WORKSHEET for Evidence-Based Review of Science for Veterinary CPCR

1. Basic Demographics

Worksheet author(s)

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[redacted]

2. Clinical question: PA02

In dogs and cats with ROSC after cardiac arrest (P), does early hemodynamic optimization (I) as opposed to standard care (C), improve outcome (O) (eg. survival)?

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**

4. Search strategy (including electronic databases searched):

4a. Databases

Pub Med Search using: -ROSC -arrest -cardiopulmonary resuscitation as MeSH headings -goal directed hemodynamic optimization -early and hemodynamic optimization -dog -cat -post arrest syndrome -targeted therapy -cardiac dysfunction -lactate, ScVO2 -sepsis -myocardial dysfunction -outcome as textwords in any field. **AHA master library using**: -cardiopulmonary resuscitation and goal directed hemodynamic optimization -dog and cat -ROSC -Post resuscitation syndrome **Google Scholar Search**: -ROSC -goal directed hemodynamic optimization -early and hemodynamic optimization -dog -cat -post arrest syndrome -targeted therapy -cardiac dysfunction -outcome	**Medline Search using**: -ROSC -arrest -cardiopulmonary resuscitation as MeSH headings -goal directed hemodynamic optimization -early and hemodynamic optimization -dog -cat -post arrest syndrome -targeted therapy -cardiac dysfunction -lactate, ScVO2 -sepsis -myocardial dysfunction -outcome as text words in any field

4b. Other sources

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

Inclusion criteria

Animal studies, human studies, retrospective studies in which the original question was addressed (protocols involving strategies to influence post resuscitation hemodynamic, or, protocols involving strategies to evaluate the extent to which these parameters may predict and/or influence whether outcome), English language.

Exclusion criteria

Intra-arrest intervention (chemical or mechanical, other than those common to cpcr protocols), no ROSC (resuscitation with bypass), case reports, abstracts only, studies that do not address the initial question, isolated organ studies, review articles.

4d. Number of articles/sources meeting criteria for further review: 18

5. Summary of evidence

Evidence Supporting Clinical Question

Good		Hofmeister 2009 B,C,E			Waldrop 2004 B,C,D,E Kass 1992 B,C,D,E	*Rivers 2001 E* *Sunde 2007 C,D* *Trzeciak 2009 C,D*
Fair		Stevenson 2007 B,E	Krep 2003 E Reinhart 1989 E			*Adrie B,E* *Poeze 2005 B,E* *Kliegal 2004 B,E* *Shapiro 2006B,E*
Poor						*Kern 1996 E* *Herlitz 1995 C* *Laurent 2002B,E*
	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			Michenfelder 1990 E			*Gaieski 2009 B,C,D*
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

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:

Although there have been many clinical advancement in veterinary medicine over the past few years survival to discharge rate after cardiac arrest in dogs and cats has improved very little being < 10%. (LOE 5 ;Waldrop 2004, LOE 5; Kass 1992, LOE 2; Hofmeister 2009). Despite this discrepancy very few studies have been performed evaluating therapeutic strategies to improve this outcome. In fact, the majority of information regarding therapeutic strategies in CPCR must be inferred from the human literature which also has a paucity of RCT's.

The high mortality rate secondary to post resuscitation syndrome is considered to be a result of: (1) neurologic injury, (2) myocardial dysfunction, and (3) ischemia secondary hypoperfusion. Two retrospective studies (LOE 6; Trzeciak 2009; LOE 6; Herlitz 1995) demonstrated that arterial hypotension is associated with decreased survival and neurologic outcome. Early Goal Directed Hemodynamic Optimization is a therapeutic algorithm (see figure 1) aimed at restoring and maintaining the balance between oxygen delivery and demand in septic patients (LOE 6; Rivers 2001). However as the myocardial dysfunction and ischemic/hypoperfusion of sepsis is similar to that in post arrest syndrome (LOE 6; Adrie 2002;) these strategies have been applied to CA patients as well. Unfortunately there are , to my knowledge, no RCT's, that look at the efficacy of EGDHO for patient with return of spontaneous circulation (ROSC) post CPCR in the veterinary or human literature. One study (LOE 6; Gaieski 2009) using historical controls found that although the mortality rate appeared lower with patients treated with the protocol it did not reach significance, a fact that could have been affected by the small sample size of the study. Similarly, a prospective interventional cohort study (LOE 6; Shapiro 2006) which also used a retrospective control was not sufficiently powered to demonstrate mortality differences between the treatment and control group; however, it did suggest that the patients in the treatment protocol received more efficient care than those in the control group. Another study (LOE 6; Sunde 2007) showed EGDHO did improve survival rates; however, EGDHO was part of a therapeutic package with hypothermia, thus it could not be determined to what extent EGDHO alone affected outcome.

As there is little to no veterinary literature addressing this issue the questions must be: (1)Are the goals in this protocol physiologically reasonable and, (2) Do we have the ability to achieve them as an industry as a whole. From a physiological stand point it only makes sense to attempt to improve and maintain the balance between oxygen demand and delivery. Both dogs and cats have been shown to experience a period of cerebral microcirculatory failure despite normal cerebral perfusion (LOE 3; Krep 2003; LOE 3; Michenfelder 1990) post CA. This abnormal reperfusion state can last for several hours to days after CA. Also, "myocardial stunning", a phenomenon in which ejection fraction decreases and left ventricular end diastolic pressure increases, can be seen as early as 6 hours post CA ,resolves over 72 hours, and is responsive to inotropic agents (LOE 6; Kern 1996; LOE 6; Laurent 2002) . Although there is little clinical evidence in veterinary medicine as to what roll either of these phenomenon plays in recovery from CA, it would logic dictates that maintaining mean arterial pressure (MAP) at least within normal limits for the patient should be sound management practice and have an impact on survival. In light of the potential for post myocardial dysfunction monitoring changes in central venous pressure (CVP,) especially in the conjunction with volume replacement, would also appear to be a prudent clinical strategy. As oxygen delivery to the tissue in relation to oxygen demand is a more important reflection of hemodynamic status than blood pressure alone, monitoring parameters such as central venous oxygen saturation ($ScvO_2$) and lactate may also be important in the post resuscitation patient. There is some precedent for the use of $ScvO_2$ monitoring as studies in humans have shown that in low perfusion states conventional methods of measuring perfusion and oxygen delivery (i.e. non invasive blood pressure monitor, pulse oximetry, etc) may not be reflective of tissue hypoperfusion and oxygen debt. Lactate has been shown in dogs to be associated with poor survival in systemically ill dogs with sepsis (LOE 5; Stevenson 2007). Two studies one retrospective study of survivors of CA (LOE 6; Kliegal 2004) and a prospective diagnostic test (LOE 6;Poeze 2005) demonstrated that lactate level was inversely associated with

likelihood of survival. Mixed venous oxygen levels are more reflective of oxygen extraction than venous oxygen saturation from a peripheral venous blood sample; however pulmonary artery catheters are expensive, difficult to place, and labor intensive to maintain. $ScvO_2$ catheters, may be relatively inexpensive may be placed with fewer complications, and may be no more difficult to keep in place than a CVP catheter. In a study conducted in dogs (LOE 3; Reinhart 1989) $ScvO_2$ measurements were shown to correlate well with mixed venous oxygen (SvO_2) measurements in a variety of low perfusion states.

Can we achieve these goals? With the exception of $ScvO_2$ all of the parameters within the EGDHO protocol are relatively easy to monitor and with a some personnel organization should be possible to achieve.

7. Conclusion

At this time it is impossible to determine the usefulness of an EGDHO in dogs and cats. There are no published RCT's in veterinary medicine which address the issue of EGDHO and its impact on survival after CA. At the moment all of the conclusions drawn must be inferred from human literature in which there are also no RCT's. Although most of the human literature is very compelling it is far from definitive. In contrasts the risks on using such a protocol involve the waste of resources, both in materials and personnel, monetary loss to the client, and potential, for in appropriate therapy for patient (e.g. urinary catheters in patients when there is no reason to monitor urinary output.) In the coming years it is imperative that we examine the issues of fluid therapy, monitoring, and inotropic and vasoactive drug administration in the post resuscitation patient.

8. Acknowledgement

9. Citation list

Waldrop JE., Rozanski EA., et al. Causes of cardiopulmonary arrest, resuscitation management, and functional outcome in dogs and cats surviving cardiopulmonary arrest. *J Vet Emerg Crit Care.* 2004; 14(1):22–29.

Objective: To describe the functional outcome of canine and feline survivors of cardiopulmonary arrest (CPA) and the clinical characteristics surrounding their resuscitation. **Design**: Retrospective study. Setting: Veterinary teaching hospital. **Animals**: Client-owned dogs (15) and cats (3) with CPA. **Interventions**: None. Measurements and main results: Eighteen animals were identified to have survived to discharge following CPA. Cardiopulmonary arrest was associated with anesthesia with or without preexisting disease in 10 animals, cardiovascular collapse in 5 animals, and chronic disease with an imposed stress in 3 animals. All CPAs were witnessed in the hospital. The most common initial rhythm at CPA was asystole (72%). Return of spontaneous circulation (ROSC) was achieved in less than 15 minutes from the onset of cardiopulmonary cerebral resuscitation (CPCR) in all animals. No animals had a recurrence of CPA after the initial CPA. Animals were of a wide range of ages (0.5–16 years) and breeds. Two animals were neurologically abnormal at discharge, one of which was normal at 2 months following CPA. **Conclusions:** A good functional recovery after CPCR was documented in the small number of CPA survivors presented in this study. This may be due to the reversible nature of their inciting cause of CPA, early detections of CPA ('witnessed'), and/or the animal's underlying normal health status.

LOE 5; no industry support

Kass PH. and Haskins SC. Survival following cardiopulmonary resuscitation in dogs and cats. *Veterinary Emergency and Critical Care.* 1992; 2(2):57-65 .

Dogs and cats receiving cardiopulmonary resuscitation (CPR) were evaluated for factors leading to cardiac arrest and for survival following the procedure. One-hundred-thirty-five canine and forty-three feline patients seen at the University of California, Davis Veterinary Medical Teaching Hospital that received CPR between August 1987 and December 1991 were studied. Initial resuscitation attempts were unsuccessful in 72% of dogs and 58% of cats. Five dogs and one cat were still alive 3 days after CPR.

Ultimately only four dogs and one cat were discharged from the hospital alive. These five patients with uniquely longer survival all had cardiac arrests associated with drug and/or anesthetic reactions

LOE 5; no industry support;.

Hofmeister EH, Brainard BM, et al. Prognostic indicators for dogs and cats with cardiopulmonary arrest treated by cardiopulmonary cerebral resuscitation at a University teaching hospital. *J Am Vet Med Assoc* 2009; 235:50–57.

Objective: To determine the association among signalment, health status, other clinical variables, and treatments and events during cardiopulmonary cerebral resuscitation (CPCR) with the return of spontaneous circulation (ROSC) for animals with cardiopulmonary arrest (CPA) in a veterinary teaching hospital. **Design**: Cross-sectional study. **Animals**: 161 dogs and 43 cats with CPA. **Procedures**: Data were gathered during a 60-month period on animals that had CPA and underwent CPCR. Logistic regression was used to evaluate effects of multiple predictors for ROSC. **Results**: 56 (35%) dogs and 19 (44%) cats had successful CPCR. Twelve (6%) animals (9 dogs and 3 cats) were discharged from the hospital. Successfully resuscitated dogs were significantly more likely to have been treated with mannitol, lidocaine, fluids, dopamine, corticosteroids, or vasopressin; had CPA while anesthetized; received chest compressions while positioned in lateral recumbency; and had a suspected cause of CPA other than hemorrhage or anemia, shock, hypoxemia, multiple organ dysfunction syndrome, cerebral trauma, malignant arrhythmia, or an anaphylactoid reaction and were less likely to have been treated with multiple doses of epinephrine, had a longer duration of CPA, or had multiple disease conditions, compared with findings in dogs that were not successfully resuscitated. Successfully resuscitated cats were significantly more likely to have had more people participate in CPCR and less likely to have had shock as the suspected cause of CPA, compared with findings in cats that were not successfully resuscitated. **Conclusions and Clinical Relevance**: The prognosis was grave for animals with CPA, except for those that had CPA while anesthetized.

LOE 2; no industry support.

Krep H, Bottiger BW, et al. Time course of circulatory and metabolic recovery of cat brain after cardiac arrest assessed by perfusion- and diffusion-weighted imaging and MR-spectroscopy. *Resuscitation.* 2003; 58:337-348.

Brain recovery after cardiac arrest (CA) was assessed in cats using arterial spin tagging perfusion-weighted imaging (PWI), diffusion-weighted imaging (DWI), and 1H-spectroscopy (1H-MRS). Cerebral reperfusion and metabolic recovery was monitored in the cortex and in basal ganglia for 6 h after cardiopulmonary resuscitation (CPR). Furthermore, the effects of an hypertonic/hyperoncotic solution (7.5% NaCl/6% hydroxyl ethyl starch, HES) and a tissue-type plasminogen activator (TPA), applied during CPR, were assessed on brain recovery. CA and CPR were carried out in the MR scanner by remote control. CA for 15- 20 min was induced by electrical fibrillation of the heart, followed by CPR using a pneumatic vest. PWI after successful CPR revealed initial cerebral hyperperfusion followed by delayed hypoperfusion. Initial cerebral recirculation was improved after osmotic treatment. Osmotic and thrombolytic therapy were ineffective in ameliorating delayed hypoperfusion. Calculation of the apparent diffusion coefficient (ADC) from DWI demonstrated complete recovery of ion and water homeostasis in all animals. 1H-MRS measurements of lactate suggested an extended preservation of post-ischemic anaerobic metabolism after TPA treatment. The combination of noninvasive MR techniques is a powerful tool for the evaluation of therapeutic strategies on circulatory and metabolic cerebral recovery after experimental cerebral ischemia.

LOE 3; small # of animals in each group, decreases statistical power; supported by Deutsche Forscungsgemeinschaft.

LOE 6; low sample size; human study demonstrating that cerebral hemodynamics are altered during the first 72 hrs after ROSC; no industry support.

Michenfelder JD and Milde JH. Post ischemic canine cerebral blood flow appears to be determined by cerebral metabolic needs. *Journal of Cerebral Blood Flow and Metabolism*. 1990;10:71-76.

Summary: Following a period of complete global cerebral ischemia and reperfusion there ensues a low flow state referred to as the delayed post ischemic hypoperfusion state. It is unknown whether this low flow state contributes to neuronal injury or whether the magnitude of hypoperfusion correlates with the duration of ischemia. The latter question was addressed in 20 dogs in which complete global ischemia was induced by cerebrospinal fluid (CSF) compression for periods of 3, 9, 12, or 18 min. Following reperfusion, CBF (by sagittal sinus outflow) and CMR02 were determined for 90 min, and results were correlated with the duration of ischemia. At 90 min post ischemia the magnitude of decrease in CBF correlated crudely with the duration of ischemia ($r = - 0.67$, $p< 0.01$). For CMR02 correlation of the magnitude of decrease with the duration of ischemia was more evident ($r = -0.74$, $p < 0.001$). Furthermore, the post ischemic ratio of CBF to CMR02 was virtually identical for all dog groups regardless of the ischemic time. The adequacy of

the ratio of CBF to CMR02 was reflected by adequate oxygen levels in the sagittal sinus blood of all dogs. The authors conclude that the delayed post ischemic hypoperfusion state is probably not an important determinant of neuronal injury since its magnitude appears to be primarily determined by the metabolic needs of the brain.

LOE 3; no specific control group. each animal acted as its own control. CBF decreases post ischemia, but the magnitude is dependent on $CMR0_2$. no industry support.

Kern KB, Hilwig RW, et al. Myocardial dysfunction after resuscitation from cardiac arrest: an example of global myocardial stunning. *J Am Coll Cardiol.* 1996; 28:232-40.

Objective: This study investigated the effect of prolonged cardiac arrest and subsequent cardiopulmonary resuscitation on left ventricular systolic and diastolic function. **Background**: Cardiac arrest from ventricular fibrillation results in cessation of forward blood flow including myocardial blood flow. During cardiopulmonary resuscitation, myocardial blood flow remains suboptimal. Once the heart is defibrillated and successful resuscitation achieved reversible myocardial dysfunction, or "stunning," may occur. The magnitude and time course of myocardial stunning from cardiac arrest is unknown. **Methods**: Twenty-eight domestic swine (26 $\pm$ 1 kg) were studied with both invasive and noninvasive measurements of ventricular function before and after 10 or 15 min of untreated cardiac arrest. Contrast left ventriculograms, ventricular pressures, cardiac output, isovolnmetric relaxation time (tau) and transthoracic Doppler echo cardiographic studies were obtained. **Results:** Twenty-three of 28 animals were successfully resuscitated and post resuscitation data obtained. Left ventricular ejection fraction showed a significant reduction 30min after resuscitation ($p < 0.05$). Regional wall motion analysis revealed diffuse, global left ventricular systolic dysfunction. Left ventricular end-diastolic pressure increased significantly in the post resuscitation period ($p < 0.05$). Isovolumetric relaxation time (tau) was significantly increased over baseline by 2h after resuscitation ($p < 0.05$). Similar findings were noted with the doppler echo cardiographic analysis, including a reduction of fractional shortening ($p < 0.05$), a reduction mitral valve deceleration time ($p<0.05$) and an increase in left ventricular isovolumetric relaxation time at 5 h after resuscitation ($p < 0.05$). by 24 h, these invasive and noninvasive variables of systolic and diastolic left ventricular function had begun to improve. At 48 h all measures of left ventricular function had returned to baseline levels. **Conclusions:** Myocardial systolic and diastolic dysfunction is severe after 10 to 15 min of untreated cardiac arrest and successful resuscitation. Full recovery of this post resuscitation myocardial stunning is seen by 48 h in this experimental model of ventricular fibrillation cardiac arrest.

LOE 6; no control group; no industry support.

Adrie C, Adib-Conquy M, et al. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. *Circulation*. 2002;106:562-568.

Background: We investigated the immunoinflammatory profile of patients successfully resuscitated after cardiac arrest, representing a model of whole-body ischemia/reperfusion syndrome. **Methods and Results**: Plasma cytokine, endotoxin, and ex vivo cytokine production in whole-blood assays was assessed in 61, 35, and 11 patients, respectively. On admission, high levels of plasma interleukin (IL)-6, IL-8, IL-10, and soluble tumor necrosis factor (TNF) receptor type II could discriminate between survivors and nonsurvivors. Among nonsurvivors, the initial need for a vasopressor agent was associated with higher levels of IL-1 receptor antagonist, IL-10, and IL-6 on day 1. Plasma endotoxin was detected in 46% of the analyzed patients within the 2 first days. Endotoxin-induced TNF and IL-6 productions were dramatically impaired in these patients compared with healthy control subjects, whereas an unaltered production was observed with heat-killed *Staphylococcus aureus*. In contrast, IL-1 receptor antagonist productions were enhanced in these patients compared with healthy control subjects. The productions of T-cell– derived IL-10 and interferon-_ were also impaired in these patients. Finally, using in vitro plasma exchange between healthy control subjects and patients, we demonstrated that the endotoxin-dependent hyporeactivity was an intrinsic property of patients' leukocytes and that an immunosuppressive activity was also present in their plasma.
Conclusions :Altogether, the high levels of circulating cytokines, the presence of endotoxin in plasma, and the dysregulated production of cytokines found in these patients recall the immunological profile found in patients with sepsis.

LOE 6; no industry support.

Trzeciak S, Jones AE, et al. J. Significance of arterial hypotension after resuscitation from cardiac arrest. *Crit Care Med.* 2009; 37(11): 2895–2903.

Objective*:* Expert guidelines advocate hemodynamic optimization after return of spontaneous circulation (ROSC) from cardiac arrest despite a lack of empirical data on prevalence of post-ROSC hemodynamic abnormalities and their relationship with outcome. The objective was to determine whether post-ROSC arterial hypotension predicts outcome among post cardiac arrest patients who survive to intensive care unit admission. **Design***:* Cohort study utilizing the Project IMPACT database (intensive care unit admissions from 120 U.S. hospitals) from 2001–2005.

Setting*:* One hundred twenty intensive care units. **Patients***:* Inclusion criteria were: 1) age >18 yrs; 2) non-trauma; and 3) received cardiopulmonary resuscitation before intensive care unit arrival. **Interventions***:* None. **Measurements and Main Results***:* Subjects were divided into two groups: 1) Hypotension Present—one or more documented systolic blood pressure <90 mm Hg within 1 hr of intensive care unit arrival; or 2) Hypotension Absent—all systolic blood pressure >90 mm Hg. The primary outcome was in-hospital mortality. The secondary outcome was functional status at hospital discharge among survivors. A total of 8736 subjects met the inclusion criteria. Overall mortality was 50%. Post-ROSC hypotension was present in 47% and was associated with significantly higher rates of mortality (65% vs. 37%) and diminished discharge functional status among survivors (49% vs. 38%), $p < .001$ for both. On multivariable analysis, post-ROSC hypotension had an odds ratio for death of 2.7 (95% confidence interval, 2.5–3.0). **Conclusions***:* Half of post cardiac arrest patients who survive to intensive care unit admission die in the hospital. Post-ROSC hypotension is common, is a predictor of in-hospital death, and is associated with diminished functional status among survivors. These associations indicate that arterial hypotension after ROSC may represent a potentially treatable target to improve outcomes from cardiac arrest.

LOE 6; hypotension post ROSC associated with in hospital death, survivors-diminished function at discharge. support from Novo Nordisk, Eli Lilly, Hutchinson Technologies, Istat, Biosite, and Artisan.

Herlitz J, Ekstrtim L, et al. Hospital mortality after out-of-hospital cardiac arrest among patients found in ventricular fibrillation. *Resuscitation.* 1995; 9(1): l- 21.

Objective: To describe factors associated with in-hospital mortality among patients being hospitalized after out-of-hospital cardiac arrest and who were found in ventricular fibrillation. **Methods**: The study was set in the community of Giiteborg, Sweden. The subjects consisted of all patients who were hospitalized alive after out-of-hospital cardiac arrest, being reached by the mobile coronary care unit and who were found in ventricular fibrillation, between 1981
and 1992. **Results:** In all, 488 patients fulfilled the inclusion criteria of which 262 (54%) died during initial hospitalization. In a multivariate analysis including age, sex, history of cardiovascular disease chronic medication prior to arrest and circumstance at the time of arrest, the following appeared as independent predictors of hospital mortality: (1) interval between collapse and first defibrillation ($P < 0.001$); (2) on chronic medication with diuretics ($P < 0.01$); (3) age($P< 0.01$); (4) bystander initiated CPR ($P < 0.05$); and (5) a history of diabetes($P < 0.05$). In a multivariate analysis considering various aspects of status on admission to hospital, the following were independently associated with death: (1) degree of consciousness ($P < 0.001$) and (2) systolic blood pressure($P < 0.05$). **In conclusion**, among patients with out of hospital cardiac arrest found in ventricular fibrillation and being hospitalized alive, 54% died in hospital. The in-hospital mortality was related to patient characteristics before the cardiac arrest as well as to factors at the resuscitation itself.

LOE 6. retrospective study, hospital registry, no controls; in hospital death post ROSC associated with systolic blood pressure; poor

Rivers E, Nguyen B, et al. Early goal directed therapy in the treatment of the severe sepsis and septic shock. N Engl J Med. 2001; 345(19):1368-77.

Background: Goal-directed therapy has been used for severe sepsis and septic shock in the intensive care unit. This approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the intensive care unit. **Methods**: We randomly assigned patients who arrived at an urban emergency department with severe sepsis or septic shock to receive either six hours of early goal-directed therapy or standard therapy (as a control) before admission to the intensive care unit. Clinicians who subsequently assumed the care of the patients were blinded to the treatment assignment. In-hospital mortality (the primary efficacy outcome), end points with respect to resuscitation, and Acute Physiology and Chronic Health Evaluation (APACHE II) scores were obtained serially for 72 hours and compared between the study groups. **Results***:* Of the 263 enrolled patients, 130 were randomly assigned to early goal-directed therapy and 133 to standard therapy; there were no significant differences between the groups with respect to base-line characteristics. In-hospital mortality was 30.5 percent in the group assigned to early goal-directed therapy, as compared with 46.5 percent in the group assigned to standard therapy ($P=0.009$). During the interval from 7 to 72 hours, the patients assigned to early goal directed therapy had a significantly higher mean ($\pm$SD) central venous oxygen saturation (70.4$\pm$10.7 percent vs. 65.3$\pm$11.4 percent), a lower lactate concentration (3.0$\pm$4.4 vs. 3.9$\pm$4.4 mmol per liter), a lower base deficit (2.0$\pm$6.6 vs. 5.1$\pm$6.7 mmol per liter), and a higher pH (7.40$\pm$0.12 vs. 7.36$\pm$0.12) than the patients assigned to standard therapy ($P\leq0.02$ for all comparisons). During the same period, mean APACHE II scores were significantly lower, indicating less severe organ dysfunction, in the patients assigned to early goal-directed therapy than in those assigned to standard therapy (13.0$\pm$6.3 vs. 15.9$\pm$6.4, $P<0.001$). **Conclusions:** Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock.

LOE 6; industry support from Edwards Life Sciences and Nova Biomedical.

Gaieski DF, Banda RA, et al., Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Resuscitation* 2009; 80:418–424.

Background*:* Comatose survivors of out-of-hospital cardiac arrest (OHCA) have high in-hospital mortality due to a complex pathophysiology that includes cardiovascular dysfunction, inflammation, coagulopathy, brain injury and persistence of the precipitating pathology. Therapeutic hypothermia (TH) is the only intervention that has been shown to improve outcomes in this patient population. Due to the similarities between the post-cardiac arrest state and severe sepsis, it has been postulated that early goal-directed hemodynamic optimization (EGDHO) combined with TH would improve outcome of comatose cardiac arrest survivors. **Objective:** We examined the feasibility of establishing an integrated post-cardiac arrest resuscitation (PCAR) algorithm combining TH and EGDHO within 6 h of emergency department (ED) presentation. **Methods***:* In May, 2005 we began prospectively identifying comatose (Glasgow Motor Score < 6) survivors of OHCA treated with our PCAR protocol. The PCAR patients were compared to matched historic controls from a cardiac arrest database maintained at that institution. **Results:** Between May, 2005 and January, 2008, 18/20 (90%) eligible patients were enrolled in the PCAR protocol. They were compared to historic controls from 2001 to 2005, during which time 18 patients met inclusion criteria for the PCAR protocol. Mean time from initiation of TH to target temperature (33 ◦C) was 2.8 h (range 0.8-23.2; SD = h); 78% (14/18) had interventions based upon EGDHO parameters; 72% (13/18) of patients achieved their EGDHO goals within 6 h of return of spontaneous circulation (ROSC). Mortality for historic controls who qualified for the PCAR protocol was 78% (14/18); mortality for those treated with the PCAR protocol was 50% (9/18) (p = 0.15). **Conclusions:** In patients with ROSC after OHCA, EGDHO and TH can be implemented simultaneously

LOE 6; support from Gaymar Industries; historic controls, small sample size; part of combine strategy with therapeutic hypothermia.

Sunde K, Pyttea M, et al. Implementation of a standardized treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation.* 2007; 73:29-39.

Background: Mortality among patients admitted to hospital after out-of-hospital cardiac arrest (OHCA) is high. Based on recent scientific evidence with a main goal of improving survival, we introduced and implemented a standardized post resuscitation protocol focusing on vital organ function including therapeutic hypothermia, percutaneous coronary intervention (PCI), control of hemodynamics, blood glucose, ventilation and seizures. **Methods:** All patients with OHCA of cardiac etiology admitted to the ICU from September 2003 to May 2005 (intervention period) were included in a prospective, observational study and compared to controls from February 1996 to February 1998. **Results***:* In the control period 15/58 (26%) survived to hospital discharge with a favorable neurological outcome versus 34 of 61 (56%) in the intervention period (OR 3.61, CI 1.66-7.84, p = 0.001). All survivors with a favorable neurological outcome in both groups were still alive 1 year after discharge. Two patients from the control period were revascularized with thrombolytics versus 30 (49%) receiving PCI treatment in the intervention period (47 patients (77%) underwent cardiac angiography). Therapeutic hypothermia was not used in the control period, but 40 of 52 (77%) comatose patients received this treatment in the intervention period.

LOE 6; comparable to LOE 2 study; no relevant dog/cat study in the literature; no industry support; fair

Poeze M, Solberg BCJ, et al. Monitoring global volume-related hemodynamic or regional variables after initial resuscitation: What is a better predictor of outcome in critically ill septic patients? *Crit Care Med.* 2005; 33(11): 2494–2500.

Objective: Regional variables of organ dysfunction are thought to be better monitoring variables than global pressure-related hemodynamic variables. Whether a difference exists between regional and global volume-related variables in critically ill patients after resuscitation is unknown. **Design:** Prospective diagnostic test evaluation. **Setting:** University-affiliated mixed intensive care unit. **Patients:** Twenty-eight critically ill patients. **Interventions:** Using standardized resuscitation, hemodynamic optimization was targeted at mean arterial pressure, heart rate, occlusion pressure, cardiac output, systemic vascular resistance, and urine output. Primary outcome variable was in-hospital mortality. **Measurements and Main Results:** During resuscitation, global volume-related hemodynamic variables were measured simultaneously and compared with regional variables. At admission no variable was superior as a predictor of outcome. During resuscitation, significant changes were seen in mean arterial pressure, central venous pressure, oxygen delivery, systemic vascular resistance, total blood volume, right heart and ventricle end-diastolic volume, right ventricle ejection fraction, right and left stroke work index, intramucosal carbon dioxide pressure, gastric mucosal pH, mucosal-end tidal PCO2 gap, indocyanine green blood clearance, indocyanine green plasma clearance, and plasma disappearance rate. Multivariate analysis identified lactate, gastric mucosal pH, mucosal end tidal PCO2 gap, mucosal-arterial PCO2 gap, indocyanine green plasma clearance, and plasma disappearance rate of dye as nondependent predictors of outcome. Patients who subsequently died had a significantly lower gastric mucosal pH, higher intramucosal carbon dioxide pressure and mucosal-end tidal PCO2 gap, and lower

indocyanine green blood clearance, indocyanine green plasma clearance, plasma disappearance rate, and right ventricular end-diastolic volume index, of which gastric mucosal pH, mucosal-end tidal PCO2 gap, and indocyanine green blood clearance were the most important predictors of outcome. **Conclusions***:* Initial resuscitation of critically ill patients with shock does not require monitoring of regional variables. After stabilization, however, regional variables are the best predictors of outcome.

LOE 6; no industry support.

Reinhart K, Rudolph T, et al. Comparison of central-venous to mixed-venous oxygen saturation during changes in oxygen supply/demand. *Chest.* 1989; 95:1216-21.

Because central venous saturation, superior vena cava, $ScvO_2$, can be monitored with less patient risk than mixed venous oxygen saturation, pulmonary artery SvO_2, we examined the correlations between SvO_2 and $ScvO_2$ over a broad range of cardiorespiratory conditions, including hypoxia, hemorrhage, and resuscitation in anesthetized dogs. The correlation coefficient (r) between SvO_2 and $ScvO_2$ in 179 simultaneously drawn blood samples from 22 dogs was 0.97. In another nine dogs, the two sites were continuously and simultaneously monitored with fiberoptic catheters; r was 0.96 with a mean difference of 3.7:t:2.9 percent (SD) saturation. In each dog the changes in $ScvO_2$ closely paralleled the changes in SvO_2. Although absolute values of $ScvO_2$ are not sufficiently identical to SvO_2 to calculate O_2 uptake or pulmonary shunt precisely, close tracking of changes in the two sites across a wide range of hemodynamic conditions warrant further consideration of $ScvO_2$ for patient monitoring of trends in O_2 supply/demand.

LOE 3; no randomization; no industry support.

Kliegel A, Losert H, et al. Serial lactate determinations for prediction of outcome after cardiac arrest. *Medicine.* 2004; 83(5): 274– 279.

The investigators investigated the relationship between lactate clearance and outcome in patients surviving the first 48 hours after cardiac arrest. We conducted the study in the emergency department of an urban tertiary care hospital. We analyzed the data for all 48-hour survivors after successful resuscitation from cardiac arrest during a 10-year period. Serial lactate measurements, demographic data, and key cardiac arrest data were correlated to survival and best neurologic outcome within 6 months after cardiac arrest. Parameters showing significant results in univariate analysis were tested for significance in a logistic regression model. Of 1502 screened patients, 394 were analyzed. Survivors (n = 194, 49%) had lower lactate levels on admission (median, 7.8 [interquartile range, 5.4–10.8] vs. 9 [6.6–11.9] mmol/L), after 24 hours (1.4 [1–2.5] vs. 1.7 [1.1–3] mmol/L), and after 48 hours (1.2 [0.9–1.6] vs. 1.5 [1.1–2.3] mmol/L). Patients with favorable neurologic outcome (n = 186, 47%) showed lower levels on admission (7.6[5.4–10.3] vs. 9.2 [6.7–12.1] mmol/L) and after 48 hours (1.2 [0.9–1.6] vs. 1.5 [1–2.2]mmol/L). In multivariate analysis, lactate levels at 48 hours were an independent predictor for mortality (odds ratio [OR]: 1.49 increase per mmol/L, 95% confidence interval [CI]: 1.17–1.89) and unfavorable neurologic outcome (OR: 1.28 increase per mmol/L, 95% CI: 1.08–1.51). Lactate levels higher than 2 mmol/L after 48 hours predicted mortality with a specificity of 86% and poor neurologic outcome with a specificity of 87%. Sensitivity for both end points was 31%. Lactate at 48 hours after cardiac arrest is an independent predictor of mortality and unfavorable neurologic outcome. Persisting hyperlactatemia over 48 hours predicts a poor prognosis.

LOE 6; no industry support.

Stevenson CK, Kidney BA, et al. Serial blood lactate concentrations in systemically ill dogs. *Vet Clin Pathol*. 2007;36:234–239.

Background: Lactate concentration often is quantified in systemically ill dogs and interpreted based on human data. To our knowledge, there are no published clinical studies evaluating serial lactate concentrations as a prognostic indicator in ill dogs. **Objectives:** Our objective was to perform a prospective study, using multivariate analysis, to determine whether serial lactate concentrations were associated with outcome in ill dogs requiring intravenous fluids. **Methods:** Eighty sick dogs had lactate concentrations evaluated, using an analyzer that measures lactate in the plasma fraction of heparinized whole blood, at 0 hours and 6 hours after initiation of treatment. Severity of illness and outcome (survivor, nonsurvivor) were determined by reviewing the patient's record 2 weeks after admission. Lactate concentrations, age, body weight, gender, and severity of illness were evaluated using multivariate analysis to determine their effects on outcome. **Results**: Dogs with lactate concentrations greater than the reference interval at 6 hours were 16 times (95% confidence interval 5 2.32–112.71 times, P ,.01) more likely not to survive compared to dogs with lactate concentrations within the reference interval. Lactate concentrations above the reference interval at 0 hours were not significantly related to outcome. However, hyperlactatemia that did not improve by _50% within 6 hours was significantly associated with mortality (P 5 .024). **Conclusion:** Dogs with a lactate concentration higher than the reference interval at 6 hours were more likely not to survive. These results indicate an association between lactate concentration and outcome and emphasize the importance of serial lactate concentrations in evaluating prognosis.

LOE 5; no industry support.

Laurent I, Monchi M, et al. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. *J Am Coll Cardiol.* 2002; 40:2110–6.

Objective: The aim of the study was to assess the hemodynamic status of survivors of out-of-hospital cardiac arrest (OHCA). BACKGROUND The global prognosis after successfully resuscitated patients with OHCA remains poor. Clinical studies describing the hemodynamic status of survivors of OHCA and its impact on prognosis are lacking. **Methods**: Among 165 consecutive patients admitted after successful resuscitation from OHCA, 73 required invasive monitoring because of hemodynamic instability, defined as hypotension requiring vasoactive drugs, during the first 72 h. Clinical features and data from invasive monitoring were analyzed. **Results**: Hemodynamic instability occurred at a median time of 6.8 h (range 4.3 to 7.3) after OHCA. The initial cardiac index (CI) and filling pressures were low. Then, the CI rapidly increased 24 h after the onset of OHCA, independent of filling pressures and inotropic agents (2.05 [1.43 to 2.90] 8 h vs. 3.19 l/min per m2 [2.67 to 4.20] 24 h after OHCA; $p < 0.001$). Despite a significant improvement in CI at 24 h, a superimposed vasodilation delayed the discontinuation of vasoactive drugs. No improvement in CI at 24 h was noted in 14 patients who subsequently died of multiorgan failure. Hemodynamic status was not predictive of the neurologic outcome. **Conclusions**: In survivors of OHCA, hemodynamic instability requiring administration of vasoactive drugs is frequent and appears several hours after hospital admission. It is characterized by a low CI that is reversible in most cases within 24 h, suggesting post-resuscitation myocardial dysfunction. Early death by multiorgan failure is associated with a persistent low CI at 24 h.

LOE 6; comparable to LOE 2, no industry support.

Shapiro NI, Howell MD, et al. Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol. *Crit Care Med.* 2006; 34:1025–1032.

Objective: To describe the effectiveness of a comprehensive, interdisciplinary sepsis treatment protocol with regard to both implementation and outcomes and to compare the mortality rates and therapies of patients with septic shock with similar historical controls. **Design***:* Prospective, interventional cohort study with a historical control comparison group. **Setting***:* Urban, tertiary care, university hospital with 46,000 emergency department visits and 4,100 intensive care unit admissions annually. **Patients***:* Inclusion criteria were a) emergency department patients
aged >18 yrs, b) suspected infection, and c) lactate of >4 mmol/L or septic shock. Exclusion criteria were a) emergent operation, b) pre-hospital cardiac arrest, and c) comfort measures only. Time period: protocol, November 10, 2003, through November 9, 2004; historical controls, February 1, 2000, through January 31, 2001. **Intervention***:* A sepsis treatment pathway incorporating empirical antibiotics, early goal-directed therapy, drotrecogin alfa, steroids, intensive insulin therapy, and lung-protective ventilation. **Measurements and Main Results***:* There were 116 protocol patients, with a mortality rate of 18% (11–25%), of which 79 patients had septic shock. Comparing these patients with 51 historical controls, protocol patients received more fluid (4.0 vs. 2.5 L crystalloid, $p < .001$), earlier antibiotics (90 vs. 120 mins, $p < .013$), more appropriate empirical coverage (97% vs. 88%, $p < .05$), more vasopressors in the first 6 hrs (80% vs. 45%, $p < .001$), tighter glucose control (mean morning glucose, 123 vs. 140, $p < .001$), and more frequent assessment of adrenal function (82% vs. 10%, $p < .001$), with a nonstatistically significant increase in dobutamine use (14% vs. 4%, $p = .06$) and red blood cell transfusions (30% vs. 18%, $p = .07$) in the first 24 hrs. For protocol patients with septic shock, 28-day in-hospital mortality was 20.3% compared with 29.4% for historical controls ($p = .3$). **Conclusions***:* Clinical implementation of a comprehensive sepsis treatment protocol is feasible and is associated with changes in therapies such as time to antibiotics, intravenous fluid delivery, and vasopressor use in the first 6 hrs. No statistically significant decrease in mortality was demonstrated, as this trial was not sufficiently powered to assess mortality benefits.

LOE 6; historical controls; industry support from Eli Lilly and Edward Life Sciences.

SUMMARY

Fig. 1 Protocol for early Goal-Directed Therapy.
CVP-central venous pressure, MAP-mean arterial pressure, and ScvO- central venous oxygen saturation.
from Rivers E, Nguyen B, et al. Early goal directed therapy in the treatment of the severe sepsis and septic shock. N Engl J Med. 2001; 345(19):1368-77**.**