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RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Hua-Ge Yu; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lei Wang.
Cardiac arrest secondary to pulmonary embolism treated with extracorporeal cardiopulmonary resuscitation: Six case reports

Min-Shan Qiu, Yong-Jin Deng, Xue Yang, Han-Quan Shao

Abstract

BACKGROUND
Massive pulmonary embolism (PE) results in extremely high mortality rates. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) can provide circulatory and oxygenation support and rescue patients with massive PE. However, there are relatively few studies of extracorporeal cardiopulmonary resuscitation (ECPR) in patients with cardiac arrest (CA) secondary to PE. The aim of the present study is to investigate the clinical use of ECPR in conjunction with heparin anticoagulation in patients with CA secondary to PE.

CASE SUMMARY
We report the cases of six patients with CA secondary to PE treated with ECPR in the intensive care unit of our hospital between June 2020 and June 2022. All six patients experienced witnessed CA whilst in hospital. They had acute onset of severe respiratory distress, hypoxia, and shock rapidly followed by CA and were immediately given cardiopulmonary resuscitation and adjunctive VA-ECMO therapy. During hospitalization, pulmonary artery computed tomography angiography was performed to confirm the diagnosis of PE. Through anticoagulation management, mechanical ventilation, fluid management, and antibiotic treatment, five patients were successfully weaned from ECMO (83.33%), four patients survived for 30 d after discharge (66.67%), and two patients had good neurological outcomes (33.33%).

CONCLUSION
For patients with CA secondary to massive PE, ECPR in conjunction with heparin anticoagulation may improve outcomes.

Key Words: Extracorporeal cardiopulmonary resuscitation; Cardiac arrest; Pulmonary embolism; Outcomes; Shock; Case report

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Core Tip: Massive pulmonary embolism (PE) remains the leading clinical cause of death. Unfortunately, relatively few new technologies are available to reduce the morbidity and mortality of massive PE. Anticoagulation therapy is still the gold standard treatment for PE. In this study, we report the clinical details of six patients with cardiac arrest secondary to massive PE treated with extracorporeal cardiopulmonary resuscitation (ECPR) in conjunction with heparin anticoagulation. Our findings suggest that the use of ECPR is feasible in this cohort of patients and may improve resuscitation success rate and neurologically intact survival.

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INTRODUCTION
Massive pulmonary embolism (PE) is an obstructive shock that can lead to right ventricular afterload and hemodynamic instability. The overall mortality rate of PE can be as high as 50% and can even reach 52%–84% for patients with cardiac arrest (CA) secondary to PE. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) can provide necessary circulatory and oxygenation support and is an effective means of rescuing patients with massive PE[1,2]. A multifactorial regression analysis by Hobohm et al[3] showed that patients with PE who developed CA and were treated with VA-ECMO alone had a lower risk of in-hospital death [odds risk (OR) = 0.68, 95%CI: 0.57–0.82, P < 0.001] than patients who were treated with thrombolysis alone (OR = 1.04, 95%CI: 0.99–1.01, P = 0.116). However, most current studies of patients with CA secondary to PE who underwent VA-ECMO were conducted in patients with return of spontaneous circulation prior to VA-ECMO, and there are relatively few studies examining the use of extracorporeal cardiopulmonary resuscitation (ECPR) in patients with CA secondary to PE[4]. Here, we review the clinical data of six patients admitted to our hospital between June 2020 and June 2022 who underwent ECPR for CA secondary to PE, as well as the experience of other researchers in the existing literature.

CASE PRESENTATION

Chief complaints
Patients presented with acute onset severe respiratory distress, hypoxia, and shock rapidly followed by cardiac arrest.

History of present illness
We included a total of six patients admitted to the intensive care unit (ICU) of Dongguan People’s Hospital between June 2020 and June 2022 who received ECPR for CA secondary to massive PE in the study. The demographic characteristics, laboratory test results, imaging findings, ECMO data, and clinical outcomes of patients were collected. Data are presented in Tables 1–3.

History of past illness
Two patients (33.33%) had at least one underlying disease (including hypertension, diabetes, hyperlipidemia), and all patients had at least one pre-disposing factor for thrombosis (including recent hospitalization, cancer, trauma, travel, or thrombosis) (Table 1).

Personal and family history
The personal and family history was determined to be noncontributory.

Physical examination
All patients were experienced witnessed CA in hospital. They lost consciousness, no heartbeat was apparent, and blood pressure was undetectable.

Laboratory examinations
The patients had significantly elevated D-dimer and lactate levels at the time of transfer to the ICU. Four patients (66.67%) had acute kidney injury requiring continuous renal replacement therapy (Table 2).
<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>BMI (kg/m²)</th>
<th>Hypertension</th>
<th>Diabetes</th>
<th>Hyperlipidemia</th>
<th>Recent hospitalization</th>
<th>Cancer</th>
<th>Trauma</th>
<th>Travel</th>
<th>Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>63</td>
<td>19.48</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>68</td>
<td>31.25</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>73</td>
<td>17.58</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>51</td>
<td>23.43</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>40</td>
<td>20.54</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>47</td>
<td>24.8</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>

BMI: Body mass index; F: Female; M: Male; N: No; Y: Yes.

| Table 2 Clinical indicators of patients with cardiac arrest secondary to pulmonary embolism treated with extracorporeal cardiopulmonary resuscitation
<table>
<thead>
<tr>
<th>Laboratory indexes</th>
<th>Case</th>
<th>D-dimer (μg/mL)</th>
<th>CK-MB (IU/L)</th>
<th>Troponin (ng/ml)</th>
<th>BNP (pg/mL)</th>
<th>Lactate (mmol/L)</th>
<th>RV/LV</th>
<th>CT</th>
<th>CRRT</th>
<th>APACHE II score</th>
<th>SOFA score</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>&gt; 20</td>
<td>2.7</td>
<td>0.04</td>
<td>778</td>
<td>12</td>
<td>25/43</td>
<td>Emboli in multiple pulmonary artery branches in the distal left main pulmonary artery and multiple emboli in the bilateral pulmonary artery branches</td>
<td>Y</td>
<td>24</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.97</td>
<td>9.7</td>
<td>0.182</td>
<td>275</td>
<td>13.1</td>
<td>35/34</td>
<td>Emboli in the bilateral main pulmonary arteries</td>
<td>N</td>
<td>38</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&gt; 20</td>
<td>41.6</td>
<td>5.119</td>
<td>42</td>
<td>&gt; 15</td>
<td>26/34</td>
<td>Emboli in the distal right main pulmonary artery trunk and multiple emboli in the bilateral pulmonary artery branches</td>
<td>N</td>
<td>47</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3.55</td>
<td>81.9</td>
<td>0.193</td>
<td>119</td>
<td>11.8</td>
<td>23/51</td>
<td>Emboli in the bilateral lower lobar arteries</td>
<td>Y</td>
<td>46</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&gt; 20</td>
<td>263.6</td>
<td>0.31</td>
<td>643</td>
<td>14.22</td>
<td>36/26</td>
<td>Emboli in multiple pulmonary artery branches</td>
<td>Y</td>
<td>33</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>7.42</td>
<td>151.6</td>
<td>0.05</td>
<td>225</td>
<td>9</td>
<td>42/39</td>
<td>Emboli in the distal pulmonary trunk, left and right main pulmonary arteries, and bilateral pulmonary artery branches</td>
<td>Y</td>
<td>30</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

CK-MB: Creatine kinase isozyme; BNP: B-type natriuretic peptide; RV/LV: Right ventricle/left ventricle; CT: Computed tomography; CRRT: Continuous renal replacement therapy; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment score; Y: Yes; N: No.

**Imaging examinations**
Diagnosis of PE was confirmed in all patients by computed tomography (CT)-pulmonary angiography. Echocardiographic findings revealed a right ventricle/left ventricle ratio > 1 in three patients (50%) (Table 2). Example echocardiographic images are presented in Figure 1.

**FINAL DIAGNOSIS**
Considering the patients’ history and CT-pulmonary angiography results, all six patients were diagnosed with CA secondary to PE.
Figure 1 Echocardiographic examination of the patient in case 5. A: Parasternal long axis view revealed that left ventricular end diastolic dimension was 26.2 mm; B: Apical 4 chamber view revealed that right ventricular end diastolic dimension was 36.1 mm. Right ventricle/left ventricle ratio > 1.

TREATMENT

With reference to an expert consensus[5], patient selection and intervention timing were as follows: (1) Patients aged 18–75 years; (2) CA witnessed by medical personnel, with effective cardiopulmonary resuscitation (CPR) implemented and a no-flow time < 5 min; (3) Standard CPR > 10 min without return of spontaneous circulation > 1 min; and (4) able to initiate ECPR within 60 min. Exclusion criteria were as follows: (1) Concomitant severe irreversible or advanced disease, such as cancer and advanced cirrhosis; and (2) Uncontrolled bleeding from trauma. This study was approved by the Clinical Ethics Committee of Dongguan People’s Hospital, No. KYKT2021-028.

When the criteria were met, all patients were immediately given CPR and VA-ECMO therapy. None of the patients underwent thrombolysis, surgical embolization, or percutaneous catheter-directed therapy. After all cases in the present study were successfully initiated onto ECMO, their coagulation status was evaluated. Cerebral hemorrhage was ruled out by cranial CT examination, and heparin therapy was initially administered by continuous intravenous infusion at 4–10 U/kg/h. The activated clotting time can guide the dosage of heparin, with a target of 180–220 s or maintaining the activated partial thromboplastin time at 1.5–2.5 times the normal value.

OUTCOME AND FOLLOW-UP

The median low-flow time of the six patients was 41.5 min [interquartile range (IQR): 29.5–52.00 min]. The median duration of ECMO support was 61 h (IQR: 40.00–228.75 h). The median duration of ICU stay was 18.5 d (IQR: 9.75–27.75 d). Five patients (83.33%) were successfully weaned from ECMO. Four patients (66.67%) survived for 30 d after discharge; of these, two patients (33.33%) had good neurological outcomes (Table 3). Three patients (50%) had ECMO complications, including two cases of hemorrhage (33.33%). Emboli in the pulmonary arteries of survivors were decreased after 30 d of therapy (an example is shown in Figure 2).

DISCUSSION

Despite recent advances in techniques such basic and advanced life support, the overall survival rate from CA remains very low[6]. VA-ECMO is an effective means of providing mechanical circulatory assistance. In patients with CA secondary to PE, ECMO not only provides near-full-flow support and improves systemic circulatory perfusion, but also reduces right heart afterload and pulmonary artery pressure by bypassing the native pulmonary circulation and returning blood into the systemic circulation. This typically occurs via the femoral artery, thus assisting right heart function, improving hypoxemia[7], and providing more time for the diagnosis and treatment of PE. However, the use of ECMO for the treatment of patients with CA secondary to massive PE is still in the exploratory phase, and whether systemic thrombolysis, surgical thrombolysis, or percutaneous catheter-directed therapy should be performed remains a matter of debate. According to the 2019 European guidelines for the diagnosis and management of acute PE[8], ECMO combined with surgical thrombolysis or percutaneous catheter-directed therapy can be considered, but their recommendation and evidence levels are not high, at IIb and C, respectively. This is because the results of a multi-center study by Meneveau
Table 3 Extracorporeal membrane oxygenation data and clinical outcomes of patients with cardiac arrest secondary to pulmonary embolism treated with extracorporeal cardiopulmonary resuscitation

<table>
<thead>
<tr>
<th>Case</th>
<th>Low-flow time (min)</th>
<th>Duration of ECMO support (h)</th>
<th>ECMO complications</th>
<th>Weaned from ECMO</th>
<th>Duration of ICU stay (days)</th>
<th>30-d CPC score</th>
<th>30-d survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>19</td>
<td>DIC, intra-abdominal hemorrhage</td>
<td>Y</td>
<td>17</td>
<td>3</td>
<td>Y</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>218</td>
<td>None</td>
<td>Y</td>
<td>42</td>
<td>2</td>
<td>Y</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>54</td>
<td>DIC, airway hemorrhage</td>
<td>Y</td>
<td>23</td>
<td>3</td>
<td>Y</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>68</td>
<td>Ischemia of right first metatarsal</td>
<td>Y</td>
<td>6</td>
<td>5</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>47</td>
<td>None</td>
<td>Y</td>
<td>20</td>
<td>1</td>
<td>Y</td>
</tr>
<tr>
<td>6</td>
<td>43</td>
<td>261</td>
<td>None</td>
<td>N</td>
<td>11</td>
<td>5</td>
<td>N</td>
</tr>
</tbody>
</table>

ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; CPC: Glasgow-Pittsburgh cerebral performance category; DIC: Disseminated intravascular coagulation; Y: Yes; N: No.

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Figure 2 Pulmonary artery computed tomography angiography examination of the patient in case 1. A: Emboli in the left main pulmonary artery (arrow); B: Emboli in the pulmonary artery were substantially decreased after 30 d of therapy (arrow).

et al[9], to which the recommendation refers, showed that in 39 patients with CA who received different treatment strategies (including ECMO + fibrinolysis, ECMO + surgical embolization, and ECMO treatment alone), patient mortality exceeded 70%, with no statistically significant differences ($P = 0.17$). A meta-analysis by Loyalka et al[10] also suggests that the in-hospital mortality rate of patients with CA secondary to PE treated with surgical embolization or percutaneous catheter-directed therapy remains high, at 46.3% in patients presenting with CA before surgical embolization. In the present study, the median low-flow time was 41.5 min (IQR: 29.5–52.00 min) in the six patients with CA secondary to PE treated with emergency VA-ECMO-assisted therapy; all patients were successfully initiated onto ECMO within 60 min, and the two neurologically intact survivors were initiated onto ECMO within the shortest time (< 30 min) from the onset of arrest. None of the patients underwent thrombolysis, surgical embolization, or percutaneous catheter-directed therapy. Five of the patients (83.33%) were successfully weaned from ECMO, and four (66.67%) survived for 30 days after discharge, including two (33.33%) with good neurological outcomes. Both the survivors with neurologically intact (Glasgow-Pittsburgh cerebral performance category 1&2) survival had the shortest low-flow times. This suggests that it may be beneficial to initiate ECPR as soon as possible following PE-induced CA as it is likely that conventional CPR is not very effective in these circumstances.

Thrombosis or hemorrhage is a common complication in patients with CA undergoing ECPR due to the presence of ischemia-reperfusion injury, exposure of the blood to the surface of a non-endothelialized artificial extracorporeal circuit, a systemic inflammatory response, and activation of the coagulation system, all of which disrupt the balance of the coagulation system in the body[11]. In such patients, anticoagulation is a top priority in clinical management. Heparin can activate the body’s own fibrinolytic mechanism and promote thrombolysis while effectively preventing re-thrombosis. After all patients in the present study were successfully initiated onto ECMO, their coagulation status was evaluated. Cerebral hemorrhage was ruled out by cranial CT examination, and heparin therapy was initially administered by continuous intravenous infusion at 4–10 U/kg/h. Activated clotting time is the primary method for immediate monitoring of heparinization during ECMO support. Repeated monitoring of the activated clotting time can guide the dosage of heparin, with a target of 180–220 s or
maintaining the activated partial thromboplastin time at 1.5–2.5 times the normal value, depending on the risk of hemorrhage[12,13]. Heparin therapy was discontinued midstream in cases 1 and 3 due to secondary disseminated intravascular coagulation and active hemorrhage. After the disseminated intravascular coagulation and hemostasis was corrected, anticoagulation therapy was resumed, and the patients survived.

CONCLUSION

Massive PE can lead to severe respiratory distress and shock rapidly followed by CA. VA-ECMO can provide adequate circulation and gas exchange support. Our findings indicate that the treatment protocol of applying ECPR in conjunction with heparin anticoagulation provides improved outcomes for the resuscitation of patients with CA secondary to PE. Small sample size of this single center case series limits interpretation of the neurologically intact survival, however this preliminary data is encouraging.

ACKNOWLEDGEMENTS

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FOOTNOTES

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