WORKSHEET for Evidence-Based Review of Science for Veterinary CPCR

1. Basic Demographics

Worksheet author(s)

Katie Sakakeeny	**Date Submitted for review:**

[redacted]

2. Clinical question:

In cardiac arrest patients (asystole, pulseless electrical activity, pulseless VT and VF), does the use of atropine (IV, IO, or ET) or atropine in combination with other drugs compared with not using drugs or a standard drug regime, improve outcomes (ROSC, survival to discharge, neurologic outcome)?

3. Conflict of interest specific to this question:

None

4. Search strategy (including electronic databases searched):

4a. Databases

Medline via PubMed (1960- May 2011)

Keywords:

1. Atropine
2. Cardiac arrest
3. Asystole
4. Pulseless electrical activity
5. Cardiopulmonary resuscitation

Results for 1 and 2: 500 total, 34 relevant
Results for 1 and 3: 120 total, ~ 3 additional relevant hits
Results for 1 and 4: 3 relevant hits
Results for 1 and 5: 25 relevant hits

-CAB (1960 to July 2011)
-OVID (1970 to July 2011)

4b. Other sources

VIN

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

Inclusion criteria

Clinical studies with emphasis on animals receiving atropine during cardiac arrest were included. In addition to randomized and controlled prospective studies, retrospective studies, case series, and human clinical studies also included. Individual case reports only included for animal patients.

Exclusion criteria

Review articles, consensus statements, patients without cardiac arrest, and patients in which outcome was not evaluated. Individual human case reports were excluded.

4d. Number of articles/sources meeting criteria for further review:
15, 5 animal-based studies, and 10 human-based studies. Of the human literature, there were a total of 3 retrospective studies, 1 observational, and 6 prospective clinical studies. Of the veterinary literature, there were 3 experimental studies, 1 observational study, and 1 retrospective case series.

5. Summary of evidence

Evidence Supporting Clinical Question

Good						
Fair			Blecic 1992, A, E			
Poor					Waldrop 2004, A, B, D	Ohshige 2005, A, B,C
	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			DeBehnke 1995, A, B			
Fair				Hofmeister 2009, A		Herlitz 1995, C; Meert 2009, C,D
Poor			Redding 1983, A			Robinson 2010, A,B,C,E; Coon 1981, A, C; Stiell 2004, A-D; Stiell 1995, A,C
	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						Herlitz 2003,C; Walraven 1998, A
Poor						Moler 2011, C,D
	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:

There is no level 1 or level 2 study to support the use of atropine in the use of cardiopulmonary arrest to improve outcome. There is a paucity of studies specifically evaluating the use of atropine in both human and veterinary patients with CPA in regards to outcome. The highest LOE studies reported were LOE 3, with only one study (DeBehnke 1995, neutral) ranked as good. The other two LOE 3 studies were ranked as fair (Blecic, 1992, supportive), and poor (Redding 1983, neutral). There were only 3 studies that showed opposing data, and all were LOE 6 and either fair to poor. This suggests the least amount of compelling evidence claiming that the use of atropine worsens outcome. Alternatively, there were only 3 studies that supported the use of atropine (Blecic 1992, LOE 3 fair; Waldrop 2004, LOE 5 poor; Ohshige 2005 LOE 6 poor). However Oshige 2005 provided little relevance given the study design of OHCA and EMT response in humans. This study also did not specifically elucidate whether lidocaine, atropine, or both were given in the second phase of CPR which makes atropine use difficult to assess as contributing to outcome. Also, lidocaine use was not controlled which could have independently contributed to outcome. Waldrop 2004 was ranked a poor LOE 5 due to its small sample size for a case series and the lack of data presented regarding atropine use. The authors reported that a majority of patients with asystole or bradycardia were treated with atropine (15/18). However, without a control group the use of atropine contributing to outcome in these patients cannot be determined. The categorization of this study as being supportive, therefore, may not be entirely accurate and is assumed only because all patients in this study had survived CPA and most had received atropine. Blecic 1992 was a fair study because it was a small experimental canine study which only evaluated atropine for the use of PEA. Duration of CPR was shorter for the atropine group and the atropine group had higher stroke volume, cardiac output, heart rate, and arterial pressure. The time elapsed before starting CPR was only 2-4 minutes, which may not be realistic when comparing actual duration of CPA in veterinary patients before starting CPR, and the dose used in this study was 0.025 mg/kg, which is lower than the standard published dose of 0.04 mg/kg. This raises several questions: whether the published doses for atropine may be incorrect, whether lower doses may be more effective for outcome in CPA, and whether the dose given was subtherapeutic and thus atropine did not actually contribute to outcome in this study. These questions make interpretation of this study difficult.

The majority of evidence appears to lie within the neutral zone. Again, there are no level 1 or level 2 studies in this category, but the most compelling study is DeBehnke 1995 (LOE 3). This was ranked as a good study because it had a larger study group, was randomized, controlled and blinded, and was more relevant than some of the other experimental canine studies. Canines had PEA induced via asphyxiation, and 10 minutes elapsed before starting CPR. Epinephrine was used in this study but was considered controlled as all patients received it. Patients were divided into 1 of 5 groups: placebo,standard dose atropine (0.04 mg/kg), 0.1 mg/kg atropine, 0.2 mg/kg atropine, and 0.4 mg/kg atropine. The standard dose of 0.04 mg/kg did not show any significant increase in ROSC or survival compared to placebo. Additionally, the use of higher doses of atropine was associated with a decrease in rate of ROSC compared to standard dose and placebo. The other LOE 3 neutral study was by Redding 1983. This was a poor study based on population size, date of study, and lack of controls (despite being referred to as a controlled study). Study emphasis was on the use of methoxamine, which is uncommonly used in CPR compared to epinephrine, so relevance was also low. There were four groups: atropine, calcium chloride, methoxamine, and the saline group (control). If there was failure of ROSC in any of the non-methoxamine groups, the patients then received methoxamine, which would theoretically eliminate the controlled nature of the study. Authors made broad conclusions based on small amount of data obtained. It was assumed that the 5 of 10 dogs who had ROSC after receiving atropine were resuscitated due to basic CPR and not atropine because of the time that elapsed between drug administration and ROSC. There was no significant difference in ROSC

among the atropine, calcium chloride, and saline group. Meert 2009 (LOE 6, neutral) was a fair human retrospective cohort study evaluating in-hospital cardiac arrest patients who experienced greater than 1 minute of chest compressions and ROSC greater than 20 minutes. There was no significant difference in survivors vs. nonsurvivors given atropine (35 vs. 38%), although atropine was not one of the main variables of interest in this study (i.e, was statistically reviewed but not controlled for). Herlitz 1995 (LOE 6) was ranked as a fair prospective human study evaluating survival following OHCA with EMD. This study is not as relevant given that the primary focus of this study was on the prevalence of EMD/PEA and not on an actual treatment. This study was also limited in its applicability to veterinary medicine based on an OHCA model using an EMS response team.

In summary, the majority of evidence provided seems to support the neutral hypothesis. However, the overall quality of the literature for each category is questionable, mainly due to the paucity of veterinary studies, the LOE, and the lack of controlled studies using atropine as the main focus for outcome following CPR.

7. Conclusion

There is insufficient evidence to support or refute the routine use of atropine in cardiac arrest to improve outcome. More studies are needed in the veterinary literature, especially prospective, controlled clinical trials, that specifically evaluate the use of atropine in CPA and how it affects outcome.

8. Acknowledgement

none

9. Citation list

1) Joseph R Redding, MD, Raleigh B Haynes, MD, John D Thomas, MD (1983). Drug therapy in resuscitation from electromechanical dissociation. Crit Care Med, 11(9), 681-684.

LOE 3 Poor study, neutral findings.
Although reported as a controlled study, numbers small and methoxamine (the variable in question) was given to several of the other tx groups after failure of ROSC. Relevance not as high given that focus was to evaluate methoxamine, not atropine. Broad conclusions made based on small amount of data obtained, especially when methoxamine not directly compared to epinephrine. Outcome was ROSC.
1983 study. 4 groups of dogs, 10 in each group. All anesthetized and then ET occluded and waited until PEA/cardiac arrest. Five minutes after last aortic pressure wave seen on monitor, CPR started. Group A received 5 ml saline; Group B received 0.5 mg atropine, Group C received CaCl2, and Group D received methoxamine. Outcome was ROSC after 10 min CPR. 5/10 in the atropine group had ROSC while 10/10 of the methoxamine had ROSC (<.005). 6/10 of the CaCl2 had ROSC and 2/10 of the saline group had ROSC. Authors did not believe that ROSC was due to atropine in CaCl2 in each group due to time lapse between drug given and ROSC; attributed to basic CPR efforts instead. No sig difference in ROSC among the atropine, saline, and CaCl2 group. Atropine did not have significant change in heart rate compared to saline whereas CaCl2 and methoxamine had a significant increase (<0.01).

2) Johan Herlitz, Lars EkstrGm, Bertil Wennerblom, Asa Axelsson, Angela E&g, Stig Holmberg (1995). Survival among patients with out-of-hospital cardiac arrest found in electromechanical dissociation. Resuscitation .29; 97- 106.

   LOE 6, fair. Neutral. Relevance not as high due to OHCA population and not directly evaluating atropine use and outcome, looking more at % with EMD. Only made up small subset of population observed.
   Prospective clinical study, no control. Outcome was survival to hospital discharge (SD).
   3434 patients, divided into category of arrest rhythm. According to initial protocol, only patients with asystole were scheduled to receive atropine but reportedly only 24% of asystolic patients received atropine, followed by 17% with EMD and 19% of v fib. The % given atropine with EMD was stat significantly less than the % given atropine with asystole.

Conclusion: Of all the patients with out-of-hospital cardiac arrest that had CPR performed by the EMS, 22% were found in electromechanical dissociation.Of these,13% were hospitalized alive and 2% could be discharged from hospital. No independent predictor of an increased chance of survival was found. Atropine was not given in a controlled setting and when given was not found to have any difference in survival to hospital or discharge compared to patients not given atropine.

3) J Herlitz, A Bång, J Gunnarsson, J Engdahl, B W Karlson, J Lindqvist, L Waagstein (2003). Factors associated with survival to hospital discharge among patients hospitalised alive after out of hospital cardiac arrest: change in outcome over 20 years in the community of Göteborg, Sweden. Heart;89:25–30.

   Prospective clinical cohort study
   LOE 6, fair. Opposing.

   Evaluated OHCA over 20 year period, compared 1980-1990 and 1990-2000 outcomes. Outcomes were survival to discharge (SD). Of 5505 patients w/OHCA, 24% hospitalized alive. Predictors for SD included witnessed CPA, bystander CPR, conscious at hospitalization, sinus rhythm at hospitalization, vfib/vtach as arrest rhythm, and tx w/lidocaine at ER. Independent negative predictors for survival included age >70, requiring atropine, and chronic diuretic therapy.

   Confusing terminology- could be atropine directly assoc w/survival vs. bradyarrhythmias requiring atropine as being negatively assoc. w/survival. Relevance not high due to OHCA population w/medical history of MI/ACS or other uncommon veterinary diseases as cause of death. No standardization of tx or protocol. Only 9% of the population in 1980-90 and 6% of 1990-2000 received atropine.

4) Frank W. Moler, MD; Amy E. Donaldson, MS; Kathleen Meert, MD; Richard J. Brilli, MD; Vinay Nadkarni, MD; Donald H. Shaffner, MD; Charles L. Schleien, MD; Robert S. B. Clark, MD; Heidi J. Dalton, MD;

Kimberly Statler, MD; Kelly S. Tieves, DO; Richard Hackbarth, MD; Robert Pretzlaff, MD;
Elise W. van der Jagt, MD; Jose Pineda, MD; Lynn Hernan, MD; J. Michael Dean, MD; for the Pediatric Emergency Care Applied Research Network (2011). Multicenter cohort study of out-of-hospital pediatric cardiac arrest**.** Crit Care Med; Vol. 39, No. 1

Retrospective cohort study.
LOE 6, fair to poor, opposing.

138 cases retrospectively evaluated over an 18 month period that were b/w 1 day-18 yrs of age, OHCA with >1 min chest compressions and ROSC for > 20 min. Outcomes were SD and neurologic function (based on scoring system). Overall mortality (NS) was 62%, SD 38%. Atropine was administered to 21% of the survivors and 67% of NS and was found to be an independent significant risk factor for mortality. Suitable sample size for veterinary study but small for human study. Did not evaluate patients receiving atropine in relation to patients receiving multiple doses of epinephrine which may have reflected longer duration of CPR in patients with poor outcomes receiving more drugs than a patient who was quickly resuscitated. Patients with longer duration of CPR, asystole at any time, or initial bradyarhythmia all assoc with mortality which makes atropine use more likely in this group. Relevance low due to pediatric population (although more relevant than adult and geriatric population due to different disease distribution), OHCA, and only included those with ROSC.

5) Kathleen L. Meert, MD, FCCM; Amy Donaldson, MS; Vinay Nadkarni, MD, FCCM; Kelly S. Tieves, DO; Charles L. Schleien, MD, MBA, FCCM; Richard J. Brilli, MD, FCCM; Robert S. B. Clark, MD; Donald H. Shaffner, MD; Fiona Levy, MD; Kimberly Statler, MD; Heidi J. Dalton, MD, FCCM; Elise W. van der Jagt, MD, MPH; Richard Hackbarth, MD; Robert Pretzlaff, MD, MS; Lynn Hernan, MD; J. Michael Dean, MD, MBA, FCCM; Frank W. Moler, MD, MS, FCCM; and for the Pediatric Emergency Care Applied Research Network (2009). Multicenter cohort study of in-hospital pediatric cardiac arrest. Pediatr Crit Care Med; Vol. 10, No. 5

Retrospective cohort
LOE 6, fair. Neutral.

353 patients between 1 day and 18 yrs age w/IHCA, >1 min chest compressions, and ROSC > 20 min. Outcomes were SD and neurologic outcome. 48.7% SD, of those 76.7% had good neurologic outcomes. Same limitations apply as in above study with exceptions being more relevant as IHCA and sample size doubled. Did not have a significant difference in S vs NS given atropine. (35 vs.38%). Atropine was not one of the major variables of interest in this study.

6) Simon Robinson, Andrew H. Swain, Sarah R. Hoyle, Peter D. Larsen (2010). Survival from out-of-hospital cardiac arrest in New Zealand following the 2005 resuscitation guideline changes. Resuscitation 81: 1648–1651.

LOE 6, fair to poor, neutral.
Retrospective cohort

Compared OHCA from July 2005-June 2006 (old guidelines, OG) and June 2007-May 2008 (new guidelines, NG) with emphasis on implementation of different shock strategy for NG. There were 162 OG and 170 NG. Outcomes were SD with additional endpoints of survival to hospital admission, individual shock success, and ROSC. NS found among SD b/w groups, but trend toward increase in ROSC ($p< 0.07$) and significant increase in survival to hospitalization with NG. Drug use altered in line with the guideline changes and it is
not known whether this influenced the outcomes measured. Atropine was given to 75% of patients during the first study period but only 5.3% during the second (and then only for bradycardia) conforming with the withdrawal of atropine from the New Zealand Resuscitation Council Guidelines in 2005. In this study, discontinuing

the use of atropine in asystole had no identifiable adverse effect on survival. Limitations included OHCA, small sample size and limited use of atropine.

7) Kenji Ohshige, Shuji Shimazaki, Hiroyuki Hirasawa, Masataka Nakamura, Hiroshi Kin, Chiiho Fujii, Kazuo Okuchi, Yasuhiro Yamamoto, Katsuya Akashi, Junzo Takeda,Takashi Hanyuda, Osamu Tochikubo (2005). Evaluation of out-of-hospital cardiopulmonary resuscitation with resuscitative drugs: a prospective comparative study in Japan. Resuscitation 66; 53–61.

LOE 6, fair to poor, supportive
Prospective nonrandomized controlled study

162 in experimental group and 272 in control group. Outcome was ROSC, and survival to hospitalization (SH), and 1-month survival. Very complex study evaluating the EMT response using control (non-physician EMTs) vs. experimental group (Physician-manned ambulance) for OHCA. Control group only allowed to implement BLS and defibrillation, experimental group divided into 3 phases of CPR: 1) BLS followed by epinephrine if no ROSC, 2) epinephrine plus lidocaine or atropine if still no ROSC, and 3) implementation of "other drugs" (not specified) until ROSC or admitted to ICU. Duration of CPR before implementing therapies was not clear. Use of lidocaine and atropine not clearly explained. Unclear if all patients entering phase 3 received both lidocaine and atropine and what dose was given, or if physicians chose lidocaine or atropine as a single drug therapy.
Experimental group had significantly more trauma patients but worse outcomes compared to control although NS. In patients with non-traumatic CPA, there was a significant increase in SH and 1 month survival in the experimental group. Limitations: OHCA, provided very little information specifically pertaining to atropine dose and concurrent use with lidocaine, duration of CPR between phases unknown, relevance low.

8) Jennifer E. Waldrop, DVM, DACVECC, Elizabeth A. Rozanski, DVM, DACVECC, DACVIM (Internal Medicine), Erica D. Swanke, DVM, Therese E. O'Toole, DVM and John E. Rush, DVM, MS, DACVECC, DACVIM (Cardiology) (2004). Causes of cardiopulmonary arrest, resuscitation management, and functional outcome in dogs and cats surviving cardiopulmonary arrest. Journal of Veterinary Emergency and Critical Care 14(1); 22-29.

LOE 5, fair, supportive
Retrospective case series.
Outcomes were ROSC, SD, and functional (neurologic) outcome.

Dogs and cats that underwent CPA and survived to hosp discharge were included in a retrospective analysis from 1997 -2003. There were 18 subjects total (15 dogs, 3 cats) Documented CPA rhythms in the 18 animals included asystole in 13/18 (72%), ventricular fibrillation (VFIB) in 3/18 (17%), and pulseless electrical activity (PEA) in 2/18 (11%). In all but 1 subject neurologic outcome was normal following SD. Atropine was not specifically evaluated in relation to outcome, nor was it documented how many patients received atropine and at what dose. The authors did comment that a majority of the patients with asystole or bradycardia were treated with atropine in this study but no numbers were provided and thus there is weak evidence reported here to strongly advocate the use of atropine.

9) Carl van Walraven, MD, M, SIan G Stiell, MD, MSc, George A Wells, MSc, PhD, Paul C Hébert, MD, MHSC, Katherine Vandemheen, BScN, For the OTAC Study Group (1998). Do Advanced Cardiac Life Support Drugs Increase Resuscitation Rates From In-Hospital Cardiac Arrest? Ann Emerg Med November;32:544-553.

LOE 6, fair, opposing
prospective multicenter, controlled cohort trial

773 patients prospectively analyzed following in-hospital CPA. Outcome was ROSC for at least 1 hour. Patients were excluded if they were under the age of 16, had a terminal illness, had been without basic CPR for more than 15 minutes, had acute trauma or exsanguination, had a recent sternotomy, or were in the operating, delivery, or recovery rooms at the time of arrest. The use of epinephrine, atropine, lidocaine, sodium bicarbonate, calcium, and bretylium were analyzed. There was a significant association with poor outcome with the use of epinephrine, atropine, bicarbonate, calcium, and lidocaine. There was a higher percentage overall in the number of NS given atropine vs. S in the first 20 minutes of CPR, and there was no significant difference in time to atropine administration in the NS vs. S (6.27 to 6.43 minutes,respectively). Although listed as a controlled study, could not control for certain arrest rhythms and drugs were given based on these rhythms, which could have changed during the course of CPR. Also, patients with PEA or asystole generally are perceived to have a worse outcome, and these are the rhythms in which atropine has classically been given. Whether atropine is causally linked to poor outcome or whether the underlying arrest rhythm leads to poor outcome is not clearly determined in this study, although many studies have speculated that the latter is more likely. Both epinephrine and atropine have been linked to poor outcome in patients who have endured prolonged CPR, raising the question of whether the outcome is truly due to the drugs administered or because these represent a subset of patients who are not responding to CPR efforts. In this study there was no significant difference in time until atropine was administered between S and NS, making the evidence more opposing for the use of atropine rather than being selective for a sicker group of patients. Relevance is low given exclusion of trauma, exsanguination, terminal illness, or any anesthetic or surgical-related death.

10) Coon, G. A., JE. Clinton, Ernest Ruiz (1981). Use of atropine for brady-asystolic prehospital cardiac arrest. Ann Emerg Med 10(9): 462-467.

LOE 6, poor, neutral
Prospective controlled (nonrandomized) study

Twenty-one OHCA with either asystole or PEA divided into atropine or non-atropine groups. Outcome was ROSC and SD. Control group received bicarbonate, epinephrine, calcium, isoproterenol, dexamethasone, and transthoracic pacing. Atropine group received 1 mg atropine IV with a repeat dose at 1 minute if no rhythm change occurred. Then they were given the same tx as the control group. Only 1 patient from each group had ROSC, and only the control group patient survived to discharge. No significant difference was found between groups. Study size was very small, relevance is low based on OHCA and date of study (1981). Many of the treatments described in the control group (eg, isoproterenol, dexamethasone) are not standard ALS drugs given in veterinary CPR today making comparison difficult.

PEA and asystolic patients were combined into one group of patients instead of being independently evaluated.

11) Ian G. Stiell, M.D., George A. Wells, Ph.D., Brian Field, A.C.P., M.B.A.,bDaniel W. Spaite, M.D., Lisa P. Nesbitt, M.H.A., Valerie J. De Maio, M.D.,Graham Nichol, M.D., M.P.H., Donna Cousineau, B.Sc.N., Josee Blackburn, B.Sc., Doug Munkley, M.D., Lorraine Luinstra-Toohey, B.Sc.N., M.H.A., Tony Campeau, M.Ed., Eugene Dagnone, M.D., and Marion Lyver, M.D., for the Ontario Prehospital Advanced Life Support Study Group (2004). Advanced Cardiac Life Support in Out-of-Hospital Cardiac Arrest. N Engl J Med 2004;351:647-56.

LOE 6, fair to poor, neutral

Multi-center, combined prospective and retrospective, controlled study.
Evaluated rate of survival in OHCA with implementation of rapid defibrillation compared to patients with rapid defibrillation plus ALS. Primary outcome was SD, secondary and tertiary outcomes were % admitted to the hospital, ROSC, and cerebral performance score. Excluded were children younger than 16 years of age, persons who were dead, patients with trauma, and others with disorders that clearly had a noncardiac cause. Of the ALS subgroup, 4247 patients were enrolled, and 1391 patients were enrolled in the rapid defibrillation-only subgroup. 87.3% of the ALS patients received atropine. There was no benefit found between the ALS group and the control in regards to outcome. Advantages to the study were its large sample size and prospective evaluation of the ALS subgroup. Relevance to veterinary CPR is low, however, based on OHCA and exclusion criteria listed above, which makes interpretation of this population difficult if not impossible to compare to veterinary patients with CPA.

12) Ian G. Stiell MD, MSc, George A. Wells PhD, Paul C. Hebert MD, MHSc, Andreas Laupacis MD, MSc, Brian N. Weitzman MD (1995). Association of Drug Therapy with Survival in Cardiac Arrest: Limited Role of Advanced Cardiac Life Support Drugs. Academic Emergency Medicine, 2: 264–273.

LOE 6, poor, neutral

Observational cohort study
Adults with CPA either in-hospital or out-of-hospital and requiring epinephrine for ALS were evaluated. Outcomes were survival to one hour and SD. Six ALS drugs NOT including epinephrine were assessed for association with survival from resuscitation to one hour and to hospital discharge (atropine, bretylium, calcium, lidocaine,procainamide, sodium bicarbonate). A total of 529 patients were evaluated and no significant difference was found in either outcome with the use of atropine, bretylium, calcium, or lidocaine. Atropine was only found to have better survival when given late in the ALS period. Only procainamide showed an increased correlation with survival. Patients with respiratory cause for arrest were associated with higher resuscitation rates. The intiating cause, time until use of ALS drugs, and duration of ALS were correlates of survival, but the standard drugs used had little association with survival (except procainamide). Relatively small study and not well-controlled. The use of atropine late in ALS associated with increased survival is not intuitive and may have been a result of other factors, including small sample size.

13) Serge Blecic MD, Christo Chaskis MD, and Jean-Louis Vincent MD,PhD (1992). Atropine administration in experimental electromechanical dissociation. Am J Emerg Med 10(6): 515-518.

LOE 3, fair, supportive
Randomized controlled, experimental canine study

Fifteen anesthetized and mechanically ventilated dogs had PEA induced by ventricular fibrillation followed by an external countershock. The rhythm was observed for 2 minutes before starting CPR. After 5 minutes of chest compressions, either 0.5 mg atropine or D5W were administered, and the same injection was repeated every 5 minutes until recovery. Primary outcome was ROSC; secondary outcomes were HR, SV, blood pressure, cardiac output, and time to recovery. Epinephrine was given in each group alternating between injections of the atropine or D5W. Each dog was subjected to 2 episodes of CPR with either repeated doses of atropine or D5W randomly assigned. Of 28 total CPR attempts, 5 were successful with chest compressions alone [presumably due to the timing of injection and ROSC]. In the tx group, 10/11 were successful with atropine, and 8/12 were resuscitated with D5W ($p< 0.01$). Duration of CPR was significantly shorter for atropine group and during the recovery period the atropine group had higher arterial pressure, heart rate, cardiac output and stroke volume. Small study with controlled experimental setting only evaluating PEA, and all animals received epinephrine. Dose for atropine (0.025 mg/kg) seemed low compared to standard published doses of 0.04 mg/kg. Time elapsed before starting CPR was only 2-4 minutes.

14) Daniel J. De Behnke MD, Gary L. Swart MD, David Spreng (1995). Standard and Higher Doses of Atropine in a Canine Model of Pulseless Electrical Activity. Acad Emerg Med 2(12): 1034-1041.

LOE 3, good, neutral to opposing.

Prospective, randomized, blinded controlled experimental canine study. PEA was induced via asphyxiation in 75 dogs and left untreated for 10 minutes. Outcomes were ROSC and survival. Dogs were randomized into 1 of 5 groups: placebo, 0.04 mg/kg atropine, 0.1 mg/kg atropine, 0.2 mg/kg atropine, and 0.4 mg/kg atropine. All dogs received 0.02 mg/kg epinephrine every 3 minutes during CPR. There was no significant increase in ROSC or survival using standard dose atropine (0.04 mg/kg) vs. placebo. There was a decrease in rate of ROSC in higher dose atropine vs. placebo and standard dose. Higher population size than other canine model experiments and more relevant than many of the other studies. Although epinephrine was given to all dogs, atropine was only other variable in this study (i.e., not affected by use of other drugs or therapies). Controlled experimental setting vs. clinical setting, but did allow 10 minutes of untreated PEA to ensue before beginning CPR, which may be more applicable to our population. Opposes use of atropine at higher than standard dose of 0.04 mg/kg.

15) Erik Hofmeister, DVM, MA, DACVA, Benjamin Brainard, VMD, DACVA, DACVECC, Christine M. Egger, DVM, MVsc, DACVA, Sangwook Kang, PhD (2009). Prognostic indicators for dogs and cats with cardiopulmonary arrest treated by cardiopulmonary cerebral resuscitation at a university teaching hospital. J Am VetMed Assoc; 235:50-57.

LOE 4, fair, Neutral

Cross-sectional study (observational) evaluating 161 dogs and 43 cats with CPA. Outcome was ROSC. Over a 60 month period, 35% of dogs and 44% of cats had ROSC. Only 6% of this population survived to discharge

(SD). Dogs with ROSC were more likely to have received mannitol, lidocaine, dopamine, fluids, corticosteroids, vasopressin, CPR in lateral recumbency, arrest under anesthesia, or have CPA due to causes other than hemorrhage, shock, MODS, hypoxemia, cerebral trauma, malignant arrhythmia, anaphlyaxis. Dogs with ROSC were also less likely to have received prolonged CPR, multiple doses of epinephrine, or multiple disease conditions. Cats with ROSC were more likely to have had more people involved in CPR and less likely to have CPA due to shock. Ninety-one percent of the population with CPA received atropine at 0.05 mg/kg, but there was no specific data pertaining to how many doses and if related to outcome. With such a large proportion of the population receiving atropine, this treatment could not be critically compared to those not receiving atropine, making relevance of this study low.