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

Worksheet author(s)

MD, PhD Markus Skrifvars

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Fifth revision May 21\textsuperscript{st}, 2009
Sixth revision October 1\textsuperscript{st} 2009

Clinical question

In adult patients with ROSC after cardiac arrest (prehospital or in-hospital) (P) diagnosed as pulmonary embolism, does the use of early fibrinolytic therapy (I) as opposed to standard care (C), improve outcome (O) (e.g. 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: Worksheets (Abu-Labban 2005, Bottiger 2005 Ornato 2005) are available on the use of thrombolytics during cardiopulmonary resuscitation not responding to conventional treatment. However, there are no worksheets on administration of thrombolysis after return of spontaneous circulation (ROSC) in patients with pulmonary embolism as the assumed cause of the arrst.

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).

Searched databases: AHA Endnote 7 Master Library, PubMed, Cochrane Database for Systematic Reviews

Searches with the following keywords:

1. cardiac arrest/heart arrest/out-of-hospital cardiac arrest/in-hospital cardiac arrest/CPR/cardiopulmonary resuscitation/resuscitation, pulseless electrical activity

\textbf{AND}

2. pulmonary embolism (PE)/embolus

\textbf{AND}

3. thrombolysis/fibrinolysis/thrombolytic treatment/post-resuscitation care

Manual searches of relevant references of Task Force Reports and reviews on diagnosis and management of PE. It is evident that there will be an abundance of relevant studies therefore studies and trials on PE with severe hemodynamic compromise will be reviewed to see whether they have included patients that have undergone resuscitation from a cardiac arrest and whether they have received thrombolysis. In addition some cardiac arrest patients may receive thrombolysis after ROSC without a specific diagnosis, i.e. myocardial infarction, pulmonary embolism and these will be reviewed as well to see whether they have included patients that might have had PE.

- State inclusion and exclusion criteria:

Included studies
1. Studies reporting the use of thrombolysis after established ROSC in cardiac arrest with a suspected and/or assumed PE as the cause.
2. Studies reporting thrombolysis during postresuscitation management of cardiac arrest patients not assumed to be due a myocardial infarction.
3. Studies reporting the use of thrombolysis in patients with suspected or confirmed PE and a severe hemodynamic instability

Excluded studies

1. Animal studies
2. Pediatric studies
3. Studies were thrombolysis was administered during CPR
4. Studies were thrombolysis was administered to patients with PE but with stable hemodynamics
5. Studies were thrombolysis was administered after ROSC but the cause was assumed to be myocardial infarction

Number of articles/sources meeting criteria for further review:

Searches were performed between July and August 2008.

Search of the endnote database did not yield any articles.

Search of PubMed yielded 12 articles of which 4 studies were included


Search of the Cochrane Database for Systematic Reviews yielded a review for “Thrombolytic therapy for pulmonary embolism” by authors Dong B et al. 2006. The review did not cover patients who have undergone CPR and included only one study on the use of thrombolytic therapy in hemodynamically unstable patients and this study was included.


Hand search of the following references in relevant reviews on guidelines PE management and postresuscitation care:


In all these the only references that might include including hemodynamically unstable PE patients or the use of thrombolysis as a part of postresuscitation care management were the cause of the arrest was assumed to be PE were:


Review of accepted abstracts for the European Society of Intensive Care Medicine’s congress held in Lisbon, Portugal in September 2008 revealed an abstract on a single center’s experience on the treatment of severe PE.


However since this study has only been published as a meeting abstract and it has not been published up until September 30th, 2009 it was decided not to include it.
Therefore all in all 9 studies were found and included in the present review.
### Summary of evidence

#### Evidence Supporting Clinical Question

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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  
*Italicics = Animal studies*

#### Evidence Neutral to Clinical question

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#### Evidence Opposing Clinical Question

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Pulmonary embolism is a common medical disorder that if untreated is associated with a mortality ranging between 15% to 35% (Goldhaber et al. Lancet 1999). A massive embolism results in hypoxaemia and failure of the right ventricle leading to hypotension and a combination of a circulatory and respiratory shock (Wood KE et al. Chest 2002). According data from a German registry about 11% of the patients with a massive pulmonary embolism experience a cardiac arrest necessitating CPR (Kasper et al. J Am Coll Card 1997).

If a patient with PE experience cardiac arrest the initial rhythm of the arrest seems mostly to be either pulseless electrical activity (PEA) or asystole but cases of ventricular fibrillation have also been reported (Comess, 2000, 351). On the other hand, in a cohort of patients with out-of-hospital cardiac arrest and PEA as the initial rhythm, 25% of the unsuccessful arrests were shown to be caused by PE (Virkkunen et al. Resuscitation 2008). The corresponding figure in in-hospital cardiac arrests seems to be about 35% (Comess, 2000, 351). The survival to hospital discharge rates of patients resuscitated from PEA with ROSC are around 21% in in-hospital cardiac arrests (Nadkarni et al. JAMA 2006) and around 16% in out-of-hospital cardiac arrest (Engdahl et al. Resuscitation 2001). The survival rates of patients with ROSC following PEA cardiac arrest and a diagnosis of PE ranges between 9% (Kürkciyan, 2000, 1529) and 25% (Comess, 2000, 351). The diagnosis of PE following a cardiac arrest seems to be possible using either transthoracic or transesophageal echocardiography based on two LOE5 studies (Kürkciyan, 2000, 1529, Comess, 2000, 351)

Mortality in PE is highly dependent on the severity of the haemodynamic compromise, and has been reported to be between 50% and 75% in patients requiring CPR (Kasper et al. J Am Coll Card 1997, Comess et al. Am J Med 2000). Most Guidelines on management of PE recommend thrombolysis as the treatment of choice in patients with PE and unstable hemodynamics (European Society of Cardiology Task Force Report 2000, British Thoracic Society guidelines 2003, The Seventh ACCP Conference on Antithrombotic and Thrombolytic therapy 2004) but there is in fact little data supporting this recommendation. Most Guidelines quote a randomized controlled trial involving only eight patients as the supporting evidence (Jerjes-Sanchez, 1995, 227). This trial, on the other hand, has been criticized because of differences between groups and the fact that the diagnosis of PE was based on clinical suspicion only. The recent Cochrane Review (Dong, 2006, Issue 2) decided not to include this study based on these methodological problems. The two meta-analysis on the use of thrombolysis in PE included in this worksheet (Wan, 2004, 744 Thabut, 2002, 1660), came to slightly different conclusions regarding the use of thrombolysis in patients with PE and shock (the meta-analysis supporting included a study by Dotter et al. Vasc Surg 1979). In addition patients with shock have a higher risk of major haemorrhage (Wan, 2004, 744 Thabut, 2002, 1660). The risk of bleeding with the use of thrombolysis in patients having undergone CPR might be increased based on a LOE5 study (Janata K, 2003, 49).

The purpose of the present worksheet was to review the evidence on the use thrombolysis as opposed to standard treatment (no treatment or heparin only) in patients with return of spontaneous circulation and resuscitated with PE as the presumed cause. There was a paucity of studies on this topic. Because of this the worksheet included studies in which thrombolysis was administered to PE patients with severe hemodynamic instability if they were found to include cases with a CA. In addition it was decided to studies on cardiac arrest patients that received thrombolysis during immediate postresuscitation care if it was not evident that the reason for thrombolysis was a myocardial infarction.
Alphabetical citation list with worksheet author’s comments

Institution: Mission Hospital, Mission Viejo, California, USA
Conflict of interest: The authors have declared that they have no financial conflicts of interest

Worksheet author’s comments: A case report describing a patient with a massive pulmonary embolism resulting in cardiac arrest. Due to an assumed PE the patient was given tissue plasminogen activator (tPA) systemically but this did not improve the patient’s haemodynamics and therefore a pulmonary angiography was performed. This revealed multiple lung emboli that were treated with pulse sprays of tPA. Thus, this would indicate that the systemically administered tPA was not very effective in removing the initial PE. It is nevertheless unlikely that only administering heparin would have changed this. Therefore this study is neutral to the research question, LOE4, poor quality.

Institution: Department of Internal Medicine/Cardiology Division, Surgery/Vascular Section and Harborview Medical Center and University of Washington, Seattle, Washington.
Conflict of interest: The presence, or absence of, has not been addressed in the manuscript.

Worksheet author’s comments: A prospective study on the use of transesophageal echocardiography in diagnosing the cause of the arrest in patients resuscitated in the emergency department. Of the patients with pulseless electrical activity (PEA) 36% were diagnosed with PE. The survival of patients with PE was 25%. On of these two patients one received thrombolysis and the other one had embolectomy. The main findings of this study are that PE seems to result in PEA and that the outcome of these patients does not seem to be all bad (25% survival). However, no conclusion can be drawn on the use of thrombolysis in PE patients with ROSC as compared to heparin only. The study is designated as being neutral to the study question, LOE 5, poor quality.

Institution: Department of Emergency Medicine, Vienna General Hospital, Waehringer Guertel 18-20, 6D, A-1090, Vienna, Austria. karin.janata@akh-wien.ac.at
Conflict of interest: The presence, or absence of, has not been addressed in the manuscript.

Worksheet author’s comments: A retrospective case series of 66 out-of-hospital cardiac arrest patients with an assumed cause of pulmonary embolism based on clinical suspicion, electrocardiographic signs, echocardiography suggesting right ventricular strain. The diagnosis was confirmed using spiral-computed tomography, scintigraphy and/or autopsy. Thrombolysis was administered to 36 patients and 30 were not given thrombolysis. Thrombolysis was administered just after return of spontaneous circulation in only five patients. The outcomes of these five patients are not reported separately in the paper. Patients receiving thrombolysis, both during and after CPR, had a slightly higher likelihood of ROSC and survival at 24 hours, but not to hospital discharge. Major bleeding was more common in patients receiving thrombolysis, i.e. 25% compared to 10%. The conclusion of the study is still that benefits may outweigh the risks. Because only five patients were treated after ROSC the study is designated as a LOE5, fair quality.

Institution: Department of Emergency Care-, Respiratory-, Echocardiographic-, Nuclear Medicine Department, Hospital de Cardiologica, National Medical Center, Mexico City, Mexico
Conflict of interest: The presence, or absence of, has not been addressed in the manuscript.

Worksheet author’s comments: This is a randomized controlled trial comparing thrombolysis and heparin with heparin alone in patients with massive PE and cardiogenic shock as defined as systolic blood pressure below 90 mmHg. Eight patients were randomized to receiving streptokinase and heparin and eight to receiving heparin only. The mortality in the streptokinase group was 0% and it was 100% in the heparin only group. The trial was stopped prematurely. This is the study most often referred to when in different PE guidelines it is recommended that thrombolysis should be performed in cases of severe hemodynamic instability. The study is a RCT study but does not include patients that thrombolysis after ROSC. Therefore the LOE is 5, good quality.

Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Massive pulmonary embolism. Circulation 2006 ; 113 ; 577-582.
Institution: Cardiovascular Division, Department of Medicine, University Hospital Zurich, Zurich, Switzerland.
Conflict of interest: The presence, or absence of, has not been addressed in the manuscript.
**Worksheet author’s comments:** This study is subgroup analysis of patients included in the ICOPER registry a prospectively collected registry on treatment and outcomes of patients with pulmonary embolism. This is to best of the author’s knowledge the largest series of patients with PE and hemodynamic instability as defined by a systolic arterial blood pressure less than 90 mmHg. Among these patients the author’s studies the outcomes depending on the treatment modality. There was a trend towards lower 90 day mortality with thrombolysis (46% vs. 55%) but this was not significant. The study does not include information regarding whether any of the patients had had a cardiac arrest. Therefore the study is labeled LOE 5 of good quality.


**Institution:** University Clinic of Emergency Medicine, University of Vienna, Medical School, Wien, Austria.

**Conflict of interest:** The presence, or absence of, has not been addressed in the manuscript.

**Worksheet author’s comments:** A retrospective case series of 60 out-of-hospital cardiac arrest patients with PE as the cause of the arrest as verified by either transthoracic or transesophageal echocardiography, spiral computed tomography, ventilation-perfusion scan or autopsy. In this series 42 patients were correctly diagnosed as having PE while alive and therefore considered for thrombolysis. Of these patients, 21 received thrombolysis and 21 did not. Six patients received thrombolysis after the return of spontaneous circulation. The study does not report separately the outcome of those patients who received thrombolysis after RORS. Overall mortality was high with 90% not surviving. The patients that received thrombolysis had a slightly higher chance of ROSC, but there was no difference in survival to hospital discharge. Severe bleeding complications occurred. Because only 6 patients received thrombolysis after ROSC the present study is designated LOE 5, fair quality.


**Institution:** Department of Cardiology, University Hospital Jean-Minjoz, France and Department of Cardiology, Second Affiliated Hospital, Sun Yat-sen University, China

**Conflict of interest:** Not reported in the manuscript.

**Worksheet author’s comments:** This is a retrospective case series on patients that have undergone thrombolysis during early management of PE. Of 249 patients included in the study, 9 patients presented with shock. The study assessed factors associated with short and long-term mortality. The study did not have a control group of patients not treated with thrombolysis. The main finding was the recovery of right ventricular function predicts outcome and should be measured during management. The study is designated LOE5, poor quality.


**Institution:** Service de Pneumologie et Réanimation Respiratoire, Hôpital Beaujon, Clichy and Service d’Hépato-Gastroentérologie, Hôpital Pitié-Salpêtrière, Paris, France

**Conflict of interest:** The presence, or absence of, has not been addressed in the manuscript.

**Worksheet author’s comments:** A meta-analysis including nine RCT trials on the use of thrombolysis and heparin compared to heparin only. Most of the studies did not include patients in shock, the only one that did so exclusively is the study by Jerjes-Sanchez and colleagues. One other study included patients in shock but did not report the results separately. However a post hoc sensitivity analysis focusing on the patients with PE shock failed to show any benefit of thrombolysis in these patients. In addition thrombolysis was associated severe hemorrhage. The studies included were not likely to contain any patients that have undergone a CA prior to the arrest. Therefore the study is designated LOE5, good quality.


**Institution:** School of Medicine and Pharmacology, University of Western Australia and Department of Haematology, Royal Perth Hospital Perth, West Australia, Australia, Department of Radiology King’s College Hospital, London, UK and Department of Internal Medicine, University of Perugia, Perugia, Italy.

**Conflict of interest:** The presence or absence of has not been addressed in the manuscript.

**Worksheet author’s comments:** A meta-analysis including nine RCT trials on the use of thrombolysis and heparin compared to heparin only. This meta-analysis includes most of the studies included in the meta-analysis of Thabut et al. However this meta-analysis offers an analysis of those studies that included patients with hemodynamic instability and the conclusion was that in this group of patient’s thrombolysis might be beneficial. This is because a minimal difference in the included studies (Dotter 1979, Vasc Surg) Nevertheless, none of the studies included patients with a cardiac arrest, therefore the study are designated LOE5, good quality.