**WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**

**Worksheet author(s)**
- Allan de Caen
- Mark Coulthard did same worksheet topic (Peds 024B)

**Date Submitted for review:**
- Oct 9, 2009

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**Clinical question.**

In pediatric patients with ROSC after cardiac arrest (pre-hospital [OHCA] or in-hospital [IHCA]) who have signs of cardiovascular dysfunction (P), does the use of any specific cardioactive drugs (I) as opposed to standard care (or different cardioactive drugs) (C), improve physiologic endpoints (oxygen delivery, hemodynamics) or patient outcome (eg, survival to discharge or survival with favorable neurologic outcome) (O)?

**Is this question addressing an intervention/therapy, prognosis or diagnosis?**
- Therapy

**State if this is a proposed new topic or revision of existing worksheet.**
- Revision of existing worksheet

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**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet?
- No

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**Search strategy (including electronic databases searched).**

All searches build on the previous worksheet for this topic performed by this worksheet author for C2005, who used the same search strategy (ie. Current searches limited to post-Jan 2004)

**PubMed**

A. (“Cardiopulmonary Bypass”[Mesh] OR "Cardiac Surgical Procedures"[Mesh] OR "Myocardial Stunning"[Mesh])

AND

(“Vasoconstrictor Agents”[Mesh] OR "Cardiotonic Agents"[Mesh] OR "Vasodilator Agents”[Mesh])

(no difference in hits when searched for all individual cardiotonics and pressors together as ‘OR’)

Limited to: All Infant: birth-23 months, Preschool Child: 2-5 years, Child: 6-12 years

**70 hits**


no limits

**173 hits**

**Combination of A) and B) thinned to 6 relevant citations**

**When strategy A) searched selecting adults, and children over 12 years age (and limiting for high quality papers, ie. RCTs and metaanalyses), 114 hits with 10 selected for further review**

**EMBASE**

1. vasoconstrictor Agent
2. Phosphodiesterase Inhibitor
3. milrinone
4. amrinone
5. hypertensive Agent
6. levosimendan
7. adrenalin
8. dobutamine
9. dopamine
10. inotropic Agent
11. heart arrest
12. Heart Surgery
13. Cardiopulmonary Bypass
14. myocardial stun
15. cardiopulmonary resuscitation
16. 11 or 12 or 13 or 14 or 15
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
18. 16 and 17


**All Cochrane databases**

1. heart arrest
2. cardiopulmonary arrest
3. cardiopulmonary resuscitation
4. myocardial stun
5. cardiopulmonary bypass
6. cardiac surgery
7. heart surgery
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. milrinone
10. amrinone
11. levsimendan
12. adrenalin
13. dobutamine
14. dopamine
15. norepinephrine
16. vasopressin
17. inotropic agent
18. cardiotonic
19. vasopressor
20. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 8 and 20

47 hits; none relevant

Hand search of papers’ references: 2 hits (Vasquez and Nijhawan)

Web of Science of major articles (post-arrest): 0 supplemental hits

AHA Master library: 0 supplemental hits

The search strategies were run again on Oct 1, 2009 with no additional hits found.

<table>
<thead>
<tr>
<th>State inclusion and exclusion criteria</th>
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<tr>
<td>• Only searched literature published since Jan 1, 2004</td>
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<tr>
<td>• Adult studies examining pre-CPB drug use or on-CPB were excluded from analysis as it was felt inappropriate to extrapolate findings from these studies to the post-cardiac arrest setting</td>
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<td>• Case reports and editorials excluded</td>
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<table>
<thead>
<tr>
<th>Number of articles/sources meeting criteria for further review:</th>
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<tr>
<td>Since 2005 worksheet</td>
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<td>13 LOE 5</td>
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I have included relevant 'high impact' studies from the 2005 worksheet |
| 6 LOE 5 |
### Summary of evidence

#### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
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<th>Poor</th>
<th>Evidence Supporting Clinical Question</th>
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<td>Hoffman 2003 E</td>
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<td>Huang 1, 2005 AB</td>
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**Level of evidence**

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

*Italics = Animal studies*
### Evidence Neutral to Clinical question

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**Level of evidence**

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### Evidence Opposing Clinical Question

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**Level of evidence**

- A = Return of spontaneous circulation
- B = Survival of event
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- D = Intact neurological survival
- E = Other endpoint

*Italicics = Animal studies*
Animals and humans that are successfully resuscitated from cardiac arrest often have biventricular myocardial dysfunction (systolic and diastolic) that is transient. Hemodynamics improve with the short term use of cardiotonic agents after successful resuscitation (Kern 1997, Meyer 2002, Studer 2005). Whether this improves long-term survival, let alone neurologic prognosis, is far from clear. Controversy continues as to what the best cardiotonic agent is to use in this setting, as well as what the desired hemodynamic target is (a specific cardiac output or blood pressure, diastolic function, systolic function, reduced myocardial 02 consumption, etc). Some investigators have described a post-resuscitation vasodilatory state (low systemic vascular resistance or SVR) that might respond to vasopressor support as opposed to primary inotropic support (Mayr, 2007). Animal studies have not documented this post-resuscitation condition, and if anything (extrapolating from the post-CPB literature), a high SVR state as opposed to a low SVR state is a more common outcome in survivors of cardiopulmonary arrest. Further investigation of this post-resuscitative state is needed before a vasopressor-based treatment strategy can be recommended.

Most human studies of post-cardiac arrest myocardial dysfunction and its treatment have come from the cardiac surgical literature. Variations in study design make it difficult to compare the results of many of these studies, let alone extrapolate their results to the post-cardiac arrest setting.

- Studies have examined the myocardial dysfunction that ensues after a period of cardioplegia and cardiac arrest. The use of a controlled systemic circulation while on cardiopulmonary bypass (CPB) allows for most organ systems to continue to be perfused while the heart is rendered ischemic. In the post-cardiac arrest setting, it is not only the heart, but all body organ systems that have sustained a hypoxic-ischemic injury.
- Much of the cardiac surgical literature has studied the post-bypass response to inotropes in patients with ‘good’ pre-operative cardiac function, and not patients in pre-cardiac arrest low cardiac output (typical of most patients post-cardiac arrest).
- Is it appropriate to compare the results of a study that examines starting an inotrope before CPB/ cardioplegia, to a study examining the use of the same inotrope after separation from CPB?
- Is it appropriate to extrapolate the results of studies that examine loading a patient with a drug while they are still hemodynamically supported on CPB (especially drugs that have significant effects on patient hemodynamics), to the ‘fragile’ post-cardiac arrest patients?
- Animal studies investigating myocardic dysfunction post-cardiac arrest have dealt predominantly with cardiac arrest following VF, and not asphyxial arrest. It is unclear whether the myocardial dysfunction seen after non-asphyxial insults is the same as that seen after the progressive hypoxemia/ ischemia culminating in asphyxial cardiac arrest (as is seen in the vast majority of pediatric cardiopulmonary arrests).
- Only one pediatric animal study exists, and this is a CPB model of myocardial dysfunction. There is no published pediatric (animal or human) study specifically investigating the role of inotropes after cardiac arrest (asphyxial or non-asphyxial).

The animal literature suggests that the use of drugs with inotropic, afterload reducing and luciotropic properties might benefit the patient (and his/her heart) after cardiac arrest. Post-VF arrest studies in pigs suggest that dobutamine can fulfill all of these roles, but that doses higher than 5 mcg/ kg/ min may have an associated metabolic cost of increased tachycardia and myocardial 02 consumption that could exceed available myocardial 02 delivery (Vasquez, 2004). Studies of the pediatric patient after CPB suggest that the early (post-injury) use of agents such as milrinone can reduce the likelihood of the patient progressing into a low cardiac output state after the injury created by cardiotoximoy and cardioplegia/ myocardial ischemia (Hoffman, 2003). Human (adult post-CPB) literature suggests that either low dose epinephrine or milrinone may achieve the same endpoints of improved cardiac output and reduced SVR, but that the efficacy of either of these agents as lucitropes may be limited to a short period of time (ie. several hours) post-CPB (Lobato, 2005).

The majority of animal studies of post-cardiac arrest cardiotonic use (since the C2005 worksheet) have focused on levosimendan, a calcium-sensitizing agent with inotropic, luictropic and vasodilatory effects. Porcine post-VF arrest studies suggest that in comparing levesosimendan (L) and dobutamine (D), L has less associated tachycardia, equivalent inotropy and cardiac output, but improved luciotropy over D (Huang, 2005). These same investigators have performed one of the few animal studies investigating longer term survival (72 hrs) in an animal (rat) VF model, and found a survival benefit to both L and D over the control group, but an increased survival benefit specifically with the use of L.

A study in a piglet CPB model (Stocker, 2007) compared the ease of separation from CPB using either L (80 mcg/ kg load and 0.7 mcg/ kg/ min infusion) or M (2 mcg/ kg/ min). Diastolic function, contractility and the degree of vasodilation were superior with the use of L as compared to M. Varied dosing strategies for levosimendan have been investigated in adults post-CPB (Nijhawan, 1999, Alvarez 2006, Jorgensen 2008). Concern remains that with the use of higher doses of L (36 mcg/kg bolus followed by infusion of 0.3 mcg/ kg/ min) that the benefits of increased cardiac output and systemic vasodilation might be outweighed by drug-related tachycardia (baroreceptor-related?) and an associated myocardial metabolic burden (ie. increased 02 consumption) (Nijhawan, 1999). The pediatric post-operative cardiac literature studying L use is limited, and addresses multiple patient subgroups simultaneously (single ventricle, biventricular, R or L sided congenital heart defects, large age ranges within studies, pre or post-CPB use), making it difficult to interpret this data, let alone extrapolate it to use in infants/ children after cardiac arrest in the non-CPB setting (Egan, 2006).

Animal studies have investigated the role of agents such as propanolol in reducing myocardial 02 consumption in the post-VF arrest state. A concern has been that the negative inotropic effects of this agent might counteract any benefit gleaned by improving the myocardial 02 delivery/consumption balance. An adult pig study (Wang, 2005) combined the use of L and propanolol in a VF cardiac arrest model. It found that pre-defibrillation dosing with propanolol helped to reduce the number of shocks necessary to defibrillate, using a significantly lesser total energies of shocks, and leading to significantly reduced post-resuscitation premature ventricular beats (PVB) and associated ST-changes. The treatment of animals with levosimendan after successful resuscitation increased the animals’ ejection fraction beyond that seen with either placebo animals or animals that were only treated intra-arrest with propanolol.

As stated in the C2005 worksheet, there is a need to study the use of cardiotonic support in children after cardiac arrest. For the time being, conclusions must be extrapolated from the post-operative cardiac literature and animal models. Short term goals (such as hemodynamic...
parameters, venous oxygen saturation, lactate concentration or other correlates of cardiac output) will continue to be targeted without knowing what the best parameters are to use as therapeutic endpoints. Until definitive data exists suggesting improved outcomes with specific drug regimes, the choice of cardiotonic agents to support the child post-resuscitation will continue to be physician and patient-dependent, weighing the relative benefits/ side effects of the various cardiotonic agents, and the clinical setting that the practitioner is operating in.

Acknowledgements: Nil

Citation List


An open randomized trial in adults post-CPB (n=41) with low cardiac output syndrome or LCOS (CI <2.2L/ min/ m2 and PCP> 15 mm Hg) comparing the use the use of dobutamine (D) (7.5 mcg/ kg/ min) to Levosimendan (L)(loading dose of 12 mcg/ kg then infusion of 0.2 mcg/ kg/ min) started upon ICU admission and continued for 24 hrs. Patients were excluded from the study for protocol violation, including changes in doses of L or D, need to continue agents for >24 hrs for LCOS, need to add other inotropes or vasoactive agents.

Main findings
1) HR rose with the use of both agents, but became significantly higher in the L group by 24 hrs post-op (as the D group HR began to fall once D therapy was stopped); L has metabolites that appear to linger for longer periods of time
2) CI rose to higher levels in the L group, but took up to 12 hrs to reach higher levels than D group, and remained higher past the discontinuation of study drugs at 24 hrs (retention of metabolites in L group as above)
3) MAP was persistently higher in D group even out to 48 hrs (24 hrs past d/c of study drugs); right and left-sided cardiac filling pressures, ad SVR, remained lower in L group out to 48 hrs (prolonged vasodilatory effect)
4) SV02 was higher in L group as of 6 hrs, and continued as such out to 48 hrs; D02 was higher in L group as of 6 hrs, and remained higher than D group out to 48 hrs

Limitations
1) small study
2) although randomized, no blinding
3) no comment made as to S/A of therapy (eg. hypotension and need for fluid requirements in either group); they do allude to hypotension in their conclusions of their abstract (ie. reduce the loading dose of L to reduce its effect), but do not give data to support their concerns
4) non-pediatric model
5) non-asphyxial model
6) non-cardiac arrest model

LOE: 5
Quality: Fair
Supportive


A case series (n=15) describing the echo-based measurement of ‘myocardial performance index’ in infants treated with open label milrinone post-cardiac surgery for low cardiac output syndrome (clearly defined in the paper). Patients had serial echos post-operatively, at ~3 hrs and 18-24 hrs post-operatively. All patients had milrinone started after the first echo (no loading dose, infusion between 0.3-0.6 mcg/ k/ min). Biventricular function improved with milrinone treatment as measured by the R and L myocardial performance index’ demonstrate improved contractility, and not just a vasodilatory effect.

Limitations of the paper include:
• Case series nature (absence of a control group)
• Wide range of infusion dosing
• Many concurrent factors are not accounted/ controlled for that could have varied between groups
  o Cross-clamp and CPB times
  o Use of intra-operative hypothermia
  o Use of and amount of inotropes/ catecholamines in the post-operative phase

LOE: 5
Quality: Fair
Supportive

A retrospective cohort study describing the patient characteristics surrounding the use of levosimendan (L) in the intra- and post-CPB care of children having congenital heart surgery. There were 19 patients described over a 32-month period that were treated with L. Hemodynamic data was collected at 3 time points: the hour prior to starting treatment with L, 4 hrs after starting L-infusion and 1 hr after the 24-hr infusion of L finished. The authors retrospectively divided the patients into 2 groups; one group (n=6) where L had been started empirically before separation from CPB, as the patients had been identified by the caregivers as being ‘high-risk’; the second group (n=13) had L started after separation from CPB as rescue therapy (no set criteria). Of the patients treated, 1/6 of the ‘empirical treatment’ group did not have hemodynamic data collected from the study, while 5/13 of the ‘rescue therapy’ group did not contribute hemodynamic data to the study. Drug dosing/delivery was inconsistent (4/19 patients did not receive a bolus dose of L).

The limited data shows that heart rate increased and then fell post-op, and that blood pressure fell and then rose, in the ‘rescue therapy’ group. Looking at the ‘empiric group’, lactates rose and then fell post-op. Other hemodynamic changes are described, but these are just trends, and do not reach statistical significance. The authors describe this as a safety study.

Weaknesses/limitations of the study include:
• In the absence of a control group, these findings potentially just reflect the natural post-CPB changes of these variables, with no relevance to the use of L
• The study conclusions are severely limited, even as a safety study, by the small numbers
• It is unclear how exactly the patient groups differ other than timing of dosing, as the criteria used to justify starting L are not specified (‘refractory to conventional inotropes’)
• There is a significant fall-out of patients from the data collection that raise concern as to the validity of the data
• Relevance to post-asphyxial cardiac arrests such as occurs in most pediatric cardiac arrests?
• Many concurrent factors are not accounted/controlled for that could have varied between groups
  o Cross-clamp and CPB times
  o Use of intra-operative hypothermia
  o Use of and amount of inotropes/catecholamines in the post-operative phase

LOE: 5
Quality: Poor
Supportive


A multicenter prospective double blinded randomized placebo controlled trial investigating the response of children with biventricular cardiac repairs to milrinone, that were within 90 minutes of PICU arrival post CPB, and at risk for a low cardiac output state. Milrinone at low dose (25 mcg/ kg bolus over 60 min and infusion at 0.25 mcg/ kg/ min) and high dose (75 mcg/ kg bolus over 60 min followed by infusion at 0.75 mcg/ kg/ min) were compared to the placebo arm. Progression into a low cardiac output syndrome (LCOS) was the primary endpoint, as defined by set clinical criteria of worsening cardiac output, doubling of inotrope score, the addition of a new open label inotrope, or the use of ECMO.

There was a significant and progressive reduction in the incidence of post-operative LCOS when comparing placebo and high dose milrinone (although not in comparing placebo to low dose milrinone). In assessing secondary study endpoints, there was no difference between groups in duration of assisted ventilation or hospital stay. Progression into prolonged hospital stay was highest with placebo, followed by high dose and then low dose milrinone groups. While there was a significant drop in BPs and BPd immediately after the milrinone bolus (both milrinone groups relative to placebo), there was no significant difference by the 12 hr mark of the study. HR was significantly higher in the treatment arms at 1, 12 and 24 hrs into the study. There was no significant inter-group differences in hypotension, dysrhythmia or thrombocytopenia.

Limitations of the study are pointed out by the authors. Some patients that would have been eligible for study inclusion were empirically dosed in the OR with milrinone outside of the study protocol (how many?). Low cardiac output was defined by clinical criteria, and not by objective measurement of cardiac output (echo or thermodilution technique). Patients were both L and R sided lesions, so potentially may have responded differently to the study drugs (although they were evenly distributed between study groups, subgroup differences in response may have been hidden in the larger group analysis). All limitations considered, this is the closed study that exists looking at inotrope usage that would be “the gold standard study”.

LOE: 5
Quality: Good
Supportive


This is a RCT in an adult rat model, comparing the use of Levosimendan (L) to dobutmaine (D) to saline control in the post-resuscitative care of animals resuscitated from VF-cardiac arrest, looking at hemodynamics and survival to 72 hrs as endpoints. Animals were randomized immediately pre-study into 3 groups (there was no blinding of the investigators). After anesthesia and instrumentation, baseline hemodynamics were measured. An 8 min untreated VF-cardiac arrest followed, followed by 6 min of CPR. A strict resuscitation protocol was followed that did not include adrenergic
agents as part of it. Study drugs were started 10 minutes after ROSC; D (3 mcg/kg/min), L (12 mcg/kg bolus over 10 min, followed by 0.3 mcg/kg/min), or saline control. After resuscitation, animals were followed by 72 hrs.

Baseline hemodynamics were comparable between L, D and saline control groups. All animals were successfully resuscitated after comparable resuscitation times. Significantly greater heart rates were noted in the D group post resuscitation. Although there were no differences in blood pressure between groups, cardiac index was higher in the D and L groups. Both D and L improved contractile and lusitropic function (preventing the drop in cardiac output seen post-resuscitation in the control group), but only L produced a significant drop in LVEDP. There was a significantly higher PaC02 and EtC02 in the dobutamine group, which was felt to be on the basis of increased metabolic activity created via the drug (although the anaerobic threshold was apparently not crossed, as there was no intergroup differences in mixed venous 02 sats or lactates). Interestingly, PaC02 was consistently <30 in the post-resuscitation control groups, 30-35 in the L group and 35-40 in the D group. No comment is made suggesting whether minute ventilation was reduced post-resuscitation. There was a significant difference in survival, with L and D being better than control, but L being even better than D. Outcomes in the best survival group (L) were still poor (16 +/- 2 hrs).

Strengths of the study include a clearly laid out protocol. Limitations include:

- The initiation of study drug was 10 minutes post ROSC (very soon after resuscitation); is this realistic in most clinical settings?
- Relevance to post-asphyxial cardiac arrests such as occurs in most pediatric cardiac arrests?
- Although there is not a statistically significant difference between the groups in regards PaC02, there is evidence of hyperventilation that would not be in keeping with current clinical practice/guidelines; did this in any way contribute to the poor outcomes?

LOE: 5
Quality: Good
Supportive

Labeled as Huang 1 in chart


This is a prospective RCT comparing the use of levosimendan (L) 20 microg/kg over 10 mins followed by a 220-min infusion of 0.4 microg/kg/min or dobutamine (D) 5 microg/kg.min, to saline control for post-resuscitation care of adult pigs with VF-induced cardiac arrest. Immediately prior to study, animals were randomized to a study group by the sealed envelope method. After induction of VF, animals were left in VF without treatment for 7 minutes, following which CPR was initiated. Defibrillation was attempted 5 minutes after starting resuscitation using a biphasic waveform (150J) with 100% success. It is unclear whether any adrenergic agents were necessary to resuscitate the animals. Animals had an infusion of study drug started 10 min after ROSC, and therapy was continued for a further 230 minutes.

Study groups were equivalent in baseline characteristics. There were no differences in the number of shocks necessary to resuscitate. Hemodynamics (measured invasively) showed no differences in MAP in drug intervention groups (L and D) in comparison to control. Significantly lower PA pressures, wedge pressures and right atrial pressures were observed in the L group relative to saline control from the initiation of drug therapy. Significantly greater cardiac output was demonstrated for both L and D groups compared to placebo when measuring ejection fraction and fractional area change by transesophageal echocardiogram, but greater as well for the L group compared to D group. Study conclusions were that L has the potential to be an alternative to D as an inotropic agent for the resuscitation of post-resuscitation myocardial dysfunction.

A well designed animal study with some important limitations:

- Animals were free of heart disease (does this emulate the pediatric model even better than other models?)
- The initiation of study drug was 10 minutes post ROSC (very soon after resuscitation); is this realistic in most clinical settings?
- Short duration for study (for clinical relevance to patients): what would have happened beyond 4 hrs?
- Relevance to post-asphyxial cardiac arrests such as occurs in most pediatric cardiac arrests?
- Blood gases were analyzed post-resuscitation, but it is not clear (not reported) whether there were any differences in PaC02 between groups post-resuscitation (inadvertent hyperventilation? Vent'n rates were apparently not reduced post-resuscitation)

Funding was partially industry-based (Abbott laboratories)

LOE: 5
Quality: Good
Supportive

Labeled as Huang 2 in chart


Summary

- There was a dose dependent increase in Cardiac output, stroke volume, and a drop in systemic vascular resistance, and a trend towards increased...
There is improved diastolic relaxation (luciotropy) post CPB in this group of pts with the use of L

Well designed study: only limitations of study design include:
  - Blinding of echocardiographers/ investigators but not of anesthestists caring for the patients

Limitations of the study include:

- adult CPB model; non-arrested pts
- pts had normal ejection fraction pre-op
- duration of study is only 1 hr post-ischemic insult (separation from CPB): difficult to extrapolate to post-resuscitation care in meaningful way

LOE 5
Quality Good
Supportive


A prospective non-randomized controlled investigation of the effect of dobutamine on post-resuscitation myocardial function after prolonged fibrillatory cardiac arrest (15 minutes) in an adult swine model. After the fibrillatory period and subsequent 'ACLS resuscitation', a group of animals were placed on dobutamine infusions (5 or 10 mcg/ kg/ min started 15 min after successful resuscitation) and their hemodynamics observed over the ensuing hour. The lower dose dobutamine group was studied separately without a concurrent control group.

The deterioration in LV systolic and diastolic function was prevented by the use of post-resuscitation dobutamine (greater beneficial drug effects at 10 rather than 5 mcg/ kg/ min). HR was significantly greater in the dobutamine treated animals(dose dependent) at all times (compared to controls), but stroke volumes were increased, and wedge pressures significantly reduced in the dobutamine group.

Limitations of the model include the animal nature of the study group, but (regardless of the fibrillatory trigger) it would appear to mimic the hypoxic ischemic model of the resuscitated child (although, was ventilation stopped at the time of the fibrillaritary arrest?).

LOE: 5
Quality: Good
Supportive


A prospective randomized controlled trial comparing the effect of low dose epinephrine infusion (E: 0.03 mcg/ kg/ min; n=12) or milrinone infusion (M: 0.5 mcg/ kg/ min; n=13) in their effects (compared to control (C) receiving no inotropic support separating from CPB (n=11) on echocardiogram-evaluated diastolic dysfunction in adults after elective CPB for CABG. Patients were intra-operatively (after CPB separation but before protamine administration) divided into three groups after informed consent and computer-randomization. Nine patients were excluded form study intra-operatively as they required inotropes in order to successfully separate from CPB. All patients routinely separated from CPB on nitroglycerin 1 mcg/ kg/ min. Echo images were generated pre-CPB, immediately post-separation from CPB, after the study was initiated (5 min post-epinephrine infusion starting or after loading with milrinone), and after sternal closure (intra-operative). These images were evaluated by an echocardiographer blinded to patient allocation.

Patient group characteristics differ only in that the epinephrine group had a lesser number of patients with chronic hypertension, and a lesser number of patients on beta-blocker therapy pre-operatively. The cross clamp and CPB times were comparable between groups. The hemodynamic data showed the following:

- BP was lower post-CPB in the drug intervention groups compared to baseline, but not in comparison to concurrent control patients
- SVR dropped post-CPB in all three groups; the M and E groups had statistically lower SVR in comparison to control patients after drug dosing and after sternal closure
- Both drug intervention drug groups had a significant increase in cardiac index in comparison to pre-CPB

Echo data however showed the following:

- There was a significant improvement in measured diastolic function in only one of the measured indices but this difference between drug group resolved within 5 minutes of starting the study drugs; LV relaxation appeared to improve in all patients post-CPB, that was unchanged by the addition of either study drug; these differences in luciotropy had returned to baseline in all groups by the time of sternal closure
- The only way to observe differences in measured diastolic function as noted above was with the pooling of the M and E group data and comparing it to the control group. When evaluating individual group differences (ie. M vs E vs control), there were no differences

Limitations of the study include:

- Small numbers of patients
- Select patient population

Just looking at changes in luciotropy in patients with normal pre-op systolic function and mild diastolic function; pertinence to the patient with pre-op moderate or severe dysfunction, let alone post-arrest systolic and diastolic dysfunction?
Patients examined only included those that separated from CPB without the need for inotrope support

- Relevance to post-asphyxial cardiac arrests such as occurs in most pediatric cardiac arrests?

LOE: 5
Quality: Good
Supportive


A retrospective study of the use of vasopressin infusion for fluid and inotrope/vasopressor resistant shock after resuscitation from adult cardiac arrest (no controls). Concurrent with the use of vasopressin, there was an increase in blood pressure and a reduction in the dose of vasopressors and inotropes necessary to maintain blood pressure (as per protocol). There were no differences in hemodynamics or laboratory response to the use of vasopressin between survivors and non-survivors. The major limitation of the study is that based upon its case control nature, it is unclear which of the physiological and laboratory value changes are on the basis of vasopressin or other concurrent factors.

LOE: 5
Quality: Poor
Supportive


A prospective randomized controlled non-blinded trial studying the effects of dobutamine on post-resuscitation RV function in an adult swine model. Animals had a 15 min fibrillatory arrest, followed by an 'ACLS resuscitation'. After successful resuscitation, study drug (10 mcg/kg/min) was infused and hemodynamics monitored for the ensuing 5 hrs.

RV ejection fraction and RV end-diastolic pressure were significantly improved over the depressed values measured in the control animals (no difference in hemodynamics in dobutamine animals relative to pre-arrest baseline). HR was significantly elevated above controls at all times in the dobutamine group.

LOE: 5
Quality: Good
Supportive


A prospective randomized controlled non-blinded trial studying the effects of 'intra-resuscitation' milrinone on post-resuscitation hemodynamics/outcome in an adult swine model. Animals underwent a relatively short (5 min) fibrillatory arrest before resuscitation. The study group was bloused with milrinone 50 mcg/kg at the time that CPR was initiated, and an infusion of 0.5 mcg/kg/min started. Hemodynamics were monitored for the ensuing 60 min.

All study drug animals were successfully converted into a perfusing rhythm (as opposed to only 10/16 control animals). At 30 min after ROSC, stroke volume and cardiac output was greater in the milrinone group (although still less than pre-arrest controls). There were no inter-group differences in HR. SVR was significantly lower in the milrinone group, but without inter-group differences in MAP. By 60 min post-return to ROSC, there was no statistically significant differences between the milrinone group and the pre-arrest baseline.

Limitations of the study include the relatively short period of cardiac arrest. As well, note should be made that the study investigated the effects of initiating milrinone while performing CPR, not later after successful resuscitation.

LOE: 5
Quality: Good
Supportive


A RCT in adults with normal heart function, undergoing CPB for CABG or valve replacement, treated with 2 dosing strategies of levosimendan (L) compared to placebo prior to separation from CPB. Hemodynamics were assessed over 6 hrs post-CPB. The study was double-blinded (preparation by pharmacist, blinded anesthetist). Intraoperative and post-operative cardiopulmonary care was protocolized. Patients were randomized to receive low dose L (18 mcg/kg load and infusion of 0.2 mcg/kg/min) or high dose L (36 mcg/kg/min load and then 0.3 mcg/kg/min infusion) throughout the study. The baseline patient demographics were similar, with each group having 6 patients. There were no inter-group differences in cross-clamp
or CPB times.

The study showed that high dose L produced a greater tachycardia than low dose L or placebo (baroreceptor-related?). Both doses of L caused equivalent drops in MAP and SVR, but rises in stroke volume and cardiac output. There was no greater incidence of dysrhythmias in either L group. Oxygen delivery and consumption were both greater in the high dose L group. In summary, it was felt that L caused increased cardiac output via increases in heart rate, reduced afterload and increased stroke volume. On balance, it was felt that the low dose L produced equivalent efficacy compared to higher dosing.

Study strengths were that it was a well designed study (double blinded placebo-controlled, protocol-driven)

Study limitations include:
1. Milrinone dose chosen is higher than is used clinically in infants
2. It is unclear how long the animals (individually or the respective groups) remained on CPB after removal of the cross clamp, so it is unclear how long each of the animals had been separated from CPB at the time that the various measurements were performed (consistency within and between groups?). This has relevance as to whether all animals received the same degree of ischemic insult and are comparable.
3. The duration of study only extended to 4 hrs after the ischemic insult, not extending beyond to the nadir of post-arrest contractility. It is unclear whether the noted findings would continue through to this time, and consequently how beneficial the observed effects would be when they were needed most.
4. Relevance to post-asphyxial cardiac arrests such as occurs in most pediatric cardiac arrests?
5. There is apparently a dosing difference between some animal models (such as this one) and the doses used in human clinical practice. How applicable some of this data is (specifically dosing) directly to the human clinical area is questionable.

Funding was partially industry-based (Orion Corporation)

LOE: 5
Quality: Good
Supportive


Levosimendan is a calcium sensitizing agent. It produces potent inotropic actions by sensitizing myocardial troponin C to calcium and exerts vasodilator effects through stimulation of the adenosine triphosphate-sensitive potassium channels of systemic, pulmonary, and coronary vascular smooth muscle cells. This was an animal based RCT examining and comparing the separate influences of milrinone (M) and levosimendan (L) in a post cardiopulmonary bypass / aortic cross clamped pediatric anima l (pig) model. Animals were placed on CPB, and then underwent a 45 minute period of aortic cross-clamp. After removal of the cross clamp, animals separated from CPB. All animals (including controls) separated from CPB with Dopamine 5 mcg/ kg/ min, as well as either milrinone 2 mcg/ kg/ min (after a 100 mcg/ kg load) or levosimendan 80 mcg/ kg, followed by a 0.7 mcg/ kg/ min infusion. Both intervention groups had the drug boluses administered 120 min after removal of the cross clamp. Hemodynamics were measured for the ensuing 2 hrs.

There were no significant changes in systemic or pulmonary blood pressure during the study period, comparing either group to control. The use of milrinone prevented the post cross clamp deterioration in cardiac output seen in the control animals, but the levosimendan group actually had an increase in cardiac output above baseline during the same study period. SVR dropped and remained lower during the study period in L relative to either the milrinone or control group (with SVR I he M group actually not being significantly different than control). Systemic 02 delivery was maintained throughout the study period in both M and L while it progressively dropped in the control group, but there was no intergroup difference in myocardial 02 delivery (coronary sinus 02 was better maintained in both L and M groups). Measures of diastolic function were improved in both M and L groups relative to controls, with L being even better than M. Measures of contractility were increased in L relative to either M or control groups. Although PVR was lower immediately after loading with L (compared to M), these inter-group differences disappeared in later time points

Limitations of the study:
1. Milrinone dose chosen is higher than is used clinically in infants
2. It is unclear how long the animals (individually or the respective groups) remained on CPB after removal of the cross clamp, so it is unclear how long each of the animals had been separated from CPB at the time that the various measurements were performed (consistency within and between groups?). This has relevance as to whether all animals received the same degree of ischemic insult and are comparable.
3. The duration of study only extended to 4 hrs after the ischemic insult, not extending beyond to the nadir of post-arrest contractility. It is unclear whether the noted findings would continue through to this time, and consequently how beneficial the observed effects would be when they were needed most.
4. Relevance to post-asphyxial cardiac arrests such as occurs in most pediatric cardiac arrests?
5. There is apparently a dosing difference between some animal models (such as this one) and the doses used in human clinical practice. How applicable some of this data is (specifically dosing) directly to the human clinical area is questionable.

LOE: 5
Quality: Good
Supportive


An RCT evaluating the effects of varied doses of dobutamine on post-resuscitation systemic and regional hemodynamics in a rat model of VF-induced cardiac arrest. Interestingly, CPR was given for 30 s post-defibrillation, emulating the new resuscitation guidelines.

Main findings
1) Dobutamine (10 mcg/ kg/ min) was more effective in restoring aortic blood flow to pre-arrest levels by 30 min post-resuscitation (compared to control),
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2) superior mesenteric blood flow was maintained at pre-arrest levels throughout the study course in all groups (regardless of the use of inotropic support)
3) Lactates had returned to normal levels in the dobutamine treated animals by 120 minutes, and were sat lower than control at that time

Limitations
1) animal model
2) non-asphyxial arrest model
3) non-pediatric model

LOE: 5
Quality: Good
Supportive


A RCT in an adult pig VF-cardiac arrest model investigating the effects of varied dosages of dobutamine on post-resuscitation hemodynamics. The study objective was to identify the optimal dosage of dobutamine needed to improve hemodynamics and cardiac performance, but minimizing the increase in myocardial 02 consumption associated with increasing dose-related tachycardia. 22 pigs were instrumented after induction of anesthesia, and then had an electrically-induced VF-cardiac arrest. After a 12.5 minute period of no treatment, the animals were resuscitated by protocol, with 20 of the 22 pigs being successfully revived. Epinephrine was potentially used as part of the protocol, but it is unclear how many of the animals required it to reestablish ROSC. While the resuscitation protocol is described, it is unclear whether there were any intergroup differences when it came to amount of resuscitation necessary to reestablish ROSC. Hemodynamics were assessed by invasive monitoring pre-arrest and for a 6 hr period post-arrest, while being treated with dobutamine (randomly assigned (method not described) to 0, 2, 5, 7.5 mcg/ kg/ min); drug therapy was initiated 30 minutes after successful resuscitation.

Ejection fraction (EF) (assessed by L ventriculogram) reached its nadir by 4 hrs in control animals; this decrease was modified by the use of dobutamine, with EF reaching baseline levels by 4 hrs with 5 and 7.5 mcg/ kg/ min of drug, and actually becoming supra-baseline by 6 hrs with the use of 7.5 mcg/ kg/ min. Heart rate (HR) increases were seen with all dobutamine groups relative to control by 6 hrs, with the highest HR being achieved with 7.5 mcg/ kg/ min. Corresponding cardiac output (CO) measurements showed normalization in all dobutamine groups by 35 min post-resuscitation, but sustained normal CO at 6 hrs occurred only with 5 mcg/ kg/ min, and supra-normal CO at 6 hrs occurred only with 7.5 mcg/ kg/ min. Control animals showed an initial increase in HR post-resuscitation, but this returned to baseline by 2 hrs post-resuscitation. LVEDP remained elevated in all study groups (including control) post-resuscitation. Isovolumetric relaxation (IVR) (assessed as Tau by ventriculogram) improved and was sustained with doses of 5 and 7.5 mcg/ kg/ min, but only 7.5 mcg/ kg/ min increased the speed of IVR to faster than baseline (pre-arrest).

Myocardial 02 consumption increased with all dobutamine groups relative to control, but was significantly greater with 7.5 mcg/ kg/ min. LV stroke work reached its nadir at 4 hrs post resuscitation, and was not modified by the use of dobutamine.

This eloquent animal study demonstrated that while cardiac output and ejection fraction can be optimized with 7.5 mcg/ kg/ min of dobutamine, the price to be paid is a high myocardial 02 consumption (despite a high myocardial blood flow) and a lower coronary sinus p02 compared to lower drug doses. The metabolic price paid is such that the optimal dobutamine dose to improve hemodynamics/ contractility/ lactiotropy and minimize myocardial metabolic demand is with the use of 5 mcg/ kg/ min.

Limitations of the study include:

* the nature of the cardiac arrest (VF vs. asphyxial) for the purposes of extrapolation to the majority of pediatric cardiopulmonary arrests.
* unclear form the paper as to whether the investigators were blinded to group assignments.
* Blood gases were analyzed post-resuscitation, but it is not clear (not reported) whether there were any differences in PaC02 between groups post-resuscitation (inadvertent hyperventilation? Vent in rates were apparently not reduced post-resuscitation)
* From the study it is unclear whether there are any differences between the groups in regards inter-group resuscitation times and doses of epinephrine doses necessary to re-establish ROSC

LOE: 5
Quality: Good
Supportive


An animal model (adult pig) RCT investigating the role of propanolol (P) and levosimendan (L) in improving post-resuscitation myocardial function after VF-induced cardiac arrest. The hope was that a non-adrenergic inotrope such as levosimendan (with no associated increase in myocardial 02 consumption) would mitigate the negative inotropic effect of dobutamine (despite being shown in earlier studies to reduce post-resuscitation myocardial dysfunction). Animals were randomized by sealed envelope to one of 3 study groups 15 min pre-study. After induction of anesthesia and instrumentation, animals had baseline investigations performed and then had VF-induced electrically. After a 6 minute period of untreated VF, animals received either IV propanolol (0.1 mg/ kg) or placebo, and then at 7 minutes were resuscitated by protocol (CPR, then biphasic defibrillation at 12 minutes into the arrest). The 3 study groups were P + L, P + saline, or saline control. All animals had ROSC established. No adrenergic agents were necessary in order to reestablish circulation. Animals 10 min after successful resuscitation then received either placebo or
levosimendan (20 mcg/ kg bolus over 10 min, followed by infusion of 0.4 mcg/ kg/ min over the following 220 min. Measurements were performed over the ensuing 4 hrs. During that time, there were no significant differences in EtC02/ blood gases reported between groups, although no comment is made as to whether the minute ventilation was reduced post-resuscitation.

Baseline hemodynamics did not differ between groups. All animals were resuscitated with a single biphasic shock and no epinephrine, so apparently the resuscitation time between groups was equivalent. There were no significant differences between groups over the next 4 hrs in regards hemodynamics, PetC02, blood gases or arterial lactates. P administered during CPR facilitated resuscitation with a significantly smaller number of shocks, a significantly lesser total energies of shocks, with significantly lesser post-resuscitation premature ventricular beats (PVB) and ST-changes. There were no differences between P and P + L groups in regards these. Post-resuscitation EF (ejection fraction) and fraction of area changes by echo were greater in P relative to control, but even greater in P + L.

This was a well designed animal study. The study demonstrated benefit to the use of propanolol pre-defibrillation, but even greater benefits when coupled with the use of L after ROSC. How relevant this is when P is not a standard of care is unclear. Only limitations obvious include:

- Blinding of investigators?
- Relevance to asphyxial cardiac arrest patients (making up the majority of pediatric cardiac arrests)
- Blood gases were analyzed post-resuscitation, but it is not clear (not reported) whether there were any differences in PaC02 between groups post-resuscitation (inadvertent hyperventilation? Vent’ n rates were apparently not reduced post-resuscitation)
- study of intra-arrest agent (propanolol) and not just of post-resuscitation cardiotonic use

Funding was partially industry-based (Abbott laboratories)

LOE: 5  
Quality: Good  
Supportive


A prospective randomized controlled double-blinded study of the effects of dopamine and dobutamine on hemodynamics on and after separation from CPB. Adult dogs were placed on CPB and experienced a 20 minute normothermic period of myocardial ischemia. Before coming off CPB (after a 30 min recovery on CPB), they were started on catecholamine infusions, and their hemodynamic effects noted on and then off CPB (to a period of 60 min post separation from CPB).

Cardiac output on either catecholamine infusion was significantly greater than that of the controls, that of dobutamine coming from a significantly increased stroke volume. For equivalent dosages, dobutamine produced a greater rise in cardiac output than dopamine.

Limitations of the study to the worksheet are the animal study nature of the work. The absence of cardioprotection is something that the human cardiac literature cannot provide, and is more relevant to the post-resuscitation setting that this worksheet addresses. This study examines the hemodynamic effects after drug resuscitation for myocardial ischemia, not circulatory arrest (which would have been more relevant to the pediatric post-resuscitation setting).

LOE: 5  
Quality: Good  
Supportive


A prospective randomized controlled trial comparing the hemodynamic effects of dopamine, dobutamine or isoproterenol on adult dogs separated from CPB. Animals were exposed to a 20 min normothermic cardiac arrest on CPB. After a 30 min period of stabilization on CPB after removal of the aortic cross-clamp, the dogs separated from CPB, and 10 min later were started on a control or catecholamine infusion.

Dobutamine (10 mcg/ kg/ min) increased cardiac output and stroke volume (and decreased SVR) without changing HR, MAP or myocardial 02 consumption. Dopamine (10 mcg/ kg/ min) did not increase cardiac output/ MAP/ HR/ stroke volume, but did increase myocardial 02 consumption. Isoproterenol (0.05 mcg/ kg/ min) did show a slight inotropic effect, but at the expense of frequent ventricular tachydysrhythmias.

Limitations of the study to the worksheet are the animal study nature of the work. The absence of cardioprotection is something that the human cardiac literature cannot provide, and is more relevant to the post-resuscitation setting that this worksheet addresses. This study examines the hemodynamic effects after drug resuscitation for myocardial ischemia, not circulatory arrest (which would have been more relevant to the pediatric post-resuscitation setting).

LOE: 5  
Quality: Good  
Supportive
### Summary of Articles cited in C2005 Worksheet (highlighted articles included in C2010 worksheet as well)

<table>
<thead>
<tr>
<th>First author</th>
<th>Pub Year</th>
<th>Age</th>
<th>Species</th>
<th>Model</th>
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<th>study duration</th>
<th>drug(s) studied</th>
<th>Low CO pts included?</th>
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<td>No</td>
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<td>VF arrest</td>
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<td>Intra arrest</td>
<td>60 min</td>
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### Summary of Articles cited in C2010 Worksheet

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<th>First author</th>
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<th>Model</th>
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<td><strong>Yamada</strong></td>
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**Comments:** normothermic myocardial ischemia on CPB
<table>
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<th>Rat</th>
<th>VF cardiac arrest</th>
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<td>Pig</td>
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<td>Wang</td>
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<td>Pranolol intra-arrest and L 10 min post-ROSC</td>
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