therapy on outcome after cardiac arrest due to ventricular fibrillation. Circulation 1990 Dec;82(6):2027-34 Survival slightly better in people not receiving drugs in between shocks.*

Procainamide

1) *Markel DT et al. Procainamide and survival in ventricular fibrillation out of hospital arrest. Acad Emerg Med 2010 17(6) 617-723. This study evaluated 10 years of witnessed out of hospital cardiac arrests. They were eligible for procainamide if they had 3 shocks and lidocaine, but had not responded. There was no benefit in this therapy. However, it was not directly compared to lidocaine, and used after failure of defibrillation to restore a perfusing rhythm, leaving open the possibility that it could be beneficial in a different patient population.*

Amiodarone

1) *Somberg JC et al. Intravenous lidocaine versus intravenous amiodarone for incessant ventricular tachycardia. Am J Cardiology 2002 90: 853-859. Amiodarone was significantly better in 24 hour survival in contrast to lidocaine for VT, Small study with veterinary like enrollment.*
2) *Dorian P et al. Amiodarone as compared with lidocaine for shock-resistant VF. New England Journal of Medicine 2002 346: 884-890. Amiodarone is better.*
3) *Frame LH.The effect of chronic oral and acute intravenous amiodarone administration on ventricular defibrillation threshold using implanted electrodes in dogs. Pacing Clin Electrophysiol. 1989 Feb;12(2):339-46. Using IV amiodarone acutely did not reduce defibrillation potential in dogs.*
4) *Anastasiou-Nana MI, Nanas JN, Nanas SN, Rapti A, Poyadjis A, Stathaki S, Moulopoulos SD. Effects of amiodarone on refractory ventricular fibrillation in acute myocardial infarction: experimental study. J Am Coll Cardiol. 1994 Jan;23(1):253-8. In this study, in dogs with induced VF via ligation of the left anterior descending coronary artery, there was significant improvement in dogs treated with IV amiodarone after failing shock and lidocaine therapy.*

Bretylium

1) *Nowak et al. Bretylium tosylate as initial treatment for cardiopulmonary arrest: A randomized comparison with placebo. Amm Emer Med 191 10;404-407- Bretylium seemed better.*
2) *Olson et al. A randomized comparison study of bretylium tosylate and lidocaine in resuscitation of patients from out-of-hospital ventricular fibrillation in a paramedic system. Ann Emerg Med. 1984 Sep;13(9 Pt 2):807-10: Neither were that great, bretylium might be small bit bet*
3) *Haynes et al. Comparison of bretylium tosylate and lidocaine in management of out of hospital ventricular fibrillation: a randomized clinical trial. Am J Cardiol. 1981 Aug;48(2):353-6. Neither worked; no episodes of successful "chemical" defibrillation.*

Magnesium

1) *Allegra J et al. Magnesium sulfate in the treatment of refractory ventricular fibrillation in the pre-hospital setting. Resuscitation 2001 49: 544-553. Magnesium did not help.*
2) *Hassan TB et al. A randomised trial to investigate the efficacy of magnesium sulphate for refractory ventricular fibrillation. Emerg Med Journal 2002 19: 57-62. Magnesium did not help.*

This article is the best summary of the current state of anti-arrhythmics in people, and the most directly translatable to this project

Resuscitation. 2011 Jun;82(6):665-70. Epub 2011 Mar 27.
The use of antiarrhythmic drugs for adult cardiac arrest: a systematic review.
Ong ME, Pellis T, Link MS.

Abstract AIMS: In adult cardiac arrest, antiarrhythmic drugs are frequently utilized in acute management and legions of medical providers have memorized the dosage and timing of administration. However, data supporting their use is limited and is the focus of this comprehensive review.**METHODS:**Databases including PubMed, Cochrane Library (including Cochrane database for systematic reviews and Cochrane Central Register of Controlled Trials), Embase, and AHA EndNote Master Library were systematically searched. Further references were gathered from cross-references from articles and reviews as well as forward search using SCOPUS and Google scholar. The inclusion criteria for this review included human studies of adult cardiac arrest and anti-arrhythmic agents, peer-review. Excluded were review articles, case series and case reports.**RESULTS:**Of 185 articles found, only 25 studies met the inclusion criteria for further review. Of these, 9 were randomised controlled trials. Nearly all trials solely evaluated Ventricular Tachycardia (VT) and Ventricular Fibrillation (VF), and excluded Pulseless Electrical Activity (PEA) and asystole. In VT/VF patients, amiodarone improved survival to hospital admission, but not to hospital discharge when compared to lidocaine in two randomized controlled trials.**CONCLUSION:**Amiodarone may be considered for those who have refractory VT/VF, defined as VT/VF not terminated by defibrillation, or VT/VF recurrence in out of hospital cardiac arrest or in-hospital cardiac arrest. There is inadequate evidence to support or refute the use of lidocaine and other antiarrythmic agents in the same settings.

Other significant articles

This article, which is almost 25 years old, supports that early defibrillation is the treatment of choice for VF in people, and suggests the relatively uselessness of IV drugs in CPR.

Am J Emerg Med. 1988 Mar;6(2):113-9.
Initial treatment of ventricular fibrillation: defibrillation or drug therapy.
Martin TG, Hawkins NS, Weigel JA, Rider DE, Buckingham BD.
Source
Milton S. Hershey Medical Center, Division of Emergency Medicine, Hershey, PA 17033.
Abstract
The belief that defibrillation of unwitnessed ventricular fibrillation frequently results in asystole, combined with perceived low survival rates, led to deviation from "standard" advanced cardiac life support (ACLS) by physicians directing paramedics in the field. In nonstandard ACLS, intubation or drug therapy preceded defibrillation. This study retrospectively compared standard and nonstandard ACLS for ventricular fibrillation. The long-term survival rates were 12.3% (7/57) and 3.6% (6/168) for the two forms of ACLS, respectively (p = 0.03). The incidence of postcountershock asystole was 35% and 28% (p = 0.45). The survival rates for patients with a postcountershock rhythm and a pulse were 83% and 17% after standard and nonstandard ACLS (p less than 0.0001). Other factors reported to have a significant effect on survival were compared, and no significant differences (p greater than 0.05) were noted for mean age, sex, cardiopulmonary resuscitation (CPR) initiated by a bystander, ACLS response time, time to CPR, lay-witnessed arrest, or time to definitive care. The significant difference in the time to defibrillation (14 and 26 minutes) was expected. This is the first clinical study to clearly confirm the ACLS recommendation of early defibrillation before drug therapy in ventricular fibrillation.
PMID: 2833285 [PubMed - indexed for MEDLINE]

This article describes some aspects of the difficulty translating experimental models to the clinic floor, include the relatively rapid time to defibrillation seen in experimental studies.

Resuscitation. 2007 Jul;74(1):13-26. Epub 2007 Mar 13.
Drug administration in animal studies of cardiac arrest does not reflect human clinical experience.
Reynolds JC, Rittenberger JC, Menegazzi JJ.
Source

School of Medicine, University of Pittsburgh, Pittsburgh, PA 15213, United States.
Abstract

INTRODUCTION: To date, there is no evidence showing a benefit from any advanced cardiac life support (ACLS) medication in out-of-hospital cardiac arrest (OOHCA), despite animal data to the contrary. One explanation may be a difference in the time to first drug administration. Our previous work has shown the mean time to first drug administration in clinical trials is 19.4min. We hypothesized that the average time to drug administration in large animal experiments occurs earlier than in OOHCA clinical trials.**METHODS:**We conducted a literature review between 1990 and 2006 in MEDLINE using the following MeSH headings: swine, dogs, resuscitation, heart arrest, EMS, EMT, ambulance, ventricular fibrillation, drug therapy, epinephrine, vasopressin, amiodarone, lidocaine, magnesium, and sodium bicarbonate. We reviewed the abstracts of 331 studies and 197 full manuscripts. Exclusion criteria included: non-peer reviewed, all without primary animal data, and traumatic models. From these, we identified 119 papers that contained unique information on time to medication administration. The data are reported as mean, ranges, and 95% confidence intervals. Mean time to first drug administration in animal laboratory studies and clinical trials was compared with a t-test. Regression analysis was performed to determine if time to drug predicted ROSC.**RESULTS:**Mean time to first drug administration in 2378 animals was 9.5min (range 3.0-28.0; 95% CI around mean 2.78, 16.22). This is less than the time reported in clinical trials (19.4min, $p<0.001$). Time to drug predicted ROSC (odds ratio 0.844; 95% CI 0.738, 0.966).**CONCLUSION:** Shorter drug delivery time in animal models of cardiac arrest may be one reason for the failure of animal studies to translate successfully into the clinical arena.

Am J Cardiol. 1999 Nov 4;84(9A):52R-55R.
Intravenous antiarrhythmic drug therapy in the resuscitation from refractory ventricular arrhythmias.
Kudenchuk PJ.
Source
University of Washington, Division of Cardiology, Seattle 98195-6422, USA.
Abstract
Prompt **cardiopulmonary resuscitation** (**CPR**) and early defibrillation significantly improve the likelihood of successful **resuscitation** from cardiac arrest and are the key components in the American Heart Association's "chain of survival." Although representing current clinical practice in the United States, there is limited evidence supporting the benefit of acute administration of such antiarrhythmic medications as lidocaine,

bretylium, magnesium, and **procainamide** to a victim of cardiac arrest. There has been only 1 published case-controlled clinical trial in which shock-refractory victims of out-of-hospital ventricular fibrillation were stratified into those who received lidocaine and those who did not. In this trial, no significant differences were observed between treatment groups in the return of an organized rhythm, admission to the hospital, or survival to hospital discharge. In the recently published ARREST trial, a significant improvement in admission alive to the hospital was observed in recipients of intravenous amiodarone, compared with placebo (44% vs 34%, respectively, $p = 0.03$). With the possible exception of intravenous amiodarone, available evidence of definitive benefit from antiarrhythmic drugs in cardiac arrest is inconclusive. Due to regulatory issues, clinical trials in cardiac arrest are extremely difficult to design and perform.
PMID: 10568660 [PubMed - indexed for MEDLINE]