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

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Date Submitted for review: August 28th, 2009

Clinical question.
In adult cardiac arrest (prehospital or in-hospital) (P), does an alternate timing for drug delivery (e.g. early or delayed) (I) as opposed to standard care (standard position in algorithm) (C) improve outcome (O) (e.g. ROSC, 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: new topic

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

Search strategy (including electronic databases searched).

Pubmed:

1. Heart Arrest, drug administration schedules and 5 drugs:
   Results: 857 articles

Cochrane:

1. (heart arrest OR cardiac arrest) and (drug administration schedule OR drug administration schedules) (all text)
   Results: 23 Cochrane reviews, 1 other review, 22 clinical trials

2. “heart arrest” or “cardiac arrest” AND vasoconstrictor agents and administration and dosage (title, abstract, keywords)
   Results: 6 Cochrane reviews, 23 other reviews

3. “heart arrest” or “cardiac arrest” AND vasopressin AND administration and dosage (title, abstract, or keywords)
   Results: 6 Cochrane reviews, 23 other reviews

4. “heart arrest” or “cardiac arrest” AND epinephrine AND administration and dosage (title, abstract, or keywords)
   Results: 6 Cochrane reviews, 23 other reviews

5. “heart arrest” or “cardiac arrest” AND atropine AND administration and dosage (title, abstract, or keywords)
   Results: 6 Cochrane reviews, 23 other reviews

6. “heart arrest” or “cardiac arrest” AND amiodarone AND administration and dosage (title, abstract, or keywords)
   Results: 6 Cochrane reviews, 23 other reviews

7. “heart arrest” or “cardiac arrest” AND lidocaine AND administration and dosage (title, abstract, or keywords)
   Results: 6 Cochrane reviews, 23 other reviews

8. “heart arrest” or “cardiac arrest” AND magnesium AND administration and dosage (title, abstract, or keywords)
   Results: 6 Cochrane reviews, 23 other reviews

Embase:

Heart arrest and drug administration schedule and 5 drugs:
(‘heart arrest’/syn) AND (‘lidocaine’/dd_ad OR ‘atropine’/dd_ad OR ‘adrenalin’/dd_ad OR ‘amiodarone’/dd_ad OR ‘magnesium’/dd_ad OR ‘vasoconstrictor agent’/exp/dd_ad OR ‘vasoconstrictor agents’:ti,ab OR ‘vasopressin’/dd_ad OR ‘vasopressins’:ti,ab OR ‘drug administration’/de OR ‘drug administration schedules’:ti,ab)

Results: 331

EndNote:

1. arrest + drug administration schedule (all searches are keyword OR title OR abstract) Results: 13
2. arrest + vasoconstrictor agents AND “administration & dosage” Results: 16
3. arrest + vasopressins + administration & dosage Results: 9
4. arrest + epinephrine + administration & dosage Results: 212
5. arrest + atropine + administration & dosage Results: 24
6. arrest + amiodarone + administration & dosage Results: 7
7. arrest + magnesium + administration & dosage Results: 10
8. a: epinephrine + time dependent Results: 2
b: epinephrine + delayed Results 20
c: epinephrine + interval Results 77
9. a: vasoconstrictor agents + time dependent Results 1
   b: vasoconstrictor agents + delayed Results 5
c: vasoconstrictor agents + interval Results 11
10. a: vasopressins + time dependent Results 0
    b: vasopressins + delayed Results 3
c: vasopressins + interval Results 8
11. a: atropine + time dependent Results 1
    b: atropine + delayed Results 9
c: atropine + interval Results 24
12. a: amiodarone + time dependent Results 1
    b: amiodarone + delayed Results 8
c: amiodarone + interval Results 48
13. a: magnesium + time dependent Results 0
    b: magnesium + delayed Results 8
c: magnesium + interval Results 59

- State inclusion and exclusion criteria:

Inclusion criteria: human or animal studies that addressed timing of medication dosage in cardiac arrest in any language

Exclusion criteria: review articles, case reports, articles in which data were not available regarding timing of medication administration in cardiac arrest.

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

71 abstracts reviewed for possible relevance, 15 articles selected for further review

Summary of evidence

Supporting: alternative timing is better
Neutral: alternative timing is not different
Opposing: alternative timing is worse

Evidence Supporting Clinical Question

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

*Italicics = Animal studies*

- **Kudenchuk 1999** B earlier or later  
  Paiva 2003 E, earlier amiodarone concurrent with epi  
  Van Walraven 1998 B, earlier or later

### Evidence Opposing Clinical Question

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

*Italicics = Animal studies*

- **Stiell 1995** B earlier lidocaine  
  Paiva 2003 E earlier amiodarone prior to epi  
  Ohshige 2005 A,B,C delayed
Assessment of the importance of time to administration of medications, and their relative position within the algorithm, is hampered by the lack of conclusive evidence for efficacy of any drug in human cardiac arrest. In addition, time to drug administration is rarely reported in studies of human cardiac arrest. In one meta-analysis of studies of out-of-hospital cardiac arrest, only 7% of studies reviewed reported time to administration (LOE 5: Rittenberger 2006, 201). This study also found an average time from EMS dispatch to first drug administration of 18 minutes, suggesting that medications may be given too late in resuscitation to have an effect.

No human studies have directly compared alternative timing of medications to standard position in algorithm in the 2005 AHA guidelines. However, several studies have shown that earlier timing of medication administration does improve outcome compared with delayed administration, and these have been classified as “supporting” the clinical question since they represent the preponderance of human evidence available to address the question. One large trial of adults with out-of-hospital VT or VF (LOE 5: Dorian 2002, 884) showed that earlier administration of amiodarone was beneficial, with a 13% decrease in survival for each one-minute delay. In another study of patients receiving amiodarone for out-of-hospital VT or VF (LOE 5: Kudenchuk 1999, 871), amiodarone was superior to placebo with no significant difference in effect related to time to administration. Other human studies reporting time to administration of medications have shown varying results. There was a detrimental effect of earlier administration of lidocaine in one study (LOE 4: Stiell 1995, 264), while another study found no effect of timing of administration for epinephrine, lidocaine, or atropine (LOE 5: van Walraven 1998, 544).

In animals, two meta-analyses (LOE 5: Reynolds 2007, 13 and LOE5: Rittenberger 2007, 154) of heterogenous animal studies of different medications in cardiac arrest have shown that time to drug administration predicted ROSC. One animal study (LOE 5: Wenzel 1999, 1379) showed higher coronary perfusion pressure with earlier administration of both epinephrine and vasopressin. A few animal studies have used alternate timing of drug delivery compared with standard position in algorithm. Several studies (LOE 5: Niemann 1992, 281; LOE 5: Menegazzi 1993, 235; LOE 5: Menegazzi 2000, 31; LOE 5: Menegazzi 2003, 261) have shown benefit with medication administration and circulation prior to countershock in animal models of ventricular fibrillation. A study comparing continuous epinephrine infusion during resuscitation with intermittent dosing of epinephrine in animals with VF (LOE 5: Johansson 2003, 299) showed improved cortical cerebral blood flow, although no difference in ROSC. A study using alternate timing of amiodarone administration in animals with VF showed worse aortic systolic, diastolic, and coronary perfusion pressures when amiodarone was given prior to epinephrine but equivalent pressures when amiodarone was given during or after epinephrine (LOE 5: Paiva 2003, 203), however the study did not address outcome.

**Acknowledgements:**
We would like to acknowledge Blair Anton, medical librarian from the Johns Hopkins University School of Medicine, for her invaluable assistance with our search of the medical literature.
## Citation List

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**Notes:**
The original study design was a randomized controlled trial of amiodarone vs. lidocaine for patients suffering an out of hospital cardiopulmonary ventricular fibrillation arrest. In addition to the primary analysis, multivariate logistic regression analysis was performed to identify variables associated with survival to hospital admission. “Among patients whose initial rhythm was ventricular fibrillation, the interval from the first shock to the administration of the drug was a significant predictor of survival (odds ratio for survival for each minute of delay 0.87; 95% confidence interval, 0.80 to 0.96, p = 0.003).” In summary, for patients in ventricular fibrillation who have already four shocks and a dose of epinephrine, there was a 13% decrease in survival for each one-minute delay in administration of amiodarone. Amiodarone was given within the sequence of the current algorithm for ventricular fibrillation, but with a median time of administration of 24 minutes from dispatch of the Emergency Medical Services crew. The finding that earlier administration of amiodarone is beneficial is supporting to the clinical question.

**LOE: 5, Quality = Good.**
This study was a large randomized controlled trial in humans, however the timing of the drug administration was not the subject of randomization.


**Notes:** Randomized trial of 24 pigs given VF for 5 minutes, then CPR started and randomized to bolus epinephrine (20 mcg/kg) every 3 minutes or a bolus followed by continuous infusion of epinephrine at 10 mcg/kg/min along with continued CPR. After 9 minutes of CPR defibrillation was attempted.

The authors found no difference in ROSC, jugular bulb oxygen saturation, coronary perfusion pressure, or oxidative injury marker 8-iso-PGF(2alpha) levels between the two groups. The authors did report a significantly increased cortical cerebral blood flow (E= other endpoint, cortical cerebral blood flow) by Laser-Doppler flowmetry in the continuous infusion group compared with the bolus epinephrine group, a result supporting the clinical question. The significance of this is unclear, however, as subsequent neurologic outcome was not reported. In addition, despite randomization the intervention (continuous infusion) group had a mean cortical cerebral blood flow closer to normal prior to administration of epinephrine (approximately 50% of normal in the infusion group as opposed to just below 40% of normal in the bolus group). While the authors adjusted for this by covariance analysis, it still calls into question whether randomization truly produced comparable groups at baseline.
in this study.

**LOE: 5**  
This is a randomized controlled animal study, **LOE=5** and **Quality=Good.**

|---|---|
| **Notes:** | Amiodarone or placebo were delivered to out of hospital patients who had developed ventricular fibrillation or pulseless ventricular tachycardia, after the patients had received three or more shocks, were intubated and had received 1 mg of epinephrine. In addition to the primary analysis, patients were stratified into quartiles of time; i.e. the time interval from dispatch to administration of amiodarone or placebo, to investigate whether there was significant interaction between the effect of amiodarone and the time at which it was administered, on the rate of admission to the hospital. “For all lengths of time to treatment, whether the interval was analyzed as a continuous variable or according to quartiles, amiodarone recipients were more likely to survive to be admitted to the hospital than those who received placebo (p = 0.008 by the Mantel-Haenszel chi-square test.”) This suggests that amidodarone is effective early or late in the course of a VF or PVT arrest in patients who have already received epinephrine. However, they did not perform logistic regression analysis to determine whether patients were more likely to survive if the amiodarone was administered earlier rather than later. Although there was a trend towards improved survival with early administration of amiodarone, this was not statistically significant and is therefore neutral to the clinical question as to whether earlier or later administration would affect outcome. **LOE: 5, Quality = Good**  
This study was a randomized controlled trial, however the timing of the drug administration was not the subject of randomization. |

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<td><strong>Notes:</strong></td>
<td>Randomized trial in swine model. After 8 minutes of VF, swine received either “standard” algorithm with up to three shocks prior to CPR and medications being given, or an experimental algorithm with high-dose epinephrine, lidocaine, bretylium, propranolol, and hyperventilation along with 1 minute of CPR to circulate the drugs. Animals in the experimental group had a trend towards improvement in ROSC (p=.057) and an improvement in survival to 1 hour in the experimental group (p=.041), a result supporting the clinical question. However, it is unclear which of the many interventions, medication, CPR, or hyperventilation prior to shock, was truly beneficial. <strong>LOE=5, Quality = Good.</strong> Randomized trial in animals.</td>
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Notes: Randomized trial in swine model of VF. After 8 minutes of VF and 1 minute of CPR, Swine were randomized into 7 groups: 1: epi, lidocaine, bretylium, propranolol, U74389G 2: epi 3: lidocaine, bretylium 4: propranolol 5: U74389G 6: normal saline 7: standard ACLS. Groups 1-6 got an additional 2 minutes of CPR prior to countershock to circulate the drugs. The authors found that group 1 (multidrug regimen prior to countershock) had improved ROSC and survival to 1 hour compared with standard ACLS. However, group 1 (multidrug regimen) was no different in outcome from group 2 (epi alone prior to countershock). CPR and medications appear to be beneficial prior to defibrillation in this model, supporting the clinical question.  
**LOE=5, Quality=Good.** Randomized trial in animals. |
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Notes: Randomized trial in swine model of VF. Swine given VF for either 8 or 11 minutes, followed by shock, 3 minutes of CPR then shock, or epinephrine with 3 minutes of CPR then shock. A final group got VF for 14 minutes then shock. The authors found that first-shock ROSC was improved with epinephrine and 3 minutes of CPR compared with immediate countershock after 8 minutes of VF, supporting the clinical question. Earlier interventions also were more beneficial than later interventions, however it was still not clear whether CPR, epinephrine, or both were responsible.  
**LOE=5, Quality = Good.** Randomized trial in animals. |
Notes: 28 dogs were given ventricular fibrillation (VF) for 7.5 minutes, then randomized to either “standard” care of an immediate defibrillation attempt (with subsequent 1-2 shocks if VF persisted or CPR and epinephrine per “standard” algorithm), or the “intervention” group where high-dose epinephrine (0.08 mg/kg of 1:10,000 solution) was given intravenously and CPR was given for 5 minutes prior to defibrillation attempt. The results show a statistically significant increase in ROSC (ROSC=A defined as arterial pulse pressure >50 x 30 mins) when the dogs with VF received epinephrine and 5 minutes of CPR prior to defibrillation attempt (9/14 with ROSC in intervention group vs. 3/14 in “standard” group, p=.014). The findings that epinephrine and CPR prior to defibrillation is beneficial in VF arrest are supporting the clinical question. However, these findings are not quite clinically relevant for several reasons, including the animal population used, the “standard” protocol did not include CPR in between defibrillation attempts, and the “intervention” protocol included both... |
high-dose epinephrine and prolonged (5 mins) CPR. It seems likely that a prolonged (7.5 min) period of VF prior to defibrillation attempt may make this approach more beneficial by restoring some coronary blood flow prior to defibrillation; what cutoff might be appropriate is not clear.

**LOE: 5**  
This is a randomized controlled trial in animals, so **LOE=5** and **Quality=Good**.

Notes: A comparison of two EMS systems, one in which physicians were members of an on-scene response team and could administer epinephrine, lidocaine, and/or atropine in addition to standard care and another “standard” system where ambulance personnel could administer epinephrine, defibrillate, and perform IV placement and tracheal intubation. The “experimental” group with the physician-manned crews had improved ROSC and survival to 1 month, opposing the clinical question since delayed administration was associated with worse outcomes. However, it is difficult to separate out the effect of earlier medication administration from other factors which may have been present (such as improved BLS or ACLS measures). **LOE=2**, prospective but non-randomized human trial. **Quality=poor** for the purposes of this worksheet because time to medication administration was not reported, and there were likely many other confounders affecting outcome. |
**Notes:** VF was induced in 30 dogs for 8 minutes each. All dogs then received a defibrillation attempt with CPR and O2. Those still in VF/VT were randomized (10 in each group) to amiodarone (5 mg/kg), epinephrine (.02 mg/kg), or combination amiodarone and epinephrine followed by CPR.  
Amiodarone alone resulted in lower aortic systolic and diastolic pressures, RA systolic pressures, and coronary perfusion pressure (**E=other endpoint**) at 1 and 2 minutes after administration when given prior to epinephrine, a result **opposing** the clinical question because alternate timing was harmful. Amiodarone given concurrently with epinephrine produced equivalent pressures to when epinephrine was given first, a result **neutral** to the clinical question because alternate timing produced no change in the outcomes measured. This result may be worthy of further investigation, however, because concurrent amiodarone and epinephrine administration could simplify the algorithm for management of VF/VT and thus improve ease of use of the algorithm and documentation. **LOE: 5**  
This was a randomized controlled trial in animals, so **LOE=5** and **Quality=Good**. |
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Notes: The authors took 119 prospective animal studies that reported time to medication administration (any medication; most were epinephrine, but some were vasopressin, magnesium, bicarbonate, norepinephrine, endothelin, and others). They did a meta-analysis on those studies and found that time to drug administration predicted ROSC. They also found that the average time to drug administration in the animal studies was 9.5 minutes, which was significantly different from a mean of 19.4 minutes in humans as previously reported by the authors.  
LOE: 5  
Each study in the meta-analysis is a prospective animal study, LOE 5. A=ROSC. The studies had concurrent controls but often were often not randomized around time to administration, therefore Quality = Fair. The results are supporting to the clinical question because they suggest that earlier timing may be beneficial. |
Notes: Meta-analysis of time to first drug delivery in more than 7000 out-of-hospital cardiac arrests. The authors found that only 7% of human studies report time to drug delivery, and the mean time is around 18 minutes. They conclude that analyzing drug effects in human cardiac arrest may be difficult when it is rarely reported, and the drugs are usually given quite late. This is not a report on outcome related to drug delivery time and therefore the results are neutral to the clinical question, however they are included because the findings underscore why analysis of this question is so difficult.  
LOE=5, Quality= Fair. Meta-analysis of several studies, many retrospective with variable quality of reporting. |
Notes: Retrospective analysis of swine resuscitation attempts from many different study protocols. ROSC logarithmically decreased with time to first shock, CPR, or medication, a result that is supporting the clinical question because earlier medication delivery improved outcome.  
LOE=5, Quality= Fair. Retrospective analysis of heterogenous animal studies. |
Notes: The authors took a cohort of adult patients who had previously been enrolled in a randomized trial to evaluate high-dose epinephrine in cardiac arrest. They were able to evaluate 529 patients (out of an original 650 in the high-dose epinephrine study) who had sufficient information about time to medication administration and met other criteria.  
Epinephrine was part of the study protocol, therefore time to administration did not vary significantly. Interestingly, among those who received lidocaine, later administration was significantly associated with resuscitation and survival to 1 hour (5.6 minute mean time of administration for survivors vs 3.6 minutes in non-survivors). In the current algorithm for pulseless VF/VT, a patient in cardiac arrest should receive a defibrillation attempt within 3 minutes, followed by 2 rounds of CPR of 2 minutes each, with epinephrine after the 2nd defibrillation. Only then, after 4-7 minutes of resuscitation, would a patient receive lidocaine after the subsequent defibrillation attempt. Therefore the group in this study that got lidocaine at a mean time of 3.6 minutes is earlier than our current standard, while 5.6 minutes is within our current standard. Since earlier administration decreased the likelihood of ROSC, these results are opposing the clinical question regarding lidocaine (B= survival of event).  
LOE: 4  
This study was a large randomized controlled trial in humans, however the timing of the drug administration was not the subject of randomization.  
Quality = Good. |
Notes: The authors used data from the OTAC study (Ontario Trial of Active Compression-Decompression Cardiopulmonary
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| **Resuscitation**, a multicenter randomized controlled trial in which patients with cardiac arrest were randomized to have active compression-decompression (ACD) or standard CPR. They examined 773 arrests out of the 1,032 from the original study, including only arrests that occurred in-hospital (after arrival to the ED), and investigated whether timing of medication administration affected survival to 1 hour (*B* = survival of event).

Administration of most drugs in this study (epinephrine, atropine, bicarbonate, calcium, lidocaine) was associated with a statistically significant decrease in survival to 1 hour, regardless of timing. For epinephrine, there was a non statistically-significant trend towards worse outcome with earlier administration (mean time 5.14 min in survivors vs. 4.42 min in non-survivors, *p*=.19), and for atropine and lidocaine timing of administration did not appear to have an effect, a result neutral to the clinical question.

**LOE: 5**
This study was a large randomized controlled trial in humans, however the timing of the drug administration was not the subject of randomization.
**Quality = Good.**

**Wenzel 1999**

24 pigs were given VF for 4 minutes. At that time, they were randomized to receive either 3 minutes of CPR (12 pigs) or 8 minutes of CPR (12 pigs). They were further randomized within each group to receive either epinephrine (6 pigs in each group) or vasopressin (6 pigs in each group) after the respective interval of CPR.

Animals given vasopressin had higher coronary perfusion pressure in both the “early” and “late” groups, for each dose, however it was statistically significant only from the 2nd dose on. Vasopressin was significantly more likely to produce ROSC compared with epinephrine (ROSC in 12/12 vasopressin animals vs. 0/12 epinephrine animals), but timing of administration did not affect ROSC. Furthermore, epinephrine did not produce coronary perfusion pressures above the threshold 20-30 mm Hg needed for successful resuscitation except with the first dose in each group; the epinephrine effect was also markedly attenuated in the “late” vs. “early” group. Since early administration produced better coronary perfusion pressures than late in both groups, these results are supporting the clinical question. (*E* = other endpoint).

**LOE: 5**
This is a randomized controlled trial in animals, so **LOE=5, Quality = Good.**
References


