

WORKSHEET for Evidence-Based Review of Science for Veterinary CPR

1. Basic Demographics

Worksheet author(s)

Lindsay Kellett-Gregory

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2. Clinical question:

In dogs and cats with ROSC that are hypotensive (P), does the use of any particular cardio-active drug/vasopressor (I) compared to standard care (C), result in improved outcome (O) (survival to discharge/neurological function)?

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 July 2011) (performed on July 25th 2011)

1. Cardiopulmonary resuscitation [Mesh term] – 9081 hits
2. Cardiopulmonary arrest [Mesh term] – 28346 hits
3. Death, sudden, cardiac [Mesh term] – 8898 hits
4. Hypotension [Mesh term] – 21277 hits
5. Post cardiac arrest syndrome [text search] – 189 hits
6. Post resuscitation myocardial dysfunction [text search] – 131 hits
7. Ventricular dysfunction [Mesh term] – 20586 hits
8. Vasopressor agents [Mesh term] – 17297 hits
9. Cardiotonic agents [Mesh term] – 11478 hits
10. Dobutamine [Mesh term] – 5312 hits
11. Dopamine [Mesh term] – 63146 hits
12. (1 OR 2 OR 3) AND (4 OR 7 OR 8 OR 9 OR 10 OR 11) OR 5 OR 6 – 1735 hits (13 relevant hits)

-CAB (1910 to July 2011) (performed on July 25th 2011)

Search as for MEDLINE using the 12 search terms above yielded no additional relevant hits

4b. Other sources

- Review of AHA 2010 guidelines/worksheets yielded 1 additional hit
- Cochrane review searches under heart and for term “postresuscitation” yielded no additional relevant hits
- GOOGLE SCHOLAR (performed on July 25th 2011)
No additional relevant hits based on forward search of 14 relevant selected articles

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

Inclusion criteria

Written in English, in peer-reviewed literature, original research article

Exclusion criteria

Letters, comments, reviews, editorials, abstracts only, non-peer reviewed, case reports, not written in English, didn't address study question, non-pharmacologic interventions only, interventions prior to ROSC only, interventions other than cardioactive/vasopressor agents, interventions not following global ischemia or cardiac arrest.

4d. Number of articles/sources meeting criteria for further review: 14

- Four relevant human studies were identified (Gaieski et al 2009, Sunde et al 2007, Mayr et al 2007, Laurent et al 2002)
- Seven studies conducted in a swine model of cardiac arrest were identified (Wang et al 2005, Huang et al 2005, Vasquez et al 2004, Meyer et al 2002, Tennyson et al 2002, Voelckel et al 1999, Kern et al 1997)
- Two studies conducted in a rat model of cardiac arrest were identified (Huag et al 2005, Struder et al 2005)
- One study was indentified that was conducted in an isolated rat heart model (Angelos et al 2002)

5. Summary of evidence

Evidence Supporting Clinical Question

Good						<i>Wang 2005 E=LV function, Studer 2005 E=Lactate clearance, Voelckel 1999 E=mesenteric blood flow & GFR</i>
Fair						<i>Sunde 2007 C, Huang 2005 C=Survival duration E=LV</i>

						<i>function,</i> <i>Huang 2005</i> <i>E=LV function,</i> <i>Vasquez 2004</i> <i>E=LV function,</i> <i>Meyer 2002</i> <i>E=RV function,</i> <i>Tennyson 2002</i> <i>E=LV function,</i> <i>Angelos 2002</i> <i>E=LV function,</i>
Poor						<i>Kern 1997 E=</i> <i>LV Function</i>
	1	2	3	4	5	6
Level of evidence (P)						

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint
 B = Survival of event D = Intact neurological survival *Italics = Non-target species studies*

Evidence Neutral to Clinical question

Good						
Fair						<i>Gaieski 2009 C</i>
Poor						<i>Mayr 2007</i> <i>E=Cardiac index & MAP,</i> <i>Laurent 2002</i> <i>E=LV function</i>
	1	2	3	4	5	6
Level of evidence (P)						

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint
 B = Survival of event D = Intact neurological survival *Italics = Non-target species studies*

Evidence Opposing Clinical Question

Good						
Fair			NONE			
Poor						
	1	2	3	4	5	6
Level of evidence (P)						

A = Return of spontaneous circulation

C = Survival to hospital discharge

E = Other endpoint

B = Survival of event
studies

D = Intact neurological survival

Italics = Non-target species

DRAFT

6. REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

There are no studies in the target species (cats or dogs) that address this question, restricting all the studies identified to level 6 evidence. Even within other species the question has not been answered in a satisfactory fashion as it is not directly addressed and there are few randomized blinded studies.

In the four human studies identified, cardio-active drugs were not the sole intervention applied to the population (Gaieski et al 2009, Sunde et al 2007) making it difficult to elucidate the role of this specific intervention, or cardiovascular parameters were the only outcomes investigated (Mayr et al 2007, Laurent et al 2002) making it impossible to assess the effect on survival or neurologic function. In the study by Sunde et al (2007) inotropic support is found to be beneficial for survival in bi-variant, but not multi-variant, analysis. In the study by Gaieski et al (2009) intervention with hypothermia cannot be separated from use of vasoactive agents and no statistical difference was found between the intervention group and historic controls, but given the small sample size (n=18) and the survival difference (50% vs 78%, p=0.15), it is tempting to think that with a larger study a benefit may have been found.

The non-human, non-target species studies identified were all experimentally induced cardiac arrest or global ischemic injury models rather than naturally occurring disease and so some caution must be applied to their interpretation. Additionally only one of these studies (Huang et al 2005) examined survival as an end-point. The majority of these studies looked at the effects of cardio-active drugs on ventricular function following resuscitation and it is perhaps not surprising that improvements in ventricular function were generally observed. Several studies not described here identify an association between post-resuscitation myocardial dysfunction and poor survival and thus it is tempting to assume that the improvements in myocardial function observed would translate to improved outcome, but this has not been shown in any species. Two studies attempted to further address this issue by examining the effect of cardio-active drugs on visceral perfusion following resuscitation (Studer et al 2005, Voelckel et al 1999). These studies identified that cardio-active drugs (dobutamine and dopamine) improved abdominal perfusion and glomerular filtration rate and hypothesized that this would be associated with superior outcome, but this was not directly shown and in fact one of those same studies (Studer et al 2005) found no improvement in intestinal ischemia, assessed by tonometry.

It is of note that there are no studies identified that oppose the clinical question and the only neutral studies are either poorly powered (Gaieski et al 2009), non-controlled (Mayr et al 2007) or non-randomized (Mayr et al 2007, Laurent et al 2002). It should be noted, however, that tachycardia (Vasquez et al 2004, Kern et al 1997) and increased myocardial oxygen demand (Vasquez et al 2004) was observed with use of high doses of dobutamine (>7.5ug/kg/min).

7. Conclusion

CONSENSUS ON SCIENCE: There is insufficient evidence, and no evidence in cats or dogs, to make conclusions about the benefits of cardio-active/vasopressor drugs in post-resuscitation hypotension with respect to survival or neurologic outcome.

One human prospective non-randomized trial (LOE 6)(Sunde et al 2007) identified inotropic support as a beneficial component of a complete standardized protocol in bi-variant, but not multi-variant analysis. A further 10 experimental animal models (LOE 6) have identified cardio-active drugs/vasopressors as being beneficial for post resuscitation myocardial function (Wang et al 2005, Huang et al 2005, Huang et al 2005, Vasquez et al 2004, Meyer et al 2002, Tennyson et al 2002, Angelos et al 2002, Kern et al 1997), visceral

perfusion (Studer et al 2005, Voelckel et al 1999) and survival duration (Huang et al 2005). A further 3 studies in humans have identified no benefit to intervention with respect to survival (Gaieski et al 2009) or myocardial function (Mayr et al 2007, Laurent et al 2002).

TREATMENT RECCOMENDATION: There is a clear physiologic rationale for the treatment of hypotension and myocardial depression. At this time no evidence exists indicating that the use of cardio-active/vasopressor drugs is contra-indicated and there is some weak evidence suggesting benefit and so cautious use of such drugs when indicated is advised. However, the need for future research and prospective clinical trials to answer this question is strongly emphasized.

8. Acknowledgement

9. Citation list

1. Resuscitation. 2009 Apr;80(4):418-24. Epub 2009 Feb 12.

Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest.

Gaieski DF, Band RA, Abella BS, Neumar RW, Fuchs BD, Kolansky DM, Merchant RM, Carr BG, Becker LB, Maguire C, Klair A, Hylton J, Goyal M.

Department of Emergency Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA. gaieskid@uphs.upenn.edu

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 6h 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 our 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 degrees C) was 2.8h (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 6h 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.

PMID: 19217200 [PubMed - indexed for MEDLINE]

Level of Evidence: 6

Study Quality: Fair (prospective, historic controls, non-randomized)

Funding: Gaymar Industries unrestricted grant

Subjects: Humans (n=18 per group)

Interventions: Goal directed hemodynamic optimization

Outcomes: Survival to discharge - C

Key points: Neutral to question – no details on individual patient treatments. Hemodynamic optimization (including pressors) didn't cause significant improvement in survival but looked like it would with larger numbers.

2. Resuscitation. 2007 Apr;73(1):29-39. Epub 2007 Jan 25.

Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest.

Sunde K, Pytte M, Jacobsen D, Mangschau A, Jensen LP, Smedsrud C, Draegni T, Steen PA.

Department of Anaesthesiology, Ulleval University Hospital, Oslo, Norway.
kjetil.sunde@medisin.uio.no

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 standardised post resuscitation protocol focusing on vital organ function including therapeutic hypothermia, percutaneous coronary intervention (PCI), control of haemodynamics, blood glucose, ventilation and seizures.

METHODS: All patients with OHCA of cardiac aetiology 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 favourable 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 favourable neurological outcome in both groups were still alive 1 year after discharge. Two patients from the control period were revascularised 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.

CONCLUSIONS: Discharge rate from hospital, neurological outcome and 1-year survival improved after standardisation of post resuscitation care. Based on a multivariate logistic analysis, hospital treatment in the intervention period was the most important independent predictor of survival.

PMID: 17258378 [PubMed - indexed for MEDLINE]

Level of Evidence: 6

Study Quality: Fair (prospective, non-randomized, historic controls)

Funding: Laerdal Foundation for Acute Medicine, Ullevål University Hospital Scientific Advisory Council & Health Region East

Subjects: Humans (n=69 per group)

Interventions: Hypothermia and cardio-active drugs/vasopressors

Outcomes: Survival to discharge - C

Key points: Positive for question. Data regarding specific treatments lacking – pressors given as needed (dopamine, norepinephrine, dobutamine). Bi-variant analysis showed benefit to inotropic support (p=0.03) not seen in multi-variant analysis.

3. Resuscitation. 2007 Jan;72(1):35-44. Epub 2006 Oct 27.

Arginine vasopressin in advanced cardiovascular failure during the post-resuscitation phase after cardiac arrest.

Mayr V, Luckner G, Jochberger S, Wenzel V, Ulmer H, Pajk W, Knotzer H, Friesenecker B, Lindner K, Hasibeder W, Dünser M.

Department of Anesthesiology and Critical Care Medicine, Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria. viktoria.mayr@uibk.ac.at

Arginine vasopressin (AVP) has been employed successfully during cardiopulmonary resuscitation, but there exist only few data about the effects of AVP infusion for cardiovascular failure during the post-cardiac arrest period. Cardiovascular failure is one of the main causes of death after successful resuscitation from cardiac arrest. Although the "post-resuscitation syndrome" has been described as a "sepsis-like" syndrome, there is little information about the haemodynamic response to AVP in advanced cardiovascular failure after cardiac arrest. In this retrospective study, haemodynamic and laboratory variables in 23 patients with cardiovascular failure unresponsive to standard haemodynamic therapy during the post-cardiac arrest period were obtained before, and 30 min, 1, 4, 12, 24, 48, and 72 h after initiation of a supplementary AVP infusion (4 IU/h). During the observation period, AVP significantly increased mean arterial blood pressure (58±14 to 75±19 mmHg, p < 0.001), and decreased noradrenaline (norepinephrine) (1.31±2.14 to 0.23±0.3 microg/kg/min, p = 0.03), adrenaline (epinephrine) (0.58±0.23 to 0.04±0.03 microg/kg/min, p = 0.001), and milrinone requirements (0.46±0.15 to 0.33±0.22 microg/kg/min, p < 0.001). Pulmonary capillary wedge pressure changed significantly (p < 0.001); an initial increase being followed by a decrease below baseline values. While arterial lactate concentrations (95±64 to 21±18 mg/dL, p < 0.001) and pH (7.27±0.14 to 7.4±0.14, p < 0.001) improved significantly, total bilirubin concentrations (1.12±0.95 to 3.04±3.79 mg/dL, p = 0.001) increased after AVP. There were no differences in the haemodynamic or laboratory response to AVP between survivors and non-survivors. In this study, advanced cardiovascular failure that was unresponsive to standard therapy could be reversed successfully with supplementary AVP infusion in >90% of patients surviving cardiac arrest.

PMID: 17069952 [PubMed - indexed for MEDLINE]

Level of Evidence: 6

Study Quality: Poor (uncontrolled, retrospective)

Funding: None

Subjects: Humans (n=23)

Interventions: Vasopressin if still in shock after standard care

Outcomes: MAP, PCWP, Cardiac index, other pressor requirement

Key points: Neutral for question. Introduction of vasopressin led to increased MAP, decreased PCWP, decreased need for other pressors but cardiac index unchanged.

4. J Lab Clin Med. 2005 Nov;146(5):256-61.

Levosimendan improves postresuscitation outcomes in a rat model of CPR.

Huang L, Weil MH, Sun S, Cammarata G, Cao L, Tang W.

Weil Institute of Critical Care Medicine, Rancho Mirage, CA 92270, USA.

weilm@911research.org

In this study we sought to determine whether a calcium sensitizer, levosimendan, would have a more favorable effect on postresuscitation myocardial function and, consequently, postresuscitation survival than beta-adrenergic dobutamine. The extreme decrease in survival before hospital discharge of resuscitated victims is attributed, in part, to postresuscitation myocardial failure, and dobutamine has been recommended for the management of postresuscitation myocardial failure. We studied a total of 15 animals. Ventricular fibrillation was induced in Sprague-Dawley rats weighing 450 to 550 g. Cardiopulmonary resuscitation (CPR), including chest compressions and mechanical ventilation, was begun after 8 minutes of untreated cardiac arrest. Electrical defibrillation was attempted after 6 minutes of CPR. Each animal was resuscitated. Animals were randomized to undergo treatment with levosimendan, dobutamine, or saline-solution placebo. These agents were administered 10 minutes after the return of spontaneous circulation. Levosimendan was administered in a loading dose of 12 microg kg(-1) over a 10-minute period, followed by infusion of 0.3 microg kg(-1) min(-1) over the next 230 minutes. Dobutamine was continuously infused at a dosage of 3 microg kg(-1) min(-1). Saline-solution placebo was administered in the same volume and over the same amount of time as levosimendan. Levosimendan and dobutamine produced comparable increases in cardiac output and rate of left-ventricular pressure increase. However, administration of levosimendan resulted in lower heart rates and lesser increases in left ventricular diastolic pressure compared with both dobutamine and placebo. The duration of postresuscitation survival was significantly greater with levosimendan (16 +/- 2 hours), intermediate with dobutamine (11 +/- 2 hours) and least with saline-solution placebo (8 +/- 1 hour). Levosimendan and dobutamine both improved postresuscitation myocardial function. However, levosimendan produced more favorable postresuscitation myocardial function and increased the duration of postresuscitation survival. PMID: 16242524 [PubMed - indexed for MEDLINE]

Level of Evidence: 6

Study Quality: Fair (prospective, randomized, non-blinded)

Funding: National Heart, Lung & Blood Institute, NIH, Abbott Laboratories

Subjects: Rats (n=5 per group)

Interventions: Levosimendan vs dobutamine vs placebo CRI after ROSC

Outcomes: Survival duration – C, LV function/Cardiac index - E

Key points: Positive for question. Livosimendan/dobutamine superior to placebo for myocardial function. Livosimendan superior to dobutamine/placebo for survival duration.

5. J Lab Clin Med. 2005 Sep;146(3):179-83.

Levosimendan improves postresuscitation myocardial dysfunction after beta-adrenergic blockade.

Wang J, Weil MH, Tang W, Sun S, Huang L.

Institute of Critical Care Medicine, 35100 Bob Hope Drive, Rancho Mirage, CA 92270, USA. weilm@911research.org

In earlier studies, we found that a nonselective beta-adrenergic blocking agent, propranolol, facilitated cardiac resuscitation, reduced postresuscitation myocardial ectopy, and improved postresuscitation survival. However, the potential adverse effects and specifically the negative inotropic actions of propranolol prompted our further investigation of the potential value of a non-beta-adrenergic inotropic drug, levosimendan, in conjunction with propranolol, for minimizing postresuscitation myocardial dysfunction after successful resuscitation from cardiac arrest. Ventricular fibrillation was induced and untreated for 7 minutes in 15 domestic pigs, which were divided into propranolol, propranolol plus levosimendan, and control groups. Propranolol was administered as a bolus dose of 0.1 mg/kg during cardiac arrest. Electrical defibrillation was attempted after 12 minutes of cardiac arrest including 5 minutes of precordial compression. Levosimendan was administered at 10 minutes after successful resuscitation in a dose of 20 microg/kg and followed by infusion of 0.4 microg/kg/min over the ensuing 220 minutes. Propranolol reduced energies or numbers of defibrillatory shocks and postresuscitation myocardial ectopy, and it improved postresuscitation myocardial dysfunction. When levosimendan was added, postresuscitation myocardial contractile function was improved even more. PMID: 16131457 [PubMed - indexed for MEDLINE]

Level of Evidence: 6

Study Quality: Good (propective, randomized, blinded)

Funding: NIH, National Heart, Lung and Blood Institute, Abbott Laboratories

Subjects: Swine (n=5 per group)

Interventions: Propranolol pre ROSC vs Propranolol pre ROSC with Levosimendan post ROSC vs placebo

Outcomes: LV function - E

Key points: Positive for question. Propranolol pre-ROSC improved post-resuscitation myocardial function. Post-ROSC levosimendan improved it further.

6. Crit Care Med. 2005 Mar;33(3):487-91.

Comparison between dobutamine and levosimendan for management of postresuscitation myocardial dysfunction.

Huang L, Weil MH, Tang W, Sun S, Wang J.

Institute of Critical Care Medicine, Palm Springs, CA, USA.

OBJECTIVE: To investigate the effects of levosimendan, a nonadrenergic inotropic calcium sensitizer, in comparison with adrenergic dobutamine for the management of postresuscitation myocardial dysfunction following resuscitation from prolonged cardiac arrest.

DESIGN: Randomized prospective animal study.

SETTING: Animal research laboratory.

SUBJECTS: Male Yorkshire-cross domestic pigs

INTERVENTIONS: Ventricular fibrillation was induced in male domestic pigs weighing between 35 and 40 kg. Cardiopulmonary resuscitation, including precordial compression and mechanical ventilation, was started after 7 mins of untreated cardiac arrest. Electrical defibrillation was attempted after 5 mins of cardiopulmonary resuscitation. Each animal was successfully resuscitated without pharmacologic intervention. Resuscitated animals were randomized to treatment with levosimendan, dobutamine, or saline placebo. The inotropic agents or an equivalent volume of placebo diluents was administered 10 mins after restoration of spontaneous circulation. Levosimendan was administered in a loading dose of 20 microg.kg over 10 mins followed by a 220-min infusion of 0.4 microg.kg.min. Dobutamine was infused into the right atrium in an amount of 5 microg.kg.min. Treatment was continued for a total of 230 mins.

MEASUREMENTS AND MAIN RESULTS: Levosimendan and dobutamine produced comparable increases in cardiac output. However, levosimendan produced significantly greater left ventricular ejection fraction and fractional area changes compared with dobutamine and saline placebo.

CONCLUSIONS: Levosimendan has the potential of improving postresuscitation myocardial function. It is likely to serve as an alternative to dobutamine as an inotropic agent for management of postresuscitation myocardial dysfunction.

PMID: 15753736 [PubMed - indexed for MEDLINE]

Level of Evidence: 6

Study Quality: Fair (prospective, randomized, non-blinded)

Funding: NIH, National Heart Lung and Blood Institute, Abbott Laboratories

Subjects: Swine (n=5 per group)

Interventions: Levosimendan vs Dobutamine vs placebo

Outcomes: LV Function - E

Key points: Positive for question. Levosimendan and dobutamine both increased cardiac output but levosimendan caused greater increases LV ejection fraction.

7. Resuscitation. 2005 Feb;64(2):227-32.

Influence of dobutamine on the variables of systemic haemodynamics, metabolism, and intestinal perfusion after cardiopulmonary resuscitation in the rat.

Studer W, Wu X, Siegemund M, Marsch S, Seeberger M, Filipovic M.

Department of Anaesthesiology and Research, University of Basel, CH-4031 Basel, Switzerland. wolfgang.studer@bluewin.ch

BACKGROUND: Global left ventricular dysfunction after successful resuscitation from cardiac arrest may be treated successfully with dobutamine but the effects on intestinal perfusion are unknown.

METHODS: In 24 male Sprague-Dawley rats ventricular fibrillation was induced.

After 4 min of untreated cardiac arrest, precordial chest compression was performed for 4 min; adrenaline (epinephrine) (90 microg kg(-1)) was injected, followed by defibrillation. Return of spontaneous circulation was achieved in 18 animals, which were allocated to receive saline 0.9% (control group, n = 6), dobutamine at 5 microg kg(-1) min(-1) (n = 6) or dobutamine at 10 microg kg(-1) min(-1) (n = 6). Measurements of haemodynamic variables and intestinal tonometer P(CO2) were made before induction of ventricular fibrillation and 15, 30, 60, and 120 min postresuscitation.

RESULTS: At 120 min postresuscitation, mean aortic pressure was 82 +/- 20, 104 +/- 19, and 113 +/- 15 mmHg for the control group, the dobutamine (5 microg kg(-1) min(-1)) group and the dobutamine (10 microg kg(-1) min(-1)) group ($P < 0.05$ for comparison of the dobutamine (10 microg kg(-1) min(-1)) group versus the control group). Respective abdominal aortic blood flow was 107 +/- 16, 133 +/- 49, and 145 +/- 18 ml min(-1) kg(-1) ($P < 0.05$ for comparison of the dobutamine (10 microg kg(-1) min(-1)) group versus the control group), and superior mesenteric artery blood flow was 25 +/- 9, 28 +/- 8, and 33 +/- 8 ml min(-1) kg(-1). Arterial lactate was significantly higher ($P < 0.05$) in the control group (2.3 +/- 0.6 mmol l(-1)) than in the dobutamine (5 microg kg(-1) min(-1)) group (1.6 +/- 0.3 mmol l(-1)) and dobutamine (10 microg kg(-1) min(-1)) group (1.5 +/- 0.3 mmol l(-1)). Tonometrically derived P(CO₂) gap was highly elevated at 15 min of postresuscitation and returned to prearrest level at 120 min postresuscitation in all groups.

CONCLUSIONS: Dobutamine enhances the recovery of global haemodynamic and metabolic variables early after cardiac arrest.

PMID: 15680534 [PubMed - indexed for MEDLINE]

Level of Evidence: 6

Study Quality: Good (randomized, probably blinded)

Funding: Swiss National Science Foundation

Subjects: Rats (n=6 per group)

Interventions: Dobutamine (2 doses) vs placebo

Outcomes: MAP, Abdominal blood flow, arterial lactate clearance - E

Key points: Positive for question. Dobutamine at 10ug/kg/min resulted in significantly higher MAP, mesenteric artery blood flow and faster lactate clearance. Intestinal tonometry (reflecting intestinal ischemia) not different between groups – attributed to sample size by authors.

8. Resuscitation. 2004 May;61(2):199-207.

Optimal dosing of dobutamine for treating post-resuscitation left ventricular dysfunction.

Vasquez A, Kern KB, Hilwig RW, Heidenreich J, Berg RA, Ewy GA.

Section of Cardiology, Department of Medicine, Sarver Heart Center, University of Arizona College of Medicine, 1501 N. Campbell Avenue, Tucson, AZ 85724, USA.

OBJECTIVES: This study was designed to determine the optimal dose of dobutamine in the treatment of post-resuscitation left ventricular dysfunction.

BACKGROUND: Global left ventricular dysfunction following successful resuscitation from prolonged, ventricular fibrillation cardiac arrest, negatively impacts long-term survival. Dobutamine can overcome this global myocardial stunning. Previous data indicate a dose of 10 mcg/kgmin improves systolic and diastolic function, but markedly increases the heart rate.

METHODS: Twenty swine (24 +/- 0.4 kg) were randomized to one of four doses (0, 2, 5, and 7.5 mcg/kgmin) of dobutamine for the treatment of post-resuscitation myocardial dysfunction following 12.5 min of untreated ventricular fibrillation cardiac arrest. Cardiac function was measured at pre-arrest baseline and serially for 6 h post-resuscitation. Left ventricular function was evaluated by contrast ventriculograms, left ventricular pressures, +dP/dt, Tau, -dP/dt, and cardiac output. Myocardial oxygen consumption and myocardial blood flow were measured to

assess the functional significance of any dobutamine-mediated heart rate responses.

RESULTS: Left ventricular dysfunction was evident at 25 min and peaked 4 h post-resuscitation. Significant ($P < 0.05$) improvements in ventricular systolic (EF, CO) and diastolic (LVEDP, Tau) function were evident within minutes of dobutamine initiation and persisted at 6h for the 5 and 7.5 mcg/kgmin groups. Tachycardia manifested with all dobutamine doses, but only affected myocardial oxygen consumption significantly ($P < 0.05$) at the highest dose (7.5 mcg/kgmin).

CONCLUSIONS: Dobutamine at 5 mcg/kgmin appears optimal for restoring systolic and diastolic function post-resuscitation without adversely affecting myocardial oxygen consumption.

PMID: 15135197 [PubMed - indexed for MEDLINE]

Level of Evidence: 6

Study Quality: Fair (randomized, non-blinded)

Funding: American Heart Association Desert/Mountain Affiliate, Max & Victoria Dreyfus Foundation

Subjects: Swine (n=5 per group)

Interventions: Dobutamine (3 doses) vs placebo

Outcomes: LV function - E

Key points: Positive for question. Dobutamine >5ug/kg/min improved LV function but also caused some tachycardia. Doses >7.5ug/kg/min increased myocardial oxygen consumption.

9. J Am Coll Cardiol. 2002 Dec 18;40(12):2110-6.

Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. Laurent I, Monchi M, Chiche JD, Joly LM, Spaulding C, Bourgeois B, Cariou A, Rozenberg A, Carli P, Weber S, Dhainaut JF.

Medical Intensive Care Unit, Cochin Port-Royal Hospital, René Descartes University, Paris, France.

OBJECTIVES: 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.

PMID: 12505221 [PubMed - indexed for MEDLINE]

Level of Evidence: 6

Study Quality: Poor (prospective, non-randomized, non-blinded – inherent differences vs controls)

Funding: Paris hospital institute

Subjects: Humans (n=165 total with 73 treated)

Interventions: Invasive monitoring and use of vasoactive drugs in those requiring it within 72hrs of ROSC

Outcomes: Cardiac index/LV function - E

Key points: Neutral for question. Cardiac index improved within 24 hours of ROSC irrespective of the use of vasoactive drugs.

10. Resuscitation. 2002 Nov;55(2):187-91.

Post-resuscitation right ventricular dysfunction: delineation and treatment with dobutamine.

Meyer RJ, Kern KB, Berg RA, Hilwig RW, Ewy GA.

Department of Pediatrics, University of Arizona Sarver Heart Center, University of Arizona College of Medicine, Tucson, AZ, USA.

BACKGROUND: Left ventricular dysfunction after resuscitation from cardiac arrest has been well described. Treatment with dobutamine improves post-resuscitation left ventricular function. Right ventricular function following resuscitation has not been investigated. The purposes of this study were to examine right ventricular function following resuscitation and determine whether dobutamine would improve post-resuscitation right ventricular function.

METHODS AND RESULTS: Right ventricular function was measured in 28 swine (29±1 kg) before and after resuscitation from 15 min of untreated ventricular fibrillation. Twelve animals received dobutamine at 10 mcg/kg/min while 16 animals served as untreated controls. Among controls, right ventricular dysfunction post-resuscitation was demonstrated by a decrease in right ventricular ejection fraction and an increase in right ventricular end-diastolic pressure. Among animals treated with dobutamine, there was a significant improvement in right ventricular function post-resuscitation compared to untreated controls.

CONCLUSIONS: This study establishes that right ventricular systolic and diastolic dysfunction does occur after prolonged cardiac arrest from ventricular fibrillation. Dobutamine can ameliorate post-resuscitation right ventricular dysfunction.

PMID: 12413757 [PubMed - indexed for MEDLINE]

Level of Evidence: 6

Study Quality: Fair (Random, non-blinded)

Funding: Arizona Disease Control Research Commission

Subjects: Swine (n=28 total, 12 treated)

Interventions: Dobutamine vs placebo

Outcomes: RV function - E

Key points: Positive for question. RV function decreased post-resuscitation but improves with dobutamine

11. Resuscitation. 2002 Jul;54(1):69-75.

Treatment of post resuscitation myocardial dysfunction: aortic counterpulsation versus dobutamine.

Tennyson H, Kern KB, Hilwig RW, Berg RA, Ewy GA.

Department of Medicine, Section of Cardiology, The Sarver Heart Center, University of Arizona College of Medicine, 1501 N. Campbell Avenue, Tucson, AZ 95724, USA.

BACKGROUND: Post resuscitation myocardial stunning is well described and recognized as a significant contributor to poor long-term outcome following cardiac arrest. Optimal strategies for treatment have not been determined.

METHODS: Ten domestic swine (49 \pm 3 kg) underwent 15 min of untreated ventricular fibrillation before being successfully resuscitated. Left ventricular systolic and diastolic function was measured at pre-arrest baseline, at 30 min and at 6 h post resuscitation. Five animals were treated immediately after resuscitation with intra-aortic balloon counterpulsation (IABP) and five were given dobutamine (5 mcg/kg per min).

RESULTS: No baseline differences were found. At 30 min post resuscitation pulmonary capillary wedge pressure and LVEDP were significantly higher (16 \pm 3 vs. 7 \pm 1 and 20 \pm 2 vs. 11 \pm 1 mmHg) while LV isovolumic relaxation ('Tau') was significantly longer (34 \pm 2 vs. 20 \pm 2 ms) in the IABP treated versus the dobutamine treated animals. Likewise, at 6 h post resuscitation LV ejection fraction was significantly less (21 \pm 6 vs. 39 \pm 4%), and LVEDP significantly higher (18 vs. 10 mmHg) in the IABP group. Heart rate was not different between the groups at any time post resuscitation.

CONCLUSION: Dobutamine was superior to IABP for treatment of post resuscitation left ventricular systolic and diastolic dysfunction. The hypothesized advantage of IABP for treatment of post resuscitation myocardial stunning without excessively raising the heart rate like dobutamine was not realized.

PMID: 12104111 [PubMed - indexed for MEDLINE]

Level of Evidence: 6

Study Quality: Fair (randomized, non-blinded)

Funding: Max & Victoria Dreyfus Foundation

Subjects: Swine (n=5 per group)

Interventions: Dobutamine vs Intraaortic balloon counterpulsation

Outcomes: PCWP and LV function - E

Key points: Positive for question. Dobutamine group had lower PCWP and superior LV function without a difference in HR.

12. Crit Care Med. 2002 Feb;30(2):410-6.

Postischemic inotropic support of the dysfunctional heart.

Angelos MG, Murray HN, Waite MD, Gorsline RT.

Department of Emergency Medicine, The Ohio State University, Columbus, OH 43210-1270, USA. angelos.1@osu.edu

OBJECTIVE: To determine relative adenine nucleotide regeneration and improvement in left ventricular (LV) function using three commonly used adrenergic agents--epinephrine, dobutamine, and phenylephrine---during reperfusion after a

period of global ischemia. After initial resuscitation from cardiac arrest, adrenergic agents are frequently required to support postischemic LV dysfunction. However, the relative effectiveness and associated bioenergetic changes associated with these agents in the postischemic heart are unclear.

DESIGN: Prospective, controlled laboratory study.

SETTING: University research laboratory.

SUBJECTS: Isolated, perfused Sprague-Dawley rat hearts.

INTERVENTIONS: After 20 mins of global ischemia, isolated rat hearts were reperfused for 30 mins with Krebs-Henseleit solution alone (control, n = 8), or with the addition of equipotent doses of epinephrine 1 microM (n = 8), dobutamine 0.3 microM (n = 8), or phenylephrine 50 microM (n = 8). In a second experiment, an alpha-1 antagonist, prazosin was given with phenylephrine to block the presumed alpha-1 agonist effect of phenylephrine.

MEASUREMENTS AND MAIN RESULTS: A constant volume balloon was placed in the left ventricle to measure LV pressure and derived parameters of LV function. Adenine nucleotide concentrations were derived at various time points using high-performance liquid chromatography. During reperfusion, the phenylephrine group had significant improvement in LV function and cardiac efficiency in contrast to epinephrine and dobutamine. Total adenine nucleotides tended to be highest in the phenylephrine group with significant increases in adenosine diphosphate and adenosine monophosphate and no significant loss of adenosine triphosphate. The phenylephrine-induced increase in heart rate and developed pressure could be blocked with an alpha-1 antagonist, prazosin.

CONCLUSIONS: In the isolated reperfused heart, phenylephrine, mediated by alpha-1 agonism, significantly improves postischemic LV dysfunction without worsening the overall myocardial metabolic state.

PMID: 11889321 [PubMed - indexed for MEDLINE]

Level of Evidence: 6

Study Quality: Fair (randomized, non-blinded)

Funding: Emergency Medicine Foundation/ Genetech Center of Excellence Award

Subjects: Isolated rat hearts (n=8 per group)

Interventions: Epinephrine vs Dobutamine vs Phenylephrine vs placebo after 20 minutes of ischemia

Outcomes: LV Function - E

Key points: Positive for question. Phenylephrine led to greatest improvements and these could be blocked by prazosin showing it is alpha-1 mediated.

13. *Anesth Analg.* 1999 Dec;89(6):1430-6.

Effect of small-dose dopamine on mesenteric blood flow and renal function in a pig model of cardiopulmonary resuscitation with vasopressin.

Voelckel WG, Lindner KH, Wenzel V, Bonatti JO, Krismer AC, Miller EA, Lurie KG.

Department of Anaesthesia and Intensive Care Medicine,

Leopold-Franzens-University of Innsbruck, Austria. wolfgang.voelckel@uibk.ac.at

Vasopressin (antidiuretic hormone) seems a promising alternative to epinephrine for cardiopulmonary resuscitation (CPR) in cardiac arrest victims, mediating a pronounced blood flow shift toward vital organs. We evaluated the effects of small-dose dopamine on splanchnic blood flow and renal function after successful resuscitation with this potent vasoconstrictor in an established porcine CPR

model. After 4 min of cardiac arrest and 3 min of CPR, animals received 0.4 U/kg vasopressin and were continuously infused with either dopamine 4 microg x kg(-1) x min(-1) (n = 6), or saline placebo (n = 6). Defibrillation was performed 5 min after drug administration; all animals were observed for 6 h after return of spontaneous circulation. During the postresuscitation phase, average mean +/- SD superior mesenteric artery blood flow was significantly (P = 0.002) higher in the dopamine group compared with the placebo group (1185+/-130 vs 740+/-235 mL/min), whereas renal blood flow was comparable between groups (255+/-40 vs 250+/-85 mL/min). The median calculated glomerular filtration rate had higher values in the dopamine group (70-120 mL/min) than in the placebo group (40-70 mL/min; P = 0.1 at 0 min and P = 0.08 at 360 min). We conclude that small-dose dopamine administration may be useful in improving superior mesenteric artery blood flow and renal function after successful resuscitation with vasopressin. **IMPLICATIONS:** Long-term survival after cardiac arrest may be determined by the ability to ensure adequate organ perfusion during cardiopulmonary resuscitation and in the postresuscitation phase. In this regard, small-dose dopamine improved postresuscitation blood flow to the mesenteric bed when vasopressin was used as an alternative vasopressor in an animal model of cardiac arrest. PMID: 10589622 [PubMed - indexed for MEDLINE]

Level of Evidence: 6

Study Quality: Good (randomized, blinded)

Funding: Solvay Pharma, Internal grants from The Leopold Franzens University of Innsbruck, Austrian National Bank

Subjects: Swine (n=6 per group)

Interventions: Dopamine CRI vs saline – started prior to ROSC and continued after

Outcomes: Mesenteric artery blood flow, GFR - E

Key points: Positive for question. Mesenteric blood flow and GFR were both higher in dopamine treated group. UOP and calculated renal function indices were not different between groups.

14. Circulation. 1997 Jun 17;95(12):2610-3.

Postresuscitation left ventricular systolic and diastolic dysfunction. Treatment with dobutamine.

Kern KB, Hilwig RW, Berg RA, Rhee KH, Sanders AB, Otto CW, Ewy GA.

University Heart Center, Tucson, AZ, USA. kernk@u.arizona.edu

BACKGROUND: Global left ventricular dysfunction after successful resuscitation is well documented and appears to be a major contributing factor in limiting long-term survival after initial recovery from out-of-hospital sudden cardiac death. Treatment of such postresuscitation myocardial dysfunction has not been examined previously.

METHODS AND RESULTS: Systolic and diastolic parameters of left ventricular function were measured in 27 swine before and after successful resuscitation from prolonged ventricular fibrillation cardiac arrest. Dobutamine infusions (10 micrograms.kg-1.min-1 in 14 animals or 5 micrograms.kg-1.min-1 in 5 animals) begun 15 minutes after resuscitation were compared with controls receiving no treatment (8 animals). The marked deterioration in systolic and diastolic left ventricular function seen in the control group after resuscitation was ameliorated in the dobutamine-treated animals. Left ventricular ejection fraction

fell from a prearrest 58 +/- 3% to 25 +/- 3% at 5 hours after resuscitation in the control group but remained unchanged in the dobutamine (10 micrograms.kg-1.min-1) group (52 +/- 1% prearrest and 55 +/- 3% at 5 hours after resuscitation). Measurement of the constant of isovolumic relaxation of the left ventricle (tau) demonstrated a similar benefit of the dobutamine infusion for overcoming postresuscitation diastolic dysfunction. The tau rose in the controls from 28 +/- 1 milliseconds (ms) prearrest to 41 +/- 3 ms at 5 hours after resuscitation whereas it remained constant in the dobutamine-treated animals (31 +/- 1 ms prearrest and 31 +/- 5 ms at 5 hours after resuscitation).

CONCLUSIONS: Dobutamine begun within 15 minutes of successful resuscitation can successfully overcome the global systolic and diastolic left ventricular dysfunction resulting from prolonged cardiac arrest and cardiopulmonary resuscitation.

PMID: 9193427 [PubMed - indexed for MEDLINE]

Level of Evidence: 6

Study Quality: Poor (non-randomized, non-blinded, historic controls)

Funding: Arizona Disease Control Research Commission

Subjects: Swine (n=27 total, 19 treated)

Interventions: Dobutamine (2 doses) vs placebo

Outcomes: LV function - E

Key points: Positive for the question. Dobutamine led to improvement in LV function of controls. Post hoc inclusion of lower dobutamine dose (5 vs 10ug/kg/min) found less improvement in LV function but still some improvement. Lower dose was associated with less tachycardia. Controls from previous study.