



## Review article

## Cardiac arrest due to pulmonary embolism

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## ABSTRACT

Pulmonary embolism (PE) is a potentially life threatening clinical condition that is fairly non-specific in presentation. Massive pulmonary embolism (PE) without cardiac arrest has been associated with a mortality rate of 30%. However, when cardiac arrest ensues, mortality may be as high as 95%. Since outcomes of cardiac arrest following PE are generally dismal, any available potentially life-saving measure must be instituted when the diagnosis of PE is suspected. Despite a lack of randomized controlled trials guiding the management of suspected PE in the cardiac arrest victim, thrombolysis and other therapies have been associated with good outcomes in the handful of published case reports and other small studies.

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## 1. Introduction

Pulmonary embolism (PE) is a potentially life threatening clinical condition that is fairly non-specific in presentation; sharing overlapping features with various other clinical conditions including acute myocardial infarction, pneumonia, chronic obstructive pulmonary disease and even anxiety spectrum disorders.<sup>1–3</sup> In the USA it is estimated that the annual incidence of PE is 1–2 per 1000 persons.<sup>4</sup> Although there is no published data on the overall incidence of venous thromboembolism (VTE) amongst the general population in India,<sup>5</sup> there is a suggestion that the incidence of VTE in Asia is similar to that in Western populations.<sup>6,7</sup> Massive PE is associated with a 30% mortality,<sup>8</sup> and where PE causes cardiac arrest the associated mortality may be as high as 95%.<sup>9</sup>

PE may be both over- and under- diagnosed in clinical practice. Whilst a post mortem study reported that the clinical diagnosis of PE was missed in 84% of all PE cases,<sup>10</sup> on the other hand, breathing motion or beam-hardening artefacts on CT scan imaging may be over diagnosed as PE by the inexperienced radiologist in approximately 25% of cases.<sup>11</sup> Many patients do not manifest

any clinical symptoms of PE. Asymptomatic or silent PE has been shown to be present in approximately two-thirds of individuals with deep vein thrombosis (DVT).<sup>12</sup>

Due to the lack of randomized controlled studies on the management of suspected PE in the cardiac arrest victim, current guidelines<sup>13–15</sup> are predominantly based on findings from retrospective studies and case reports. In this article, the basic pathophysiology, outcomes and diagnosis of PE during cardiac arrest as well as current management guidelines and recommendations (European Resuscitation Council-ERC,<sup>13</sup> American Heart Association-AHA,<sup>14</sup> European Society of Cardiology-ESC<sup>15</sup>) that describe the role of fibrinolytic therapy, surgical embolectomy and percutaneous mechanical thrombectomy are reviewed.

A search strategy was developed to identify peer reviewed publications pertaining to the definition, epidemiology, pathophysiology, diagnosis and management of pulmonary embolism in the cardiac arrest victim. The following databases: PubMed, Scopus, EMBASE, Google Scholar and Web of Science were searched (July 2017) using the following search terms: pulmonary embolus, pulmonary embolism, PE, cardiac arrest, cardiopulmonary resuscitation (CPR), venous thromboembolic disease, VTE, thrombolysis, thrombolytic therapy, fibrinolysis, fibrinolytic therapy, thrombectomy, extracorporeal membrane oxygenation (ECMO), extracorporeal life support (ECLS). References of manuscripts generated were further reviewed to identify additional relevant papers that may have been missed in the original search. Aspects from manuscripts relevant to the topics identified for

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discussion were selected, analysed and discussed amongst co-authors prior to inclusion in this review.

## 2. Discussion

### 2.1. Definitions and epidemiology

Cardiac arrest is defined as a sudden collapse associated with loss of consciousness, absence of spontaneous respiration and loss of central pulsation. In addition to the timely initiation of high quality chest compressions, early application of an external defibrillator and prompt attention to finding and correcting reversible causes of cardiac arrest are the only interventions that have been associated with outcome benefit during cardiac arrest.<sup>16</sup>

Pulmonary embolism is a recognized reversible cause of cardiac arrest and must be actively excluded in the collapsed pulseless patient. Other reversible causes of cardiac arrest can be easily remembered by recalling the “4 H's and 4 T's” memory aid; i.e. hypoxemia, hypo- or hyperkalemia (and other electrolyte disturbances), hypo- or hyperthermia, hydrogen ion imbalances (acidosis), hypovolemia, tension pneumothorax, tamponade (cardiac), thrombosis (myocardial infarction), thromboembolism (pulmonary embolism) and toxins.<sup>13,16</sup>

Approximately 90% of episodes of cardiac arrest following PE have been reported to occur within 1–2 h of symptom onset.<sup>4,17</sup> However, this may well be an underestimate of the actual duration of symptoms. Since PE is generally a process whereby initially smaller clots and later larger clots embolize to the pulmonary circulation, respiratory symptoms (due to an increase in ventilatory dead space) are expected to be the initial presenting symptoms.<sup>18</sup> It is likely that non-surviving cardiac arrest victims may not have had the opportunity to relate whether they had experienced minor respiratory symptoms in the days preceding the major event.

PE is reportedly responsible for 2–9% of all out of hospital (OHCA) and 5–6% of all in-hospital cardiac arrests.<sup>19–22</sup> However these figures are likely an underestimate, as PE is significantly underdiagnosed in clinical practice.<sup>2</sup> In a Finnish study, 10% of cardiac arrests that were initially attributed to a primary cardiac etiology, were later confirmed as secondary to PE.<sup>23</sup> An Austrian study reported that while PE was responsible for 4.8% of all cardiac arrests, the diagnosis was missed in 30% of these cases. In the same study, the majority of patients (63%) presented with pulseless electrical activity (PEA) as the initial cardiac rhythm, whereas asystole and ventricular fibrillation (VF) were responsible for 32% and 5% of cases, respectively.<sup>20</sup>

### 2.2. Basic pathophysiology of cardiac arrest following pulmonary embolism

Obstruction of the pulmonary trunk or other large pulmonary vessels, coupled with the release of vasoconstrictive mediators from thrombotic tissue, leads to a rapid increase in right ventricular afterload. The resultant decrease in venous return to the left heart, and subsequent reduction in left ventricular end diastolic volume, is further exacerbated by the pressure related leftward shift of the interventricular septum. As a result, circulatory shock and eventually cardiac arrest ensues.<sup>24</sup>

### 2.3. Diagnosing pulmonary embolism during cardiac arrest

Up to 30% of patients presenting with PE have no underlying risk factors.<sup>4</sup> In addition, many individuals that present with cardiac arrest following PE had not complained of preceding symptoms.<sup>25</sup> Although a unilateral swollen leg is suggestive of PE

as a cause of cardiac arrest,<sup>26</sup> approximately 30% of DVT's do not originate in the lower leg, whilst a good proportion of patients with DVT in the lower leg are clinically asymptomatic.<sup>27</sup> In a retrospective study amongst post gynecologic surgical patients, 76% (52/68) of subjects displayed radiological evidence of DVT despite an absence of clinical symptoms (silent DVT).<sup>28</sup>

The various point of care ultrasound (POCUS) protocols that have been described to assess the hemodynamically unstable patient in the ED, also include a search for the presence of deep vein thrombosis and pulmonary embolism.<sup>29–33</sup> The presence of DVT, right heart thrombi and other suggestive features of PE such as increased pulmonary artery or right ventricular pressures, right ventricular dilatation, tricuspid regurgitation and interventricular septal deviation can easily be determined by the trained ED clinician with the aid of POCUS.<sup>34</sup>

Emergency Department based limited compression ultrasonography (LCUS) to determine the presence of lower limb DVT has been associated with a diagnostic sensitivity and specificity of 90% and 95% respectively when conducted by the trained ED clinician.<sup>35,36</sup> During CPR, ultrasonographic evidence of a dilated RV with flattening of the interventricular septum may support the diagnosis of PE.<sup>37–39</sup> After achieving a return of spontaneous circulation (ROSC) and once the cardiac arrest victim has been stabilised, pulmonary angiographic computed tomography (CTPA) scanning should be performed to confirm the diagnosis of suspected PE.<sup>40</sup> A study demonstrated that patient outcomes were influenced by the utilization of extracorporeal life support (ECLS) in patients presenting with cardiac arrest of unknown origin. By allowing for the performance of various advanced radiological investigations such as computed tomography and pulmonary angiography, the use of ECLS was able to ‘buy time’ to confirm the underlying cause of the cardiac arrest.<sup>41</sup>

### 2.4. Management of pulmonary embolism during cardiac arrest

There are a limited number of studies that pertain to the management of PE in the cardiac arrest victim. A likely reason for this may relate to the methodological and ethical difficulties that may be encountered when designing clinical trials of this nature. Another possible reason may be due to the fact that since outcomes following cardiac arrest of any cause are generally poor, negative results, which are expected to be common in these patients, are less likely to be reported in the literature.

Fibrinolytic therapy, surgical embolectomy, percutaneous mechanical thrombectomy and ECMO have been described in the management of PE during cardiac arrest.<sup>13,14,42</sup> Prolonged CPR (at least 60–90 min) and continued resuscitative efforts are recommended when PE is suspected as the cause of cardiac arrest. Wu and colleagues reported a good outcome after thrombolysis in a patient that had underwent 100 mins of CPR.<sup>43</sup>

#### 2.4.1. Fibrinolytic therapy

Since fibrinolytic therapy is indicated in the treatment of both coronary thrombosis as well as PE and given that both together are implicated in a large proportion of cardiac arrest presentations, in theory, the routine administration of fibrinolytic therapy to all adult patients requiring CPR should be associated with overall benefit.<sup>44</sup> However evidence to support this strategy is lacking. In the TROICA study, which is the only randomized controlled trial that compared fibrinolytic therapy to placebo in patients with cardiac arrest of all causes, 1050 patients with OHCA received tenecteplase. Overall, there was no benefit ( $P > 0.05$ ) in terms of return of spontaneous circulation, 24hr survival, survival to hospital discharge, 30 day survival and neurologic outcomes when compared to the placebo group. However, the incidence of intracranial hemorrhage in the intervention group was

significantly higher.<sup>45</sup> Similar results were reported in a meta-analysis that was conducted by Li and colleagues.<sup>46</sup>

Despite a weak evidence base, both the European Resuscitation Council (ERC) as well as the American Heart Association (AHA) have recommend the use of fibrinolytic therapy when PE is either known or suspected as the cause of cardiac arrest.<sup>13,14</sup> The ERC further advocates for the administration of fibrinolytic therapy by trained practitioners in the prehospital environment.<sup>13</sup>

Renkes-Hegendörfer and Hermann were amongst the first to describe a case of a successful outcome after administering streptokinase to a patient in cardiac arrest due to PE.<sup>47</sup> Subsequently success with other thrombolytic agents including urokinase,<sup>48</sup> rt-PA (alteplase),<sup>49</sup> reteplase<sup>50</sup> and tenecteplase<sup>51</sup> have also been described.<sup>45</sup> In a retrospective comparative study of patients that received fibrinolytic therapy with rt-PA during cardiac arrest due to PE, significantly better outcomes with regards ROSC (67% vs 43%), 24h survival (53% vs 23%) and hospital discharge (19% vs 7%) were achieved in the group that received thrombolysis.<sup>52</sup>

Two separate studies conducted by Scholtz et al and Hopf et al reported good outcomes in 7/17 (41%)<sup>53</sup> and 5/6 (83%) individuals that received fibrinolytic therapy during cardiac arrest following PE.<sup>54</sup> In a review of 12 published case reports by Yanxia and colleagues, an overall survival of 88.9% was reported following thrombolytic therapy after PE related cardiac arrest. However, since poor outcomes are seldom reported in the literature, this figure is likely biased. Additionally, significant gastrointestinal or intracranial bleeding was reported in 3 of the 12 cases.<sup>55</sup> In contrast, Kürkciyan and colleagues reported a survival to hospital discharge of just 10% (2/21) despite the majority of patients (81%) achieving ROSC.<sup>20</sup>

Despite its beneficial effects, major bleeding episodes including intracranial haemorrhage is a serious concern with the use of thrombolytic therapy. Results of the PEITHO trial reported a 2% incidence of hemorrhagic stroke after administration of tenecteplase in patients with PE (versus 0.2% in the placebo arm). A significant increase in major non-intracranial bleeding events (6.3% vs. 1.5%) was also reported.<sup>56</sup> Liver rupture as well as mediastinal bleeding have also been reported in individuals receiving thrombolysis during CPR.<sup>20</sup> In post-mortem studies, hemorrhagic complications have been reported in >15% of individuals that had received thrombolysis during CPR.<sup>57</sup> However good neurologic outcomes have been reported in the majority of survivors.<sup>58–60</sup>

#### 2.4.2. Surgical embolectomy and percutaneous mechanical thrombectomy

All studies pertaining to these interventions were retrospective in nature and had enrolled only a small number of patients, with the largest study including just 96 patients that had presented over a 20 year period.<sup>61</sup> The overall evidence in favour of the benefit associated with surgical embolectomy and percutaneous mechanical thrombectomy during CPR is also weak.<sup>16</sup> The ERC recommends that consideration be given to surgical embolectomy or mechanical thrombectomy when pulmonary embolism is the known cause of cardiac arrest but however, do not recommend these interventions when pulmonary embolism is only suspected.<sup>13</sup> Surgical thrombectomy has been associated with mortality rates of 50% to 74%.<sup>61–63</sup> However, in a retrospective study, 6 out of 7 patients that had underwent percutaneous pulmonary thrombectomy during CPR survived.<sup>64</sup>

In a recently published systematic review and proportional meta-analysis that included patients with massive and submassive PE, ultrasound assisted catheter directed thrombolysis, when compared to systemic thrombolysis, was reported as safe and effective, with a potentially lower risk of major bleeding.<sup>65</sup> This

method of thrombolysis has not been explored in the setting of cardiac arrest.

#### 2.4.3. Extracorporeal membrane oxygenation

The use of ECLS techniques in specialised facilities, has also been associated with success in victims of cardiac arrest following PE.<sup>66–68</sup> However, there are no randomized controlled trials that compare ECMO with other therapeutic modalities in the setting of massive PE. Giraud and colleagues reported successful outcomes in 2 patients that were placed on ECMO after cardiac arrest secondary to massive PE. In the first case, veno-arterial (VA) ECMO was implanted in a patient in whom thrombolytic therapy was absolutely contraindicated. The second patient was placed on veno-venous (VV) ECMO due to persistent hypoxaemia despite haemodynamic stabilization following thrombolysis.<sup>42</sup> In a recent systematic review that included 78 patients with massive PE in whom ECMO was instituted, 43 patients (51.2%) received ECMO following cardiac arrest with 22 (51.2%) of these patients surviving. However, this figure is likely biased since all of the included papers were either single case reports or case series.<sup>69</sup>

### 3. Conclusion

Despite a lack of randomized controlled trials to guide the management of suspected PE in the cardiac arrest victim, success with various fibrinolytic agents and other therapeutic modalities have shown promise in the handful of published case reports and other small studies relating to this topic. A high quality, well designed multi-center randomized controlled trial is required to settle current uncertainties.

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The authors' hereby certify that this submission is not under publication consideration elsewhere, and is free of conflict of interest.

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