

WORKSHEET for Evidence-Based Review**Worksheet author(s)****Karl B Kern, MD; Sudhakar Sattur, MD****Date Submitted for review:** November 24, 2009
(Final Revision)**Clinical question.**

“In adult patients with ROSC after cardiac arrest (pre hospital or in-hospital) who have cardiovascular dysfunction (P), does the use of any specific cardio-active drugs (I) as opposed to standard care (or different cardio active drugs) (C), improve outcome (O) (eg. Survival)?”

Is this question addressing an intervention/therapy, prognosis or diagnosis: Intervention/ therapy.
State if this is a proposed new topic or revision of existing worksheet: re-revision

Search strategy (including electronic databases searched) last date search was run on 9/15/2009

1. Review of 2005 Guidelines and worksheets.
2. Pub Med search (as per the tutorial by Peter Morley)

1 Search “Death, Sudden, Cardiac”[Mesh] – 7666# 2 Search “Cardiopulmonary Resuscitation”[Mesh] – 7647

#3 Ventricular dysfunction – 17177

#4 Search Post resuscitation myocardial dysfunction – 104

#5 Search “Cardiotonic Agents”[Mesh] – 10359

#6 Search “Fibrinolytic Agents”[Mesh] – 18034

#7 Search “Dopamine”[Mesh]- 59948

#8 Search “Dobutamine”[Mesh] – 5050

#9 Search (("Cardiopulmonary Resuscitation"[Mesh]) OR ("Ventricular Dysfunction"[Mesh]) OR ("Death, Sudden, Cardiac"[Mesh])) AND (("Fibrinolytic Agents"[Mesh]) OR ("Cardiotonic Agents"[Mesh])) – 770

3. Cochrane Reviews search

1 Search “Death, Sudden, Cardiac”[Mesh] – 379

2 Search “Cardiopulmonary Resuscitation”[Mesh] – 356

#3 Ventricular dysfunction – 1303#4 Search “Cardiotonic Agents”[Mesh] – 4378

#5 Search (("Cardiopulmonary Resuscitation"[Mesh]) OR ("Ventricular Dysfunction"[Mesh]) OR ("Death, Sudden, Cardiac"[Mesh])) AND (("Fibrinolytic Agents"[Mesh]) OR ("Cardiotonic Agents"[Mesh])) – 117

4. Review of the current EndNote AHA library
5. Review of the recent Circulation publication and "related articles" on Post Cardiac Arrest Syndrome.
6. Review of articles cited in studied publications.
7. Forward search using Google scholar.

• State inclusion and exclusion criteria

We begun by including all post resuscitation therapy studies, both animal and human identified in the broad search. Several identified reviews note the paucity of human data, therefore we will keep relevant animal data in this worksheet.

• Number of articles/sources meeting criteria for further review:

15 studies met criteria for further review. Of these 10 studies were included as evidence supporting clinical question. Five studies were included as evidence neutral to clinical question.

Summary of evidence
Evidence Supporting Clinical Question

Good					<i>Wang 2005-E</i>
Fair			Sunde 2007-D		<i>Angelos 2002-E</i> <i>Meyer 2002-E</i> <i>Vasquez 2004-E</i> <i>Huang 2005-B,E</i> <i>Huang2 2005-E</i> <i>Suder 2005-E</i> <i>Tennyson 2007-E</i>
Poor					<i>Kern 1997-E</i>
	1	2	3	4	5
Level of evidence					

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

Bold indicates human clinical studies; *italics* indicates non-human studies (pigs, rats, isolated heart preps)

Evidence Neutral to Clinical question

Good					
Fair			Gaieski 2009-C		
Poor				Laurent 2002-E Mayr 2007-E	Jones 2008 Neumar 2008
	1	2	3	4	5*
Level of evidence					

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

Bold indicates human clinical studies; *italics* indicates non-human studies (pigs, rats, isolated heart preps)
 5* indicates formalized reviews of this question, rather than original scientific investigation

Evidence Opposing Clinical Question

Good					
Fair			NONE		
Poor					
	1	2	3	4	5
Level of evidence					

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

DISCUSSION: There is limited literature addressing the impact of specific cardioactive drugs (I) compared to standard care on outcomes (O) in adult patients with post resuscitation cardiovascular dysfunction (P), hence we modified the question partly to study the impact of cardioactive drugs (I) on outcomes (O) compared to standard care in patients with ROSC after cardiac arrest who have cardiovascular dysfunction (P). After extensive search, 25 studies were included for detailed review and 15 studies were included in the final summary.

A level 3 study supporting the question was performed by Sunde et al (Sunde, 2007). This study is a clinical series with historical controls during an interventional period from September 2003 to May 2005 (neither random nor blind). The historical control comes from a period of 1996 to 1998. Sixty-one patients were included in the interventional period and 58 in the historical period. A study evaluated implementation of a standardized treatment protocol for post-resuscitation care after out-of-hospital cardiac arrest. This protocol emphasized therapeutic hypothermia and early cath/PCI, as well as optimization of hemodynamics including vasopressors and oxygenation. However, therapeutic factors were evaluated in a preliminary bi-variant analysis showing that reperfusion treatment, therapeutic hypothermia, and inotropic agents significantly increased 1 year survival with odds ratios for reperfusion therapy of 27, and for inotropic agents of 2.4. This was significant for vasoactive medications at the $p=0.03$ level. Though, this benefit did not hold up in the multi-variant analysis as an independent predictor.

Gaieski et al (Gaieski, 2009, 418) performed a level 3 prospective non-randomized clinical study with historic controls addressing early goal directed hemodynamic optimization and outcomes in survivors of out of hospital cardiac arrest. Intervention was early goal directed post-resuscitation therapy including induction and maintenance of hypothermia and use of a variety of agents if needed including norepinephrine, dobutamine (from 2 to 20 mcg), dopamine or epinephrine. We categorized this evidence as neutral to the question, as there were no details about what each individual patient received, and the overall p value was non-significant at 0.15.

Mayr et al (Mayr, 2007) performed a level 4 study neutral to the question. It was an uncontrolled, retrospective study of 23 post resuscitated patients with refractory cardiovascular failure (shock), treated after standard care with vasopressin. Mean arterial pressure increased, PCWP declined, and other vasoactive medication requirements declined after administration of vasopressin, but cardiac index did not change.

Another level 4 study neutral to the question was performed by Laurent et al (Laurent, 2002, 2110). This is a prospective non randomized study of 165 survivors of out of hospital cardiac arrest addressing hemodynamic status during the first 72 hrs. Hemodynamic instability was treated using inotropic agents. Hemodynamic instability requiring administration of vasoactive agents was frequent and appeared several hours after hospital admission. The cardiac index rapidly improved 24 hours after the onset of cardiac arrest independent of use of inotropic agents. However, no specific data on the independent effect on outcome with the use of vasoactive medication was provided.

Two review articles concerning this question [(Jones, 2008, 26) and (Neumar, 2008, 2452)] are summarized in the attached materials. Both concluded that insufficient data exists to answer the question.

There are nine additional level 5 studies (animal studies) supporting the clinical question and these are included on the evidence grid. Wang et al (Wang, 2005, 179) performed a randomized, blinded, controlled study of 15 swine animals divided into propranolol alone during VF, propranolol during VF and levosimendan after resuscitation, and saline placebo groups. The outcomes measured were impact of intervention on post resuscitation myocardial dysfunction. There was a significant decrease in myocardial dysfunction in both the intervention arms compared to placebo arm. Details of other level 5 animal studies with fair and poor quality of evidence supporting the clinical question are summarized in the attached worksheet. They were limited by lack of randomization, blinding or absence of placebo /control arm.

REVIEWER'S CONFLICTS OF INTEREST:

Karl B Kern – Cardiologist . No intellectual or commercial conflicts.
Sudhakar Sattur – Hospitalist – No intellectual or commercial conflicts.

Acknowledgements: None

Citation List [1-15]

1. *Angelos MG, et al., Postischemic inotropic support of the dysfunctional heart. Crit Care Med, 2002;30(2):410-6.*

Level 5 Study: Isolated, langendorff rat hearts (n=12)
Intervention: Compare epinephrine, dobutamine, and phenylephrine
Endpoints: Non-Survival endpoint [E] (LV Function)
Quality: Fair (random, but not blind)
Conclusion: Positive for the Question

This is an evaluation of post-ischemic inotropic support of the dysfunctional heart in isolated rat hearts in the Langendorff preparation. This was randomized to different treatments, but not blinded. The endpoints were dP/dt and developed pressure divided myocardial oxygen consumption looking at dobutamine vs. epinephrine vs. phenylephrine vs. saline placebo. Active therapy improved left ventricular function measured by dP/dt max and by developed pressure over myocardial oxygen consumption, specifically for the phenylephrine group. This is a positive treatment study with fair in quality. In summary, a level of evidence 5 study looking at non-survival endpoints of left ventricular function in an isolated heart prep and quality if fair being randomized but not blinded.

2. *Gaieski DF, et al., Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. Resuscitation, 2009;80(4): 418-24.*

Level 3 Study Humans (n=18)
Intervention: Composite of goal directed hemodynamic optimization Rxs
Endpoint: Survival to hospital discharge (C)
Quality: Fair
Conclusion: Neutral for the Question

A clinical study using a retrospective historical control looking at early goal directed hemodynamic optimization and outcome in survivors of out-of-hospital cardiac arrest. Between May 2005 and January 2008, 18 patients enrolled. Historical control group comes from 2001 – 2005 with 18-patients who met inclusion criteria as historical controls. Intervention was early goal directed post-resuscitation therapy including hypothermia, and the use of vasoactive agents such as norepinephrine, dobutamine (from 2 to 20 mcg), dopamine, or epinephrine to maintain a mean arterial pressure greater than 80mmHg. There are no details about what each individual patient received. No early catheterization or PCI was included in their goal directed therapy. The study was **prospective, non-randomized with an historical control**. The mortality for historical controls was 78% (14 of 18) and the mortality for those treated with the goal directed post-resuscitation therapy was 50% (9 of 18). The “p” value was non-significant at 0.15.

3. *Huang L, et al., Levosimendan improves postresuscitation outcomes in a rat model of CPR. J Lab Clin Med, 2005;146(5):256-61.*

Level 5 Study: Rats (n=15)
Intervention: Levosimendan vs Dobutamine vs Placebo
Endpoints (2): Survival duration (D)
 Non-Survival endpoint [E] (LV Function)
Quality: Fair (randomized, but not blinded)

Conclusion: Positive for the Question

This is a non-clinical study in 15-rats comparing levosimendan dobutamine or saline placebo on improving post-resuscitation outcomes after CPR. **This is a treatment study as the interventions were given 10 minutes after return of spontaneous circulation.** The doses of dobutamine however are low at only 3 mcg/kg/min. The study was randomized but not blinded. There are two specific endpoints; one a non-survival endpoint of left ventricular function measured as cardiac index dP/dt 40, -dP/dt and left ventricular developed pressure. These non-survival endpoints were neutral comparing levosimendan vs. dobutamine, but were positive for either agent vs. placebo controls for cardiac index and dP/dt. Survival duration was also measured as an endpoint and showed an advantage for levosimendan over both control and dobutamine groups. The survival difference was in hours with the control groups surviving 8±1 hour, dobutamine 11±2 hours, and levosimendan 16±2 hours.

4. *Huang L, et al., Comparison between dobutamine and levosimendan for management of postresuscitation myocardial dysfunction. Crit Care Med, 2005. 33(3): p. 487-91.*

Level 5 Study: Swine (n=15)
Intervention: Levosimendan vs Dobutamine vs Placebo
Endpoints (2): Non-Survival endpoint [E] (LV Function)
Quality: Fair (random, but not blind)
Conclusion: Positive for the Question

This is a study comparing dobutamine vs. levosimendan vs. placebo for the management of post-resuscitation myocardial dysfunction in 15-swine **receiving the interventional treatment 10-minutes after return of spontaneous circulation.** Dobutamine in this study was administered as 5 mcg/kg/min. Both agents, levosimendan and dobutamine showed improved contractile function compared to placebo in cardiac output and ejection fraction. This is therefore a level of evidence 5 study with a non-survival endpoint of left ventricular function.

5. *Jones AE, et al., Goal-directed hemodynamic optimization in the post-cardiac arrest syndrome: a systematic review. Resuscitation, 2008;77(1):26-9.*

Level 5* Study (Review)
Intervention: NA
Endpoint: NA
Quality: NA
Conclusion: Neutral to the Question

This review on behalf of the Emergency Medicine Shock Research Network (EMSHOCKNET) found only five studies eligible for full review from 1,184 initially identified potential publications. They found that none of these five articles were eligible for final inclusion in their analysis. Their conclusion was, 'To date, no clinical trials have examined hemodynamic optimization in post-cardiac arrest patients.'

6. *Kern KB, et al., Postresuscitation left ventricular systolic and diastolic dysfunction. Treatment with dobutamine. Circulation, 1997; 95(12):2610-3.*

Level 5 Study: Swine (n=27)
Intervention: Dobutamine vs no treatment
Endpoints: Non-Survival endpoint [E] (LV Function)
Quality: Poor (neither random, nor blind)
Conclusion: Positive for the Question

This study evaluated the effect of a dobutamine infusion on post-resuscitation left ventricular systolic and diastolic dysfunction in 27-swine (29±1 kg) treated with dobutamine or saline control. This was neither randomized nor blinded and there is a post-hoc group of 5-animals done with a lower dose of 5 mcg/kg/min vs. initial dose of 10 mcg/kg/min. Endpoints are left ventricular function measures of ejection fraction, end-diastolic pressure, cardiac output, and Tau or isovolumic relaxation. Since this study was neither randomized nor blinded and used to what appears to be historical controls from previous work, the quality is less than fair. In summary, this is a level of evidence 5 study with non-survival endpoints (E) of left ventricular function and the quality is listed as poor for being non-randomized and non-blinded.

7. ***Laurent I, et al., Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. J Am Coll Cardiol, 2002. 40(12): p. 2110-6.***

Level 4 Study: Humans (n=165)
Intervention: Invasive monitoring for hemodynamic instability in patients with ROSC after cardiac arrest
Endpoints: Non-Survival endpoint [E] (LV Function)
Quality: Poor (neither random, nor blind)
Conclusion: Neutral for the Question

This is a prospective, non-randomized study of 165 survivors of out of hospital cardiac arrest addressing hemodynamic status during the first 72 hrs. Hemodynamic instability was treated using inotropic agents. Hemodynamic instability requiring administration of vasoactive agents was frequent and appeared several hours after hospital admission. The cardiac index rapidly improved 24 hours after the onset of cardiac arrest independent of use of inotropic agents. Individual patient data is not provided, nor is the independent effect on outcome of vasoactive medication usage.

8. ***Mayr V, et al., Arginine vasopressin in advanced cardiovascular failure during the post-resuscitation phase after cardiac arrest. Resuscitation, 2007;72(1):35-44.***

Level 4 Study Humans (n=23)
Intervention: Vasopressin for refractory post resuscitation cardiovascular failure (shock)
Endpoint: Mean Arterial Pressure, Vasopressor requirements, and Cardiac Index (E)
Quality: Poor
Conclusion: Neutral to the Question

This is an uncontrolled, retrospective study of 23 post resuscitated patients with refractory cardiovascular failure (shock), treated after standard care with vasopressin. Mean arterial pressure increased, PCWP declined, and other vasoactive medication requirements declined after administration of vasopressin, but cardiac index did not change. This study was neither randomized, blinded, nor controlled. No outcome data are presented.

9. ***Meyer RJ, et al., Post-resuscitation right ventricular dysfunction: delineation and treatment with dobutamine. Resuscitation, 2002;55(2):187-91.***

Level 5 Study: Swine (n=28)
Intervention: Dobutamine vs Saline placebo
Endpoints: Non-Survival endpoint [E] (RV Function)
Quality: Fair (random, but not blind)
Conclusion: Positive for the Question

This is a study in 28-swine (29±1 kg). This was a randomized trial, but not blinded. **Comparing dobutamine vs. equivalent volume saline controls given 10 minutes post-resuscitation for post resuscitation RV function.** This is a treatment trial as opposed to preventive. The endpoints are non-survival (E) endpoints of right ventricular function including RV ejection fraction and RV end-diastolic pressure, and RV tau. In summary, it is a level of evidence 5 study with non-survival endpoints of right ventricular function.

10. *Neumar RW, et al., Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. Circulation, 2008. 118(23): p. 2452-83*

Level 5* Study (Review/Summary)

Intervention: NA
Endpoint: NA
Quality: NA
Conclusion: Neutral to the Question

This is the review paper sponsored by ILCOR on the Post Cardiac Arrest Syndrome. The conclusion of this review is that, 'No individual drug or combination of drugs has been demonstrated to be superior in the treatment of post-cardiac arrest cardiovascular dysfunction. Despite improving hemodynamic values, the effect on survival of inotropes and vasopressors in the post-cardiac arrest phase has not been studied in humans.'

11. *Studer W, et al., Influence of dobutamine on the variables of systemic haemodynamics, metabolism, and intestinal perfusion after cardiopulmonary resuscitation in the rat. Resuscitation, 2005;64(2):227-32.*

Level 5 Study: Rats (n=24)
Intervention: Dobutamine vs saline controls
Endpoints (2): Non-Survival endpoint [E] (Lactate clearance)
Quality: Good/Fair (random and possible blind)
Conclusion: Positive for the Question

This is a study of the influence of dobutamine on systemic hemodynamics and metabolism after successful resuscitation from cardiac arrest induced by ventricular fibrillation. Study took place in 24-rats **randomized and possibly blinded by equal volume of therapeutic injection.** However, it is not specifically stated. Compared to saline control, dobutamine at 10 mcg/kg/min significantly increased lactate clearance. Hence, this is a level of evidence 5 study with a non-survival (E) endpoint of lactate clearance.

12. *Sunde K., et al., Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation, 2007;73(1):29-39.*

Level 3 Study **Humans (n=61)**
Intervention: **Formalized post resuscitation care protocol including Therapeutic Hypothermia, use of PCI, and Vasoactive medications**
Endpoint: **Survival to hospital discharge (C)**
Quality: **Fair (prospective, but non-randomized, nor blind)**
Conclusion: **Positive for the Question**

This study is a clinical series with historical controls during an interventional period from September 2003 to May 2005 (neither random nor blind). The historical control comes from a period of 1996 to 1998. Sixty-nine patients were included in the interventional period and 68 in the historical period. A study evaluated implementation of a standardized treatment protocol for post-resuscitation care after out-of-hospital cardiac arrest. This protocol emphasized therapeutic hypothermia and early cath/PCI, as well as optimization of hemodynamics and oxygenation. Initially therapeutic hypothermia was begun with ice cold saline and external ice bags, later with endovascular cooling or occasionally external cooling for maintenance. When vaso-pressor or inotropic agents were needed; dopamine or norepinephrine for vasopressors and dobutamine 2 to 10 mcg for inotropic assistance were utilized. **There is no way to separate the effects of different therapies as they were bundled and given in general as a group.** However, therapeutic factors were evaluated in a preliminary bi-variant analysis showing that reperfusion treatment, therapeutic hypothermia, and inotropic agents significantly increased survival with odds ratios for reperfusion therapy of 27, and for inotropic agents of 2.4. This was significant for vasoactive medications at the p= 0.03 level. (Note, the multi-variant logistic regression analysis did not detect inotropic therapies to be an independent factor improving survival.) Hence, this is a level of evidence 3 clinical study for the outcome of intact neurologic survival with a positive bi-variant analysis in favor of the use of inotropic agents. Though, this benefit seems to not hold up in the multi-variant analysis as an independent predictor, hence only fair quality.

13. *Tennyson H., et al., Treatment of post resuscitation myocardial dysfunction: aortic counterpulsation versus dobutamine. Resuscitation, 2002;54(1):69-75.*

Level 5 Study: **Swine (n=10)**
Intervention: **Dobutamine vs IABP**
Endpoints: **Non-Survival endpoint [E] (LV Function)**
Quality: **Fair (random, but not blind)**
Conclusion: **Positive for the Question**

This is a study of dobutamine vs. intraaortic balloon counterpulsation for the treatment of post-resuscitation left ventricular dysfunction. Treatment was begun starting 15 minutes post ROSC. Domestic swine were utilized weighing 49±3 kg. Endpoints were non-survival (E), left ventricular dysfunction measures including ejection fraction, end-diastolic pressure and Tau. It was randomized, but not blinded.

14. *Vasquez A., et al., Optimal dosing of dobutamine for treating post-resuscitation left ventricular dysfunction. Resuscitation, 2004; 61(2):199-207.*

Level 5 Study: **Swine (n=20)**
Intervention: **Dobutamine vs saline placebo**
Endpoints: **Non-Survival endpoint [E] (LV Function)**
Quality: **Fair (random, not blind)**
Conclusion: **Positive for the Question**

This study is looking at the optimal dosing of dobutamine for treating post-resuscitation left ventricular dysfunction. This was performed in 20 swine (24±1 kg). Resuscitated animals were randomized to therapy among four treatment groups, including saline placebo, or Dobutamine at 2, 5 or 7.5mcg/kg/min in this dosing study. Those receiving Dobutamine at either 5 or 7.5 mcg/kg/min were both superior for their effect on left ventricular dysfunction than was saline placebo, for the endpoints of left ventricular end-diastolic pressure, left ventricular dP/dt and -dP/dt, Tau or left ventricular stroke work, likewise for ejection fraction and cardiac output. Randomized, but not blinded. Hence, in summary this is a level of evidence 5 with endpoints of left ventricular function (E), including ejection fraction, left ventricular end -diastolic pressure, cardiac output, isovolumic relaxation and dP/dt showing in favor of active therapy with dobutamine.

15. Wang J., et al., Levosimendan improves postresuscitation myocardial dysfunction after beta-adrenergic blockade. *J Lab Clin Med*, 2005;146(3):179-83.

Level 5 Study: Swine (n=15)
Intervention: Levosimendan vs placebo
Endpoints (2): Non-Survival endpoint [E] (LV Function)
Quality: Good (random and blind)
Conclusion: Positive for the Question

This is a study of Levosimendan improving post-resuscitation, myocardial dysfunction after beta-adrenergic blockade in 15 swine. Propanolol as administered during cardiac arrest while levosimendan as administered 10-minutes after successful resuscitation. Animals were randomized by sealed enveloped method to propanolol alone during VF, Propanolol and levosimendan administered after resuscitation, and a saline placebo arm. This study was both randomized and blinded to the randomization (unclear if the investigators were blinded during the actual experiment or not). It is a level of evidence 5 study with an E endpoint of left ventricular function including ejection fraction which was significantly better with either active therapy arm; the best arm being the propanolol plus levosimendan arm.