

Randomized, Blinded Comparison of Epinephrine and Vasopressin for Treatment of Naturally Occurring Cardiopulmonary Arrest in Dogs

G.J. Buckley, E.A. Rozanski, and J.E. Rush

Background: Administration of epinephrine during CPR is recommended for treatment of cardiopulmonary arrest (CPA) in dogs. Administration of epinephrine during CPR might be associated with deleterious adverse effects. Vasopressin has been studied for use in CPR as an alternative.

Hypothesis: That administration of vasopressin instead of epinephrine with standard CPR techniques will result in improved outcome.

Animals: Seventy-seven client-owned dogs identified in the ER/ICU with CPA were eligible for inclusion.

Methods: Randomized, prospective clinical study. Dogs were randomized to receive epinephrine (0.01–0.02mg/kg) or vasopressin (0.5–1 U/kg) in a blinded fashion. Attending veterinarians were asked to adhere to standardized CPR protocol for the 1st 6 minutes of CPR, during which time doses of the study drug were administered at 3-minute intervals.

Results: A total of 60 dogs completed this study with 31 receiving epinephrine and 29 receiving vasopressin. Overall rate of return of spontaneous circulation (ROSC) was 60% (36/60), 32% (19/60) of dogs survived to 20 minutes, 18% (11/60) survived to 1 hour. No difference was seen in rates of ROSC between the 2 groups ($P = .20$). Dogs receiving epinephrine were more likely to survive to 1 hour (odds ratio 5.86; 95% CI: 1.19–28.95) than those receiving vasopressin ($P = .027$).

Conclusions and Clinical Importance: ROSC was similar in dogs receiving epinephrine or vasopressin. In this study, a survival advantage at 1 hour was seen in those animals receiving epinephrine. No advantage of routine use of vasopressin over epinephrine was detected. Further studies are required to examine subgroups of dogs that might benefit from specific interventions.

Key words: Anesthesiology; Cardiology; Cardiopulmonary resuscitation; Cardiovascular physiology; Clinical trials; Critical care; Evidence-based medicine; Resuscitation; Vasopressor.

Treatment of cardiopulmonary arrest (CPA) has become a widely accepted part of small animal veterinary practice. Recommendations for treatment of CPA in dogs exist in the form of expert reviews,^{1–3} but are largely extrapolated from recommendations for management of CPA in people and supplemented with opinions based on personal clinical experiences. A small number of retrospective articles document outcomes of cardiopulmonary resuscitation (CPR) in dogs and cats^{4–7} and 1 recent article evaluated prognostic factors for achievement of return of spontaneous circulation (ROSC).⁸ Traditionally in human CPR, treatment has been divided into basic life support (BLS), which includes chest compressions and provision of ventilation, and advanced life support (ALS)⁹ which includes drug therapy and other treatments. Although provision of BLS, particularly good quality chest com-

Abbreviations:

ALS	advanced life support
BLS	basic life support
CPA	cardiopulmonary arrest
CPR	cardiopulmonary resuscitation
ROSC	return of spontaneous circulation

pressions, is accepted as being beneficial,⁹ there is much controversy over the effectiveness of drug treatment during CPA in both people and animals, and there have been no prospective studies investigating different treatments during CPA in dogs.

Epinephrine is routinely used in CPR, although there is little clinical evidence of its effectiveness and significant concerns over potentially adverse effects including worsening outcomes with high doses of epinephrine,¹⁰ increases in myocardial oxygen demand, reduction in cardiac output,¹¹ neurological impairment after successful resuscitation,¹² worsening myocardial dysfunction after resuscitation¹³ and ventilation-perfusion mismatch.¹⁴ Partly because of these concerns there has been interest in investigating the use of vasopressin as an alternative drug in CPR. In addition, endogenous circulating vasopressin levels are higher in people who go on to be successfully resuscitated than in those where resuscitation efforts fail.^{15–17} Studies using a variety of animal models have demonstrated improved cerebral blood flow,¹⁸ neurological function,¹⁹ coronary blood flow,^{18,20} and higher rates of ROSC¹⁹ when vasopressin is used instead of epinephrine. An early study comparing epinephrine with vaso-

From the Department of Clinical Sciences, Cummings School of Veterinary Medicine at Tufts University, North Grafton, MA; Dr Buckley is presently affiliated with University of Florida College of Veterinary Medicine, Gainesville, FL. The study was carried out in the Intensive Care Unit and Emergency Room of the Foster Hospital for Small Animals, Cummings School of Veterinary Medicine, North Grafton, MA.

Corresponding author: Elizabeth Rozanski, Department of Clinical Sciences, Cummings School of Veterinary Medicine at Tufts University, North Grafton, MA; e-mail: elizabeth.rozanski@tufts.edu

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pressin in people with CPA demonstrated improved survival in the group receiving vasopressin,²¹ but other trials, however, have had mixed results.²² A recent meta-analysis demonstrated that although animal models show a convincing benefit of vasopressin use, clear evidence of a benefit in human clinical trials is lacking.²³

The use of vasopressin as an alternative to epinephrine is considered acceptable according to the American Heart Association guidelines for CPR in people.⁹ This recommendation has been extended to the treatment of CPA in dogs and cats although there are no prospective data evaluating the use of any CPR drug treatments during spontaneously occurring CPA in these species.^{2,3,24} One recent observational study did suggest an association between vasopressin administration and successful resuscitation.⁸

This pilot study aimed to investigate and compare the rate of ROSC and short-term outcomes following the initial administration of either arginine vasopressin or standard dose epinephrine in naturally occurring CPA in dogs.

Materials and Methods

This pilot study was designed as a randomized, blinded, controlled trial. Dogs experiencing CPA in the intensive care unit (ICU), emergency room (ER) or arriving in the ER having recently experienced CPA were candidates for the study. Exclusion criteria included lack of prompt (< 2 minutes) IV access, CPR carried out in another site within the hospital, administration of either vasopressin or epinephrine within the past 24 hours, contraindication to administration of either epinephrine or vasopressin, weight exceeding 60 kg or the presence of a do not resuscitate order. The study was approved by the institution's Clinical Studies Review Committee following review of the trial by all members of the committee. Additional safeguards were put in place, including extensive in-hospital consultation before commencement of the trial, blinded interim data analysis performed after enrollment of 50% of anticipated cases by a representative of the Clinical Studies Research Committee not involved in administration of the trial, and local advertising of the trial via the institution's website. Attributed to the nature of the trial, obtaining informed consent from owners at the time of enrollment was waived. Instead, informed consent for further neurological monitoring and study inclusion was sought from owners of surviving animals as soon as practical after enrollment, usually in those animals surviving more than 1 hour after ROSC, at which point owners were offered the choice to withdraw from the study.

The study protocol mandated provision of BLS (chest compressions, ventilation by tracheal intubation, and provision of oxygen) to all patients. Dogs were administered a weight adjusted dose of study drug according to the dosing chart (Table 1). This provided a vasopressin dosage of 0.5–1 U/kg or an epinephrine dosage of 0.01–0.02 mg/kg. The study drug was administered IV as soon as possible after establishment of IV access and again after 3 minutes unless ROSC had already occurred. The study period was defined as 6 minutes from injection of the 1st dose of study drug or until ROSC, whichever occurred first. During the study period, the attending veterinarian was allowed to administer electrical defibrillation, fluids IV, blood products, and atropine at their own discretion. Concurrent administration of other vasopressors was not allowed during the study period. During

Table 1. Dose of study drug to be administered to enrolled dogs based on their known or estimated weight.

Dog Weight	Dose of Study Drug
0–5 kg (0–11 lb)	0.15 mL
5–10 kg (11–22 lb)	0.25 mL
10–20 kg (22–44 lb)	0.5 mL
20–40 kg (44–88 lb)	1 mL
40–60 kg (88–132 lb)	1.5 mL
>60 kg >132 lb	Not eligible

the study period use of sodium bicarbonate was restricted to dogs where severe pre-existing metabolic acidosis or hyperkalemia was believed to have contributed to CPA; the administration of calcium was restricted to patients where severe pre-existing hyperkalemia or hypocalcemia was believed to have contributed to CPA. After the end of the 6-minute study period all treatments including rescue vasopressor therapy were at the discretion of the attending veterinarian. Preset digital timers^a were provided in the ER and ICU to facilitate accurate timing of the study period.

Study drugs were prepared by the pharmacy service, with a list of vial and drug assignments maintained by the hospital senior pharmacist. This list was not available to the investigators, other hospital clinicians, or personnel involved in data analysis. The study drug was provided in vials labeled "CPR Study Drug for case XX" which were kept available in the emergency carts in both the ER and the ICU. The vials were randomly assigned to contain either vasopressin^b or epinephrine^c by use of a computer generated randomization table.^d An epinephrine concentration of 0.4 mg/mL was produced by diluting 1 : 1000 epinephrine^b with 0.9% sodium chloride;^e this has previously been shown to be stable for a minimum of 7 days,²⁵ vasopressin was used at the concentration provided by the manufacturer (20 U/mL). Vials were replaced either when they were used or every 7 days to ensure drug viability.

Data were collected prospectively on a standardized form consistent with the Ustein guidelines for documentation of CPR.^{26,27} Dog information collected included breed, age, sex, and known or estimated weight. Information regarding the CPA included location of CPA, cause of CPA, whether or not it was witnessed by a staff member, and presence of IV access. Information collected about treatment included staff members present during CPR and doses and timing of all interventions including drug therapy, blood products, and defibrillation attempts.

Neurological scoring for surviving animals was performed at 1 hour, 24 hours, and at hospital discharge following ROSC. The scoring system was devised based on an experimental system previously reported for use in post-CPR swine²⁸ (Appendix 1).

The primary end point of the study was the ROSC within the study period. Secondary end points included ROSC at any time, survived event (defined in the Ustein guidelines as survival with a perfusing rhythm for 20 minutes after ROSC),^{26,27} survival to 1 hour, survival to 24 hours, and survival to hospital discharge.

Blinded data analysis was performed at the completion of the study. Statistical analysis was completed before unblinding of the investigators as to the drug allocation group. Baseline characteristics between groups were analyzed; in addition, group allocation and other variables were analyzed for relationships with the primary and secondary end points. Data were examined graphically for normality and using the Shapiro-Wilks test. A chi-squared test was used to analyze differences between categorical variables, and a student's *t*-test was used for continuous variables. Statistical significance was set at a *P* value of less than .05.

Results

Seventy-seven dogs were enrolled in this study from July 2008 to May 2010 (Figure 1). A total of 17 dogs were subsequently excluded following randomization, 12 dogs because of termination of CPR efforts at the owners' request before completion of the 6-minute study period, 3 dogs because of missing study data sheets or insufficient information recorded on data sheet, and 2 dogs because of concurrent administration of epinephrine during the 6-minute study period. Of the remaining 60 dogs that were enrolled and completed the study period, 31 dogs received epinephrine and 29 dogs received vasopressin. Baseline characteristics between the 2 groups were compared using chi-squared analysis and descriptive statistics and found not to be significantly different (Table 2).

Dosing of the study drug accurately followed the guidelines in Table 1 in 54/60 cases. The actual dose of epinephrine administered to all dogs was 0.01–0.03 mg/kg (median 0.015 mg/kg), and the actual dose of vasopressin administered to all dogs was 0.5–2 U/kg (median 0.67 U/kg). Six dogs, 3 in the epinephrine group and 3 in the vasopressin group, were administered a dose higher than that provided in the dosing chart (epinephrine 0.024–0.03 mg/kg and vasopressin 1.2–1.6 U/kg). In addition, because of the design of the dosing scheme 4 dogs, 3 in the vasopressin group and 1 in the epinephrine group received a dose higher than the normal dose range attributed to their small size despite following the dosing guidelines.

In addition to administration of the study drug, other treatments administered during the study period included atropine^f ($n = 42$), and defibrillation^g ($n = 7$), there was no difference between the groups in the likelihood of receiving either treatment ($P = .69$ and

$P = .62$). Packed red blood cells ($n = 3$) and one each of calcium gluconate,^h naloxone,ⁱ furosemide^j and a hemoglobin-based oxygen carrier solution^k were also administered to some dogs. Other treatments administered during resuscitative efforts are summarized in Table 3.

Thirty-two of 60 dogs achieved ROSC within the 6-minute study period (53%) with 13 in the vasopressin group and 19 in the epinephrine group ($P = .20$). An additional 4 dogs (2 in each group) achieved ROSC following the 6-minute study period resulting in a total rate of ROSC of (60%), 15 in the vasopressin group and 21 in the epinephrine group ($P = .20$). Nineteen dogs survived for 20 minutes (survived event) (32%) including 6 in the vasopressin group and 13 in the epinephrine group ($P = .077$). Eleven dogs (18%) survived to 1 hour, 2 receiving vasopressin and 9 receiving epinephrine ($P = .027$). Five dogs (8%) survived to 24 hours, 1 received vasopressin, 4 received epinephrine, and only 1 dog (in the epinephrine group) survived to discharge (Fig 1). Because of the small numbers of survivors at 24 hours and at discharge, further statistical analysis on these groups was not attempted.

No significant difference was detected in rate of ROSC between those dogs receiving or not receiving atropine in the 6-minute study ($P = .14$) or at any time ($P = .10$). Administration of defibrillation during the study period was associated with a reduced chance of successful ROSC ($P = .0090$). Ventricular fibrillation following drug administration occurred in 2 dogs in the vasopressin group and 3 dogs in the epinephrine group during the study period ($P = 1.0$). Three dogs in each group had ventricular fibrillation before drug administration. Four dogs in the vasopressin group and none in the epinephrine group developed ventricu-

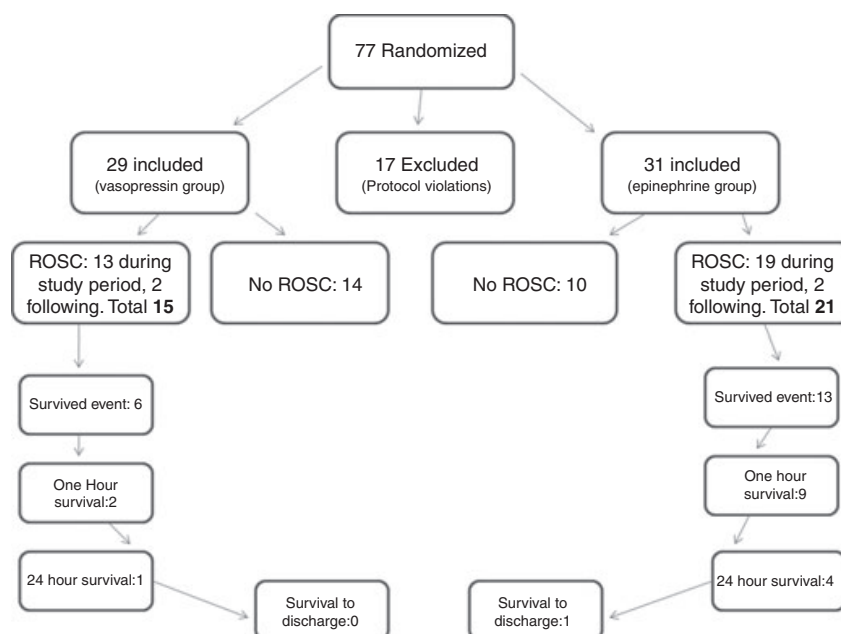


Fig 1. Summary of outcome of 77 dogs enrolled.

Table 2. Baseline characteristics of each treatment group.

	Vasopressin (n = 29)	Epinephrine (n = 31)	<i>P</i>
Sex			
Castrated male	14	10	0.63
Male	2	3	
Spayed female	11	16	
Female	2	2	
Age	0.3–17.1 (8.2) years	0.2–13.7 (9.0) years	0.93
Weight (kg)	1.4–60 (20.5)	2.8–60 (29)	0.7
Witnessed arrest	20	24	0.46
IV catheter in place prior to arrest	25	27	0.92
Type of CPR			
Closed	24	28	0.68
Open	2	1	
Both	3	2	
Location of arrest			
DOA	4	2	0.53
ER	8	6	
ICU	14	20	
Wards	3	2	
Personnel during CPR			
Intern	20	22	0.711
Resident	27	28	0.697
Faculty	15	12	0.311
Technician	28	31	0.297
Code (open, closed, none)			
Open	4	4	0.96
Closed	13	15	
None	12	12	
Presumptive cause of arrest			
Cardiac	20	15	0.56
Neuro	2	4	
Respiratory	5	10	
Trauma	1	1	
Unknown	1	1	
First recorded EKG (may be after ROSC)			
Asystole	16	12	0.16
PEA	2	5	
Ventricular fibrillation	3	4	
Sinus bradycardia	2	6	
Sinus tachycardia	2	0	
Ventricular tachycardia	0	1	

ER, emergency room; ICU, intensive care unit.

Correction added after online publication 12 October 2011: A column was mistakenly omitted from the originally published version. It has been corrected above.

lar fibrillation after the study period ($P = .050$); all 4 of these dogs received epinephrine as rescue therapy following the end of the study period and before onset of ventricular fibrillation. Not all dogs that developed ventricular fibrillation received electrical defibrillation, one received a precordial thump, and for others, CPR was discontinued before attempting defibrillation.

Of the 36 successfully resuscitated dogs, 13 were euthanized following CPR, 7/15 in the vasopressin group and 6/21 in the epinephrine group ($P = .31$).

Neurological scoring was performed on animals surviving 1 hour or longer. The scoring was not per-

Table 3. Treatments other than the study drug administered during cardiopulmonary resuscitation.

	Treatment	n (VP group)	n (Epi group)	n (total)
During study period	Atropine	20	22	42
	Defibrillation	4	3	7
	Packed red blood cells	1	2	3
	HBOC	1	0	1
	Furosemide	1	0	1
	Naloxone	1	0	1
	Calcium gluconate	1	0	1
	Total administered	22	23	45
	Epinephrine	10	8	18
	Vasopressin	8	5	13
Total	Defibrillation	8	3	11
	Packed red blood cells	1	2	3
	HBOC	1	1	2
	Calcium gluconate	1	0	1
	Sodium bicarbonate	1	2	3
	Vitamin K	1	0	1
	Naloxone	1	0	1
	Furosemide	1	0	1

formed in 2 dogs leaving 9 with complete data. All alive dogs demonstrated improving neurological scores as time progressed; because of the small numbers of dogs surviving, these data were not analyzed further. With 400 as the most severely affected dogs, and 0 as normal, in the 9 surviving dogs at 1 hour, the median score was 170, whereas at 24 hours ($n = 4$) it was 110 and in the 1 dog discharged the score was 0, having improved from 220 at 1 hour, and 30 at 24 hours.

Discussion

In this study a survival advantage at 1 hour was seen in the group receiving epinephrine compared to the group receiving vasopressin, although there was no significant difference between the 2 treatments with relation to the primary end point of ROSC at 6 minutes.

Many possible reasons might explain the failure to demonstrate a difference between vasopressin and epinephrine in ROSC at 6 minutes. One of the reported benefits of vasopressin over epinephrine is that vasopressin is effective in an acidotic environment, as might be present in animals with delayed initiation of CPR or prolonged CPR efforts. Most of the dogs in this study were hospitalized at the time of CPA, and the duration of time between CPA and initiation of CPR was very short; it is possible that vasopressin superiority could more likely be demonstrated in a group of dogs with more severe acidosis because of delayed initiation or prolonged unsuccessful CPR efforts.^{22,29} In addition, 18/29 dogs receiving vasopressin received a dose of less than 0.8U/kg, the normal recommended CPR dose. It is possible had all dogs received the

higher end of the dose range, a different effect could have been seen.¹⁸ Finally, in large-scale prospective human trials, the benefits of vasopressin have been detected in subgroup analysis of certain patient types – particularly those with asystole.²² Subgroup analysis to identify a treatment effect based on cardiac rhythm was not possible in this study because of the low number of dogs. With respect to the finding of improved survival in the epinephrine group at 1 hour, it is possible that despite randomization and blinding, the dogs with a higher chance of survival were allocated to the epinephrine group, although there were no statistical differences between the groups at baseline, the epinephrine group did contain larger numbers of dogs with respiratory mediated arrests, first noted rhythm being sinus bradycardia and more events occurring in the ICU; in contrast, the vasopressin group had higher numbers of dogs presenting DOA. These could, despite randomization, have resulted in dogs with a higher chance of survival being assigned to the epinephrine group. It is also possible that the higher rate of euthanasia in the vasopressin group, although not statistically significant, could have influenced the outcome of survival at 1 hour in favor of the group receiving epinephrine.

The rates of survival to 24 hours and survival to discharge in this study were low (8 and 1.6%, respectively) despite a higher than previously reported rate of ROSC (53%).^{4,5,8} There are a number of possible reasons for this, of which the most important is likely selection of dogs. This study was designed to examine a group of critically ill dogs in the ER or ICU, compared to other CPR studies that show a more favorable outcome for animals experiencing CPA as a result of anesthesia or drugs.⁸ As such, almost all the dogs enrolled had a serious underlying disease and so despite successful initial resuscitation, many dogs either died of progression of their disease or were euthanized for reasons of finances, prognosis, or both.

There are limitations to this study. The study was designed to assess the impact of these treatments on ROSC in a general population of dogs with CPA, but it was not powered to be able to perform subgroup analysis for certain clinical characteristics such as the impact of initial cardiac rhythm on treatment effect. In addition, long-term outcomes such as survival to 24 hours or survival to discharge cannot be assessed from this study, and future studies sufficiently powered to answer these questions will require more dogs per group. Overall, the power of this study precludes a firm conclusion on whether or not vasopressin has any advantage over epinephrine in canine CPR. An advantage was not seen in this study, however, for all of the reasons discussed above, including underpowering, high euthanasia rates, particularly in the vasopressin group and the possibility of assignment bias despite randomization, it is important to have in mind that the negative result of this trial could be because of the relatively small sample size and not attributable to the inefficacy of the intervention, a larger appropriately powered trial is needed to fully answer this question.

One of the major challenges facing CPR researchers is that by the nature of the problem being investigated, it is almost always impossible to gain informed consent from family members or in the case of veterinary studies from owners before enrollment of patients into CPR trials. Given the poor outcome of CPR in animals and the lack of high-quality evidence-based guidelines, it is clear that large-scale prospective clinical studies are going to be needed to answer some of the questions regarding efficacy of both new and existing treatment modalities. This study attempts to address this by mirroring as closely as possible the guidelines for conduction of emergency research in humans. The World Medical Association declaration of Helsinki³⁰ states that “research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative”. In the case of a veterinary CPR study, these criteria are satisfied by the fact that it is not possible to adequately explain a trial to enable an owner of an animal in cardiac arrest to give or withhold informed consent for their animal’s inclusion in the time available. The compromise that is reached is one of delayed consent where the dog is admitted into the trial, and in the event of successful resuscitation, consent is then sought from the owner for further neurological monitoring (ie, actively remaining in the trial). Additional safeguards were used in this trial as previously discussed, in particular monitoring of the interim trial results by a reviewer independent of the investigators to ensure that one group was not significantly disadvantaged. These safeguards combined with a culture of openness regarding clinical trials provides a reasonable ethical framework which balances the need for the client to be as informed as possible about the treatment that their animal is receiving, particularly when it involves research, and the need to improve the treatment of conditions that require immediate lifesaving interventions through high quality prospective clinical trials.

The neurological scoring system (Appendix 1; Table 3) used in this study has not previously been used in dogs. As all dogs remaining alive showed improving scores with time, this might be a useful tool for future studies. The prognostic implications of this score at different time points need assessment in a much larger prospective study.

Footnotes

- ^a Digital timer; Fischer Scientific, Pittsburgh, PA
^b Vasopressin 20 U/mL; APP Pharmaceuticals LLC, Schaumburg, IL
^c Epinephrine 1 mg/mL; IMS LTD, El Monte, CA
^d Randomization table (<http://www.randomization.com>)
^e 0.9% NaCl; Baxter, Inc, Deerfield, IL
^f Atropine; American Regent, Inc, Shirley, NY
^g Defibrillator LifePak 9; Medtronic Physio Control, Minneapolis, MN
^h Calcium gluconate 10% injectable; APP Pharmaceuticals
ⁱ Naloxone 0.4mg/mL injectable; Hospira Inc, Lake Forest, IL
^j Furosemide 50mg/mL injectable; Intervet International, Millsboro, DE
^k Oxyglobin; Biopure Inc, Cambridge, MA
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Appendix 1. Data collection sheet for neurological scoring for animals surviving longer than 1 hour. Scale for evaluating outcome in enrolled dogs.

	1 hour	24 hours	Discharge
Level of consciousness			
0 Normal			
30 Clouded, conscious but drowsy or irritable			
60 Stupor, motor response only to painful stimuli			
100 Coma, no motor response to painful stimuli			
Motor response to pinching toes			
0 Normal brisk withdrawal			
10 Sluggish response			
25 Very sluggish response			

(continued)

Appendix 1. Continued

	1 hour	24 hours	Discharge
50 No response			
Muscle tone (pick up and release extremities)			
0 Normal tone			
25 One of more extremities stiff or flaccid			
50 Three or more extremities stiff or flaccid			
Respiratory pattern			
0 Normal			
50 Abnormal spontaneous breathing			
100 Apnea			
Behavior (standing)			
0 Can stand			
20 Cannot stand			
Behavior (walking)			
0 Normal			
10 Unsteady gait			
20 Very unsteady or ataxic gait requiring support			
30 Cannot walk			
Behavior (response to human interaction/petting):			
0 Normal			
25 Reduced/abnormal response			
50 No response			