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

**Worksheet author(s)**

| Dine, Jessica | Date Submitted for review: |

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**Clinical question.**

"In adult cardiac arrest (prehospital or in-hospital) (P) due to pulmonary embolus (P), does use of etiology specific interventions (I) as opposed to standard care (according to treatment algorithm) (C), improve outcome (O) (eg. 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

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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).**

PubMed “heart arrest” or “cardiopulmonary resuscitation” or “cardiac arrest” or “PEA” as MESH (headings) AND “Pulmonary embolism” or “thrombolytics” or “heparin” or “thrombectomy” textword in abstract.

OVID search using text words (all fields) pulmonary embolism or thrombolytics or heparin or thrombectomy AND (cardiac arrest OR resuscitation) AHA EndNote Master library, Cochrane database for systematic reviews, Central Register of Controlled Trials, Review of references from articles.

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**State inclusion and exclusion criteria**

The following studies were excluded: Not true cardiac arrest models (eg. exsanguinations, great vessel occlusion, carotid artery occlusion), pre-arrest or during arrest cooling, resuscitation with cardiopulmonary bypass instead of CPR, reports of single cases, where pulmonary embolism was not suspected as the etiology.

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

19 studies met criteria for further review. Of these 3 were LOE 1 (RCTs), two LOE 2 (post-hoc analysis and meta-analysis), five LOE 3 (retrospective controls), nine LOE 4 (no controls), and no LOE 5 (not directly related; all animal studies).

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**Summary of evidence**

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**Evidence Supporting Clinical Question**

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<th>Good</th>
<th>Fair</th>
<th>Poor</th>
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<td>Lederer, 2004 D</td>
<td>Janata, 2003 ACE</td>
<td>Fava, 2005 BE</td>
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<td>Stadlbauer, 2006 CE</td>
<td>Kurckiyan, 2000 AB</td>
<td>Zahorec, 2002 BCD</td>
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**Level of evidence**

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

| Fair |  |  | Kurkciyan, 2003 |  |  |
| Poor |  |  |  |  |  |

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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

Evidence Opposing Clinical Question

| Good |  |  |  |  |  |
| Fair |  |  |  |  |  |
| Poor |  |  | Doerge, 1996 BE | Clarke, 1986 B | Ullman, 1999 B | Dauphine, 2005 B |

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Level of evidence

A = Return of spontaneous circulation  C = Survival to hospital discharge  E = Other endpoint
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Italics = Animal studies

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

Possible treatments of a massive pulmonary embolism include fibrinolytics, surgical embolectomy and percutaneous mechanical thrombectomy. These should be considered separately.

Fibrinolytics
Studies suggest that patients who received thrombolytics for a suspected pulmonary embolism but had suffered a myocardial infarction instead was not increased. Both studies with cohorts of patients including only pulmonary embolism diagnoses and including diagnoses of either myocardial infarction and pulmonary embolism were included. Studies investigating the effects of thrombolytics in patients with suspected myocardial infarction were not included in this analysis.

Three prospective trials (LOE1) investigating the use of thrombolytics during cardiac arrest from a massive pulmonary embolism:

1. In a double-blind randomized control trial performed by Abu-Laden et al. patients with more than one minute of pulseless electrical activity that was unresponsive to initial therapy outside the hospital or in the emergency department were eligible either received tissue plasminogen (117 patients) or placebo (116 patients). Patients were randomly assigned to receive 100 mg of t-PA or placebo intravenously over a 15-minute period in a double-blind fashion. Standard resuscitation was then continued for at least 15 minutes. The primary outcome was survival to hospital discharge. There was no in their primary outcome of survival to discharge nor in return to spontaneous circulation or major hemorrhage.

2. Fatovich et al. performed a pilot study investigating thrombolytics during cardiac arrest. This was a prospective, randomized, double blind placebo controlled trial. All victims of out-of-hospital cardiac arrests brought to the emergency department received standard advanced cardiac life support, except that the first drug the patient received was either tenecteplase 50 mg or placebo. Of the 35 patients enrolled, 19 received tenecteplase and 16 placebo. Return of spontaneous circulation occurred in 42% patients receiving tenecteplase and 6% placebo (36% difference, 95% CI 11-61%). Two
tenecteplase and one placebo patient survived to leave the emergency department, and one in each group survived to hospital discharge.

3. The Thrombolysis in Cardiac Arrest (TROICA) trial was published in the NEJM in 2008. The study design was previously published by Spöhr et al. In this study, 1050 patients with a witnessed cardiac arrest were randomized to receiving thrombolytic tenecteplase or placebo during cardiopulmonary resuscitation. The results of the study showed no difference in any of the end points, which included 30-day survival, hospital admission, return to spontaneous circulation, 24-hour survival, survival to day 30 or hospital discharge, symptomatic intracranial hemorrhage or major bleeds.

| One meta-analysis (LOE2) by Li et al. included eight retrospective cohort studies. However, of the 8 studies included, only 1 study (Karcciyian, 2000) discussed the outcomes of cardiac arrests following pulmonary embolism rather than myocardial injury. This meta-analysis showed that thrombolytic agents significantly improved the rate of return of spontaneous circulation, 24 hour survival rate, survival to discharge and long-term neurological function in patients treated with CPR. However, the patients receiving thrombolyis had a risk of severe bleeding. |
| Several studies - either retrospective controls (LOE3) or case series (LOE4) - showed either an improvement or no detriment in primary endpoints (usually return of spontaneous circulation) with the use of thrombolytics during cardiac arrest. Although bleeding events were increased in some of these series with the use of thrombolytics, most concluded that the potential benefit outweighed the risk of fibrinolytics. |

**Summary**

- The randomized controlled trials attempting to answer the question of whether fibrinolytic therapy for cardiac arrest secondary to pulmonary embolism showed no improvement in any of the endpoints examined.
- Other prospective and post-hoc analysis showed an improvement in return of spontaneous circulation although there was no effect on survival to hospital discharge (except for trend in improvement found by Stadlbauer et al.).
- Studies using retrospective controls and case series support the potential improvement in return of spontaneous circulation.
- The risk of bleeding was shown to be higher in some case series.

**Surgical embolectomy**

Only case series (LOE4) were available to review the treatment of surgical embolectomy for patients suffering cardiac arrest due to massive pulmonary embolism. Most of the series suggested increased mortality in patients who required cardiopulmonary resuscitation preoperatively compared to those that did not. Most of these studies were published in the 1990’s. The most recent, however, published in 2007 (Konstantinov et al.) reported a 30-day mortality rate of 28.5% in seven patients receiving surgical embolectomy and one treated with thrombolytics.

**Summary**

- Mortality of surgical embolectomy for massive pulmonary embolism is increased if the patient suffered preoperatively cardiac arrest.
- Although one recent study published a more favorable mortality rate, the evidence does not support the treatment of cardiac arrest patients with surgical embolectomy at this time.

**Percutaneous mechanical thrombectomy**

Only one case series (LOE4) investigated the effects of percutaneous mechanical thrombectomy for seven patients suffering cardiac arrest secondary to a massive pulmonary embolism. Three of the patients also received recombinant tissue plasminogen activator. Thrombectomy was successful in restoring pulmonary perfusion in six of the patients (85.7%), while one died of cardiac arrest.

**Summary**

- Cardiac arrest from a massive pulmonary embolism may be treated with percutaneous mechanical thrombectomy during cardiopulmonary resuscitation and might be considered if patients are not candidates for fibrinolytics.
- Further investigations are needed before it is possible to recommend percutaneous mechanical thrombectomy in addition to or instead of fibrinolytics.

**Acknowledgements:**
Citation List

Abu-Laban RB, Christenson JM, Innes GD et al. Tissue Plasminogen Activator in Cardiac Arrest with Pulseless Electrical Activity. NEJM 2002;346:1522-1528. (LOE1, good quality, neutral results)

Brief Summary: In this double-bind randomized controlled trial, 233 patients were randomized to receive tissue plasminogen activator after more than one minute of pulseless electrical activity that was unresponsive to initial therapy outside the hospital or in the emergency department. There was no difference in the main outcome of survival to discharge.


Brief Summary: This trial funded by Boehringer Ingelheim showed no difference in 30-dat survival, hospital admission, return to spontaneous circulation, 24-hour survival, survival to day 30 or hospital discharge or bleeding in patients randomized to receive thrombolytic tenecteplase or placebo during cardiopulmonary resuscitation.


Brief Summary: This small prospective study showed that the 40 out of 90 patients receiving tissue-type plasminogen activator and heparin during cardiopulmonary resuscitation had higher rates of return to spontaneous circulation and admission to the intensive care unit. Survival to 24 hours or to hospital discharge were not significantly different.

Interpretation: After initially unsuccessful out-of-hospital CPR, thrombolytic therapy combined with heparin is safe and might improve patient outcome. On the basis of our data a randomized controlled trial might be regarded as ethical.


Brief Summary: In this retrospective review of 55 patients who had undergone emergent pulmonary embolectomy, 19 patients had an episode of cardiac arrest. 14 of these patients died during or following the operation. On the other hand, in the 36 patients who did not have a cardiac arrest, 97.2% survived the operation. The authors conclude the preoperative cardiac arrest is associated with a high mortality rate of pulmonary embolectomy.


Brief Summary: This study is a retrospective chart review of 11 patients who had underwent early pulmonary embolectomy following a pulmonary embolism. The 3 patients who had died all had suffered a cardiac arrest prior to the surgery. One patient did survive the surgery after suffering a preoperative cardiac arrest. The authors conclude the preoperative cardiac arrest is associated with a high mortality rate of pulmonary embolectomy.

**Brief Summary:** In this retrospective study, the outcomes of 36 patients who had undergone pulmonary embolectomy were reviewed. Fourteen of these patients had suffered a cardiopulmonary arrest prior to the operation. 57.1% of 8 of these patients died while only 1 of the 22 patients without a preoperative cardiopulmonary arrest died.


**Brief Summary:** This prospective, randomized pilot study showed that the 19 our of 35 enrolled patients receiving tenecteplase had a significant improvement in return to spontaneous circulation but not survival to hospital discharge. The study did receive some funding from Laerdal Foundation for Acute Medicine and received medications at a discounted price from Boehringer-Ingelheim.


**Brief Summary:** Seven patients who had suffered a cardiac arrest secondary to a pulmonary embolism were treated with percutaneous mechanical thrombectomy. Three patients also received recombinant tissue plasminogen activator. One of the seven patients died and pulmonary perfusion was restored in the majority (85.7%). The authors conclude that this preliminary evidence warrants larger studies to investigate the utility of percutaneous mechanical thrombectomy during cardiac arrest by pulmonary embolism.


**Brief Summary:** This retrospective cohort study compared the outcomes of 36 patients that received thrombolytics to the outcomes of 30 patients who did not. Although bleeding complications were more common in the thrombolytics group, there was an improvement in survival after 24 hours. The group also found statistically statistically nonsignificant improvements in return to spontaneous circulation with a p-value of 0.06 and to survival of discharge with a p-value of 0.15.


**Brief Summary:** This retrospective case series reviews 8 patients suffering a cardiac arrest following a pulmonary embolism. One patient survived thrombolytics while the other seven underwent embolectomy. Two of these 7 patients died during the operation while one died several months later due to long-term surgical complications. The authors report an interoperative death rate of 28.6% (2/7). When compared to a mortality rate of more than 30% of patients suffering a cardiac arrest after a pulmonary embolism, the authors conclude that there is an improved survival by intervention with pulmonary embolectomy after suffering a cardiac arrest from pulmonary embolism.

**Brief Summary:** This is a retrospective study, the authors collected information on the clinical presentation, therapy and outcomes of patients who suffered a cardiac arrest believed to be secondary to pulmonary embolism. 21 patients had received thrombolytic therapy. The rate of return to spontaneous circulation was higher in this group when compared to the 21 patients who had not received thrombolytic therapy. The survival to discharge was not different between the two groups.


**Brief summary:** The odds ratio for the risk of bleeding with thrombolytics was found to be 2.5 (95% confidence interval 0.9 – 7.4) in this retrospective cohort study comparing 132 patients who had received thrombolytics to 133 patients who had not.


**Brief Summary:** The authors identified 108 patients who had received recombinant tissue plasminogen activator during cardiopulmonary resuscitation and 216 controls in this retrospective chart review. 19 of these patients had suffered a pulmonary embolism. There was a favorable rate of spontaneous circulation (70.4 versus 51% with a p-value of 0.001) and survival at 24 hours (48.1 versus 32.9% with a p-value of 0.003) but no difference in survival to discharge. For those 19 patients who were thought to have suffered a pulmonary embolism, 57.9% survived the first 24 hours and 31.6% to discharge. No direct comparison was made for the 19 patients with pulmonary embolism.


**Brief Summary:** This retrospective analysis reviewed the long-term outcomes of patients who had survived an out-of-hospital cardiac arrest and received recombinant tissue plasminogen activator. Of these 27 survivors, 22 were discharged without any neurological deficits. Most of the long-term survivors (18 patients were still alive at 5 to 10 years after the event) reported a good subjective quality of life.


**Brief Summary:** This analysis included eight retrospective cohort studies of which two studies looked at pulmonary embolism, four at myocardial infarctions, one at cardiologic diseases and one at non-traumatic etiologies as the underlying cause of the cardiac arrest. Thrombolytics did show improvement in rate of return to spontaneous circulation, survival to discharge and long-term neurologic function but also increased the risk of severe bleeding.

**Brief Summary:** In this retrospective review, the authors studied the outcomes of patients who underwent pulmonary embolectomy. Five patients underwent the procedure after return of spontaneous circulation, 11 during cardiopulmonary resuscitation and 11 who had not required resuscitation. The mortality rates for these three groups were 60%, 45% and 36% respectively. Only one patient suffered significant ischemic brain injury. The authors conclude that pulmonary embolectomy may improve mortality of a cardiac arrest secondary to a pulmonary embolism.


**Brief Summary:** This study presents the results of a post-hoc analysis of a randomized controlled trial of epinephrine versus vasopressin during cardiac resuscitation. The post-hoc analysis compared 99 patients receiving thrombolytics to 1,087 who did not and found that those who received thrombolytics had increased hospital admission rate but similar discharge rates.


**Brief Summary:** The mortality rate of 40 patients undergoing pulmonary embolectomy was 35% in the retrospective review. The authors performed regressions to identified risk factors for increased mortality. The most significant risk factor were the need for cardiopulmonary resuscitation (mortality rate of 63% if CPR was required versus 10% if it was not) and preoperative hemodynamic instability.


**Brief Summary:** This case series discussed three cases of successful thrombolysis during a cardiopulmonary resuscitation in the hospital. Two patients received streptase while one who had suffered a pulmonary embolism received heparin. All three patients survived the event but one (who had received streptase for a cardiac arrest secondary to a myocardial infarction) died during hospitalization. The two survivors were discharged with good neurological function.