

## WORKSHEET for Evidence-Based Review of Science for Veterinary CPR

### 1. Basic Demographics

#### Worksheet author(s)

Gareth Buckley	Date Submitted for review:

### 2. Clinical question:

In dogs and cats with cardiac arrest and suspected narcotic depression (P), does naloxone (I) when compared to effective ventilation without naloxone (C), improve outcome (O)?

### 3. Conflict of interest specific to this question:

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

No.

### 4. Search strategy (including electronic databases searched):

#### 4a. Databases

*-MEDLINE via PUBMED (1950 to May 2009) (performed on 5/30/11)*

*CPA OR CPR OR "cardiac arrest" OR resuscitation OR "cardiopulmonary resuscitation" AND naloxone OR "drug reversal" OR "opioid reversal" OR "opioid overdose"*

*10 relevant hits out of 368 total hits*

*-CAB (1910 to Feb 2011) (performed on 5/30/11)*

*CPA OR CPR OR "cardiac arrest" OR resuscitation OR "cardiopulmonary resuscitation" AND naloxone OR "drug reversal" OR "opioid reversal" OR "opioid overdose"*

*One further relevant hit, several veterinary references were located but the vast majority were reviews or case series/retrospective studies that did not deal with naloxone use*

#### 4b. Other sources

*Hand searches using terms, "CPR", "CPA", "cardiopulmonary resuscitation", "resuscitation", "cardiac arrest" of: Journal of Veterinary Emergency and Critical Care, Journal of the American Animal Hospital Association, Journal of Veterinary Internal Medicine, Journal of Veterinary Surgery, American Journal of Veterinary Research*

*No further articles of relevance identified*

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

##### Inclusion criteria

*Animals or humans with naturally occurring or experimentally induced cardiac arrest  
Documentation of naloxone use*

##### Exclusion criteria

*Reviews or editorials  
Abstracts only  
Single case reports only*

*Studies looking at naloxone in non cardiac arrest patients*

**4d. Number of articles/sources meeting criteria for further review: 11**

**5. Summary of evidence**

**Evidence Supporting Clinical Question**

<b>Good</b>						
<b>Fair</b>			Rothstein 1985 A&B			
<b>Poor</b>						<i>Seal 2005 (E): survival (unspecified)</i>  <i>Wang 2008 (A)</i>  <i>Chen 2006 (A)</i>  <i>Chen 2006 (A)</i>  <i>Wang 2010 (A,D)</i>  <i>Saybolt (E): improvement in EKG rhythm</i>
	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>
<b>Level of evidence (P)</b>						

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

<b>Good</b>						
<b>Fair</b>			Foley et al 1987, (E): hemodynamics and plasma epi/norepi levels			
<b>Poor</b>				Waldrop 2004 (D)		<i>Gervais 1997(E): hemodynamic parameters</i>
	1	2	3	4	5	6
<b>Level of evidence (P)</b>						

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

<b>Good</b>						
<b>Fair</b>						
<b>Poor</b>						<i>Sun et al 2004 (E): myocardial dysfunction</i>
	1	2	3	4	5	6
<b>Level of evidence (P)</b>						

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:

*The evidence in this area is extremely sparse. Almost all of the references and discussion of use of naloxone in the human field deals with use (and abuse) of naloxone in neonatal resuscitation, usually with a heartbeat present and so is less relevant to this PICO question. A small amount of literature, cited above, deals with use of naloxone in heroin overdose which includes some victims with presumed cardiopulmonary arrest (Saybolt, Seal). In the Saybolt study, an improvement in EKG rhythm was demonstrated in people receiving naloxone and it was recommended that naloxone should be used in the event of suspected opioid overdose; the Seal study showed a high rate (100%) of survival following naloxone administration by trained lay people in a situation of heroin overdose. In this study although CPR was performed in 80% of cases, cardiac arrest was not confirmed by medical personnel at the time of naloxone administration in all cases. Four rat studies (Wang 2008, Wang 2010, Chen 2006, Chen 2006) examined use of naloxone in CPR without opioid overdose, these studies all demonstrated that naloxone or epinephrine appeared to improve the rates of ROSC in rats subjected to asphyxial cardiac arrest, indeed the Wang paper also demonstrated decreased cerebral damage in the group administered naloxone. Unfortunately the model used (a non target species) and the fact that opioid overdose was not part of the model makes it challenging to translate these models into clinical practice. There are two papers in dogs – one of which (Waldrop) is a retrospective review of survivors of CPR, of animals experiencing cardiac arrest in association with anesthesia, 3 out of 10 survivors received naloxone, this was considered neutral to the clinical question as both animals who did and did not receive naloxone went on to survive. Rothstein et al examined dogs with experimentally induced ventricular fibrillation, this group concluded that naloxone has no benefit in facilitating defibrillation and has no hemodynamic effects, however, did appear to be associated with conversion of electro-mechanical disassociation to a perfusing rhythm following countershock. Foley, in a canine model and Gervais, in a porcine model, demonstrated that hemodynamic parameters remain unchanged by the administration of naloxone, these were both in ventricular fibrillation models. Sun demonstrated a worsening of cardiac function following ROSC in rats administered naloxone during CPR as compared to rats administered an opioid.*

*Overall, the use of naloxone cannot be recommended routinely during CPR, but based on the small studies involving humans with heroin overdose, use of naloxone during CPR in patients with known or highly suspected opioid overdose appears reasonable, this would likely be considered a class IIb intervention in the ILCOR grading scheme. It must be emphasized that this is a weak recommendation based on observations in a non-target species.*

## 7. Conclusion

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

CONSENSUS ON SCIENCE: *One human case series demonstrated an improvement in EKG following naloxone administration in humans, another human study demonstrated a high survival rate following naloxone administration for heroin overdose however this study was flawed in that CPA was not always confirmed. A variety of rat models have demonstrated that naloxone appears to improve rates of ROSC, however this involved a non opioid overdose asphyxial model with limited relevance to this question. It has been demonstrated in dogs that hemodynamic parameters do not change during CPR with or without naloxone, however, neither of these canine models included opioid overdose. Given the experience in clinical scenarios in humans with heroin overdose, and the improvements seen with naloxone administration it is reasonable to administer naloxone during CPR in cases of suspected opioid overdose (Class IIb), there is no evidence, however, to suggest that routine administration of naloxone during CPR is helpful, and, as harmful effects have been reported, this should be avoided (Class III).*

## **8. Acknowledgement**

## **9. Citation list**

Rothstein RJ, Niemann JT, Rennie CJ et al. "Use of Naloxone During Cardiac Arrest and CPR: Potential Adjunct for Postcountershock Electrical-Mechanical Dissociation." *Ann Emerg Med* 1985;14:198-203

*Naloxone has been shown to increase arterial pressure in hemorrhagic and septic shock. To determine if naloxone has salutary effects during cardiac arrest with conventional closed-chest cardiopulmonary resuscitation (CPR), ten dogs were studied during 20 minutes of ventricular fibrillation (VF) and CPR and during a 30-minute postcountershock period. Central aortic (Ao) and right atrial (RA) systolic and end-diastolic (EDP) pressures, instantaneous Ao-RA pressure difference (coronary perfusion pressure), and electromagnetic Ao flow were measured. Ao and RA samples were analyzed during a control period and at five-minute intervals during CPR for PO<sub>2</sub>, PCO<sub>2</sub>, and pH. During VE a piston-cylinder device was used to perform anteroposterior sternal depressions and positive pressure ventilations (100% O<sub>2</sub>) at standard rates and ratios. After 15 minutes of CPR, animals were randomized and given either naloxone (5 mg/kg) or epinephrine (1 mg). Defibrillation was attempted five minutes later using 1 J/kg and then, if necessary, 2, 4, 8, 12, and 16 J/kg until VF was terminated or the maximum energy dose was reached. If VF persisted or if countershock resulted in asystole or a nonperfusing rhythm (electrical-mechanical dissociation [EMD]), the alternate drug (naloxone or epinephrine) was then given. Measured systolic pressures, coronary perfusion pressures, aortic flow, and blood gases were not significantly different during the control period or at five, ten, and 15 minutes of VF and CPR between animal groups prior to drug administration. When compared to hemodynamic values measured at 15 minutes, naloxone had no significant effect on pressures or aortic flow measured five minutes after administration. Epinephrine significantly increased 20-minute values (P < .05) when compared to those at 15 minutes: Ao, 110 +/- 26 mm Hg vs 69 +/- 17; AoEDP, 50 +/- 19 vs 21 +/- 5; RA, 116 +/- 19 vs 95 +/- 16; coronary perfusion pressure, 49 +/- 29 vs 16 +/- 11. No animal that initially received naloxone prior to countershock was defibrillated despite use of the maximal energy dose; following epinephrine, countershock produced a perfusing rhythm in four of five animals. In contrast, countershock resulted in EMD in four of five of these animals that initially received epinephrine. Naloxone was then given, and all four developed a perfusing rhythm. We conclude that naloxone has no hemodynamic effect during CPR and does not facilitate defibrillation, and that naloxone may be of benefit in the management of EMD following countershock.*

Level 3, supporting, Funding: NIH, Physio-Control Corporation, Redmond, WA.

Key points: Experimental study in a target species. Dogs receiving naloxone following development of EMD after countershock developed a perfusing rhythm. Treatment with naloxone prior to development of EMD did not facilitate defibrillation or affect hemodynamics but did prevent development of EMD following epinephrine administration and countershock.

Seal KH, Thawley R, Gee L et al. "Naloxone Distribution and Cardiopulmonary Resuscitation Training for Injection Drug Users to Prevent Heroin Overdose Death: A Pilot Intervention Study." *J Urban Health*;80(2):303-311

*Fatal heroin overdose has become a leading cause of death among injection drug users (IDUs). Several recent feasibility studies have concluded that naloxone distribution programs for heroin injectors should be implemented to decrease heroin overdose deaths, but there have been no prospective trials of such programs in North America. This pilot study was undertaken to investigate the safety and feasibility of training injection drug using partners to perform cardiopulmonary resuscitation (CPR) and administer*

*naloxone in the event of heroin overdose. During May and June 2001, 24 IDUs (12 pairs of injection partners) were recruited from street settings in San Francisco. Participants took part in 8-hour training in heroin overdose prevention, CPR, and the use of naloxone. Following the intervention, participants were prospectively followed for 6 months to determine the number and outcomes of witnessed heroin overdoses, outcomes of participant interventions, and changes in participants' knowledge of overdose and drug use behavior. Study participants witnessed 20 heroin overdose events during 6 months follow-up. They performed CPR in 16 (80%) events, administered naloxone in 15 (75%) and did one or the other in 19 (95%). All overdose victims survived. Knowledge about heroin overdose management increased, whereas heroin use decreased. IDUs can be trained to respond to heroin overdose emergencies by performing CPR and administering naloxone. Future research is needed to evaluate the effectiveness of this peer intervention to prevent fatal heroin overdose.*

*Level 6, supporting, Funding: Not Specified.*

*Key Points: Assessed combination of naloxone in CPR following opioid overdose which seemed very effective. Study is limited by lack of confirmed CPA and the fact it is a non target species (humans).*

*Wang Y, Gao L, Meng L. "Naloxone Combined With Epinephrine Decreases Cerebral Injury in Cardiopulmonary Resuscitation." J Emerg Med 2010;39(3):296-300*

*Cardiopulmonary arrest is a serious disease that claims many lives every day; 30% of the patients suffer irreversible central nervous system injury after restoration of systemic circulation (ROSC). Objectives: Naloxone combined with epinephrine was tested in a cardiac arrest rat model in which asphyxia was induced to determine if this drug combination could increase the resuscitation rate (survival) and decrease the cerebral damage. Twenty-four male Wistar rats were randomly assigned to one of three groups: the group treated with 1 mL saline (SA group; n = 8), the group treated with only epinephrine 5mcg/100 g (EP group; n = 8), or the group treated with epinephrine 5 mcg/100 g combined with naloxone 1 mg/kg (NA group; n = 8). Eight minutes after arrest, cardiopulmonary resuscitation was initiated and the different drugs were administered to the rats in their respective groups at the same time. Mean arterial pressure (MAP), heart rate (HR), and neurodeficit score (NDS) were measured. The HR in the NA group (414 +/- 45 beats/min) was faster than in the EP group (343 +/- 29 beats/min) at the 5-min time point (P < 0.01). The HR in the NA group was 392 +/- 44 beats/min and 416 +/- 19 beats/min at the 60-min and 180-min time points, respectively. There were no statistically significant differences in MAP before or after ROSC. The rates of ROSC were 2 of 8, 6 of 8, and 7 of 8 animals in the SA group, EP group, and NA group, respectively. Three days later, the rates decreased to 1, 3, and 5 in the SA group, EP group, and NA group, respectively. The average resuscitation time in the NA group was significantly shorter than in the other two groups. The NDS in the NA group was 57 +/- 13, higher than in the EP group (45 +/- 13) and SA group (38). Naloxone combined with epinephrine significantly increased the resuscitation rate in a rat model. Furthermore, the combination of naloxone and epinephrine increased the NDS after cardiopulmonary resuscitation.*

*Level 6, Supporting, Funding: China Medical University, Shengjing Hospital (China).*

*Key points: Rats subjected to asphyxial cardiac arrest had better resuscitation rates and improved neurological scores when naloxone was combined with epinephrine during CPR. The study did not address opioid overdoses.*

*Chen MH, Xie L, Liu T-W, Song FQ, He T. "Naloxone and epinephrine are equally effective for cardiopulmonary resuscitation in a rat asphyxia model." Acta Anaesthesiol Scand 2006;50:1125-1130*

*It is not known whether naloxone is as efficacious as epinephrine during cardiopulmonary resuscitation (CPR). The aim of the study was to compare the effects of naloxone and epinephrine on the outcomes of CPR following asphyxial cardiac arrest in rats. Cardiac arrest was induced with asphyxia by clamping the tracheal tubes. Twenty-four Sprague-Dawley rats were randomized prospectively into a saline group (treated with normal saline, 1 ml intravenously, n ¼ 8), an epinephrine group (treated with epinephrine, 0.04 mg/kg*

intravenously,  $n = 8$ ) or a naloxone group (treated with naloxone, 1 mg/kg intravenously,  $n = 8$ ) in a blind fashion during resuscitation after asphyxia cardiac arrest. After 5 min of untreated cardiac arrest, conventional manual CPR was started and each drug was administered at the same time. The rates of restoration of spontaneous circulation (ROSC) were one of eight (12.5%), seven of eight (87.5%) and seven of eight (87.5%) in the saline, epinephrine and naloxone groups, respectively. The rates of ROSC in the epinephrine and naloxone groups were equal and significantly greater than that in the saline group ( $P = 0.01$  and  $P = 0.01$ , respectively). The administration of naloxone or epinephrine alone may increase the resuscitation rate, and both drugs are equally effective for CPR in a rat asphyxia model. However, the mechanism by which naloxone produces its efficacy during CPR remains unclear and further experimentation will be necessary.

Level 6, Supporting, Funding: Guangxi Natural Science Foundation of China.

Key Points: Asphyxial arrest in a non-target species, effect of opioid overdose not investigated. Found similar rates of ROSC in groups treated with epinephrine or naloxone, both of which were significantly higher than saline placebo.

Chen MH, Liu TW, Xie L, Song FQ, He T. "Does Naloxone Alone Increase Resuscitation Rate During Cardiopulmonary Resuscitation in a Rat Asphyxia Model." *Am J Emerg Med* 2006;24:567-572

Cardiac arrest was induced with asphyxia to identify if naloxone alone increases resuscitation rate during cardiopulmonary resuscitation in a rat asphyxia model. The animals were randomized into either a saline group (Sal-gro, treated with normal saline 1 ml iv,  $n = 8$ ), a low-dose naloxone group (treated with naloxone 0.5 mg/kg iv,  $n = 8$ ), or a high-dose naloxone group (HN-gro, treated with naloxone 1 mg/kg iv,  $n = 8$ ) in a blinded fashion during resuscitation. At the end of 10 minutes of asphyxia, cardiopulmonary resuscitation was started, and each drug was administered at the same time. The rate of restoration of spontaneous circulation was seen in 1 of 8, 3 of 8, and 7 of 8 animals in the Sal-gro, LN-gro, and HN-gro, respectively. The rate of restoration of spontaneous circulation in HN-gro was significantly higher than that in Sal-gro ( $P = 0.05$ ). Naloxone (1 mg/kg) alone can increase resuscitation rate following asphyxial cardiac arrest in rats.

Level 6, Supporting, Funding: Guangxi Natural Science Foundation of China.

Key Points: Asphyxial arrest in a non-target species, effect of opioid overdose not investigated. Rates of ROSC higher in high dose naloxone group than saline placebo.

Wang Y, Gao L, Meng L. Small-Dose Naloxone Combined with Epinephrine Improves the Resuscitation of Cardiopulmonary Arrest." *Am J Emerg Med* 2008;26:898-901.

To investigate if naloxone combined with epinephrine can increase the resuscitation rate in cardiac arrest rat models induced by asphyxia. Twenty-four rats were allocated into SA group (treated with 1 mL of saline,  $n = 8$ ), EP group (treated with epinephrine 5  $\mu$ g/100g,  $n = 8$ ), and NA group (treated with epinephrine 5  $\mu$ g/100g in combination with naloxone 100  $\mu$ g/100g,  $n = 8$ ). Eight minutes after asphyxia, cardiopulmonary resuscitation was initiated, and different drugs were used in different groups at the same time. Rates of restoration of spontaneous circulation (ROSC) were 25%, 75%, and 87.5% in SA, EP, and NA groups, respectively. The rate of ROSC in the NA group was significantly higher than that in the other 2 experimental groups ( $P = 0.05$ ). The average resuscitation time in the NA group was much lower than that in the other 2 cohorts. The administration of epinephrine alone may increase early resuscitation rate in a cardiac arrest model compared with placebo group. Moreover, the combination of naloxone and epinephrine may significantly increase resuscitation rate. The duration of ROSC in combination group is much shorter than that in the other 2 groups.

Level 6, Supporting, Funding: Laboratory of China Medical Hospital, Shengjing Hospital (China).

Key Points: Asphyxial arrest in a non-target species, effect of opioid overdose not investigated. Naloxone combined with epinephrine resulted in improved resuscitation rates and reduced time to ROSC.

Saybolt MD, Alter SM, Santos FD et al. "Naloxone in Cardiac Arrest With Suspected Opioid Overdoses." *Resuscitation* 2010;81:42-46

*Naloxone's use in cardiac arrest has been of recent interest, stimulated by conflicting results in both human case reports and animal studies demonstrating antiarrhythmic and positive inotropic effects. We hypothesized that naloxone administration during cardiac arrest, in suspected opioid overdosed patients, is associated with a change in cardiac rhythm.*

*Methods: From a database of 32,544 advanced life support (ALS) emergency medical dispatches between January 2003 and December 2007, a retrospective chart review was completed of patients receiving naloxone in cardiac arrest. Forty-two patients in non-traumatic cardiac arrest were identified. Each patient received naloxone because of suspicion by a paramedic of acute opioid use. Results: Fifteen of the 36 (42%) (95% confidence interval [CI]: 26–58) patients in cardiac arrest who received naloxone in the pre-hospital setting had an improvement in electrocardiogram (EKG) rhythm. Of the participants who responded to naloxone, 47% (95% CI: 21–72) (19% [95% CI: 7–32] of all study subjects) demonstrated EKG rhythm changes immediately following the administration of naloxone. Although we cannot support the routine use of naloxone during cardiac arrest, we recommend its administration with any suspicion of opioid use. Due to low rates of return of spontaneous circulation and survival during cardiac arrest, any potential intervention leading to rhythm improvement is a reasonable treatment modality.*

*Level 6, Supporting, Funding: None.*

*Key Points: A retrospective study which examined EKG changes following administration of naloxone during CPA in humans with suspected opioid overdose. 42% of patients demonstrated an improvement in cardiac rhythm following naloxone administration.*

Foley PJ, Tacker WA, Voorhees WD, Ralston SH, Elchisak MA et al. "Effects of Naloxone on the Adrenomedullary Response During and After Cardiopulmonary Resuscitation in Dogs." *Am J Emerg Med* 1987;5(5):357-61

*To determine the effects of naloxone, an opiate antagonist, on the adrenomedullary response to cardiac arrest, plasma epinephrine and norepinephrine levels were measured before, during, and after cardiac arrest in dogs. Ventricular fibrillation was induced in 12 dogs anesthetized with pentobarbital sodium (30 mg/kg) and standard American Heart Association cardiopulmonary resuscitation (CPR) was begun using a mechanical device. At 6.5 minutes of CPR, naloxone (10 mg/kg) or 0.9% saline (10 ml) was given intravenously. At 12 minutes of CPR, the cardiac ventricles were electrically defibrillated. Plasma epinephrine and norepinephrine levels were measured before ventricular fibrillation; at 2.5, 4.5, 9.5, and 11.5, minutes of CPR; and at 5, 10, 15, and 20 minutes after resuscitation. Epinephrine and norepinephrine increased from prearrest levels of 3.66 +/- 0.67 (+/- SE) and 24.02 +/- 3.67 ng/ml to 66.67 +/- 9.65 and 74.00 +/- 9.91 ng/ml, respectively, at 4.5 minutes of CPR. After resuscitation, norepinephrine levels remained slightly elevated, while epinephrine fell to prearrest levels. Naloxone did not cause a significant change in either epinephrine or norepinephrine from 6.5 minutes of CPR (time of treatment) through 20 minutes postresuscitation. In addition, naloxone had no effect on either the end-diastolic pressure difference during CPR or resuscitation outcome. We conclude that cardiac arrest causes significant increases in plasma epinephrine and norepinephrine levels, which remain elevated for the duration of the arrest, and that naloxone has no effect on these levels.*

*Level 3, Neutral.*

*Key Points: An experimental study in a target species (dog), fibrillation model. Naloxone had no effect on neurohormonal responses to CPA and subsequent resuscitation.*

Waldrop JE, Rozanski EA, Swanke ED, O'Toole TE, Rush JE. "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



*To describe the functional outcome of canine and feline survivors of cardiopulmonary arrest (CPA) and the clinical characteristics surrounding their resuscitation. Retrospective study. Veterinary teaching hospital. Client-owned dogs (15) and cats (3) with CPA. 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. 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.*

*Level 4, Neutral. Funding: None.*

*Key points: Three animals with anesthesia induced CPA survived to discharge following treatment with CPR including naloxone, the remaining seven did not receive naloxone and also survived.*

*Gervais HW, Eberle B, Hennes H-J et al. "High Dose Naloxone Does Not Improve Cerebral or Myocardial Blood Flow During Cardiopulmonary Resuscitation in Pigs." Resuscitation 1997;34:255-261*

*In a prospective, randomized, placebo-controlled, double-blind trial we tested the hypothesis that naloxone given during cardiopulmonary resuscitation (CPR) enhances cerebral and myocardial blood flow. Twenty-one anesthetized, normoventilated pigs were instrumented for measurements of right atrial and aortic pressures, and regional organ blood flow (radiolabeled microspheres). After 5 min of untreated fibrillatory arrest, CPR was commenced using a pneumatic chest compressor:ventilator. With onset of CPR, an i.v. bolus of 40 mg/kg b.w. of epinephrine was given, followed by an infusion of 0.4 mg/kg per min. After 5 min of CPR, either naloxone, 10 mg/kg b.w. (group N, n\_11) or normal saline (group S, n\_10) was given i.v. Prior to, and after 1, 15, and 30 min of CPR, hemodynamic and blood flow measurements were obtained. After 30 min of CPR, mean arterial pressure was significantly higher in group N (2695 vs. 1393 mmHg, PB0.05). Groups did not differ with respect to myocardial perfusion pressure or arterial blood gases at any time during the observation period. Regional brain and heart blood flows were not different between N and S at any point of measurement. We conclude that high-dose naloxone does not augment cerebral or myocardial blood flow during prolonged closed-chest CPR.*

*Level 6, Neutral, Funding: Dupont de Nemours Company, Frankfurt.*

*Key points: Experimental fibrillation CPA in a non target species (pigs). Naloxone failed to improve myocardial or cerebral perfusion measured by radiolabelled microspheres, arterial blood gases or myocardial perfusion pressure despite an improvement in MAP.*

*Sun S, Weil MH, Tang W, Kamohara T, Klouche K. "δ-Opioid receptor agonist reduces severity of postresuscitation myocardial dysfunction." Am J Physiol Heart Circ Physiol 2004;287:969-974*

*Postresuscitation myocardial dysfunction is recognized as a leading cause of early death after initially successful cardiopulmonary resuscitation (CPR). In the present study, we hypothesized that a δ-opioid receptor agonist would decrease the severity of postresuscitation myocardial dysfunction and improve survival. Fifteen Sprague-Dawley rats, fasted overnight with access to water, were anesthetized by an injection of 45 mg/kg ip pentobarbital sodium. Additional doses of 10 mg/kg were administered at hourly intervals but not within 30 min before induced ventricular fibrillation (VF). Either the δ-opioid receptor agonist pentazocine (300 mcg/kg), pentazocine pretreated with the opioid receptor-blocking agent naloxone (1 mg/kg), or saline placebo was injected into the right atrium after 5 min of untreated VF and 3 min before initiation of CPR. After an additional 8 min of CPR administration, defibrillation was attempted. All animals were successfully*

resuscitated. Left ventricular rate of pressure increase at 40 mmHg and cardiac index values were significantly improved in pentazocine-treated animals, which also had significantly longer survival times (60 +/- 11 vs. 16 +/- 7 h;  $P = 0.01$ ). Except for ease of defibrillation, the beneficial effects of pentazocine were completely abolished by pretreatment with naloxone. The concept of pharmacological hibernation employing a  $\delta$ -opioid receptor agonist is a novel and promising intervention for minimizing global ischemic injury during CPR and postresuscitation myocardial dysfunction.

*Level 6, Opposing, Funding: American Heart Association and National Heart, Lung and Blood Institute.*

*Key Points:  $\delta$ -opioid receptor agonists produced significant improvements in survival and reduced myocardial ischemic damage, this effect was abolished by naloxone.*

DRAFT