Sven Kaese[1], Pia Lebiedz[2]

[1]Department of Cardiology and Intensive Care Medicine, Johannes Wesling University Hospital, Ruhr University Bochum, Minden, Germany
[2]Medical Campus University of Oldenburg, European Medical School, Department of Internal Medicine and Intensive Care Medicine, Evangelisches Krankenhaus Oldenburg, Oldenburg, Germany

Extracorporeal life support after failure of thrombolysis in pulmonary embolism

Abstract

Introduction: Fulminant pulmonary embolism (PE) may lead to cardiogenic shock or cardiac arrest with high mortality rates (65%) despite treatment with thrombolysis. Patients not responding to this therapy might benefit from extracorporeal life support (ECLS). Only occasional case reports of ECLS in PE patients are available. We studied the use of ECLS after thrombolysis in patients suffering from refractory cardiogenic shock due to PE.

Material and methods: Patients who were admitted to our university intensive care unit (ICU) with PE, not responding to thrombolysis, and who received subsequent ECLS treatment were studied.

Results: 12 patients with severe PE were included. 6 patients were admitted by emergency medical services, 5 patients were transferred to the ICU from other hospitals and one patient presented at the emergency department by herself. 11 of 12 patients suffered from cardiac arrest and needed cardiopulmonary resuscitation (CPR) before ECLS implantation. Three ECLS were implanted during CPR and nine ECLS were implanted during emergency conditions in patients with cardiogenic shock. All patients received thrombolysis before implementation of ECLS. Mean duration of ICU treatment was 22.4 ± 23.0 days. Mean duration of ECLS therapy was 5.6 ± 6.5 days. Bleeding complications occurred in four patients. Complications directly related to the ECLS system occurred in two patients (overall complication rate 42%). Overall, 6 of 12 patients (50%) survived.

Conclusions: ECLS may be considered as a bailout therapy in PE patients not responding to prior definitive treatment such as thrombolysis. ECLS therapy seems to be feasible with an acceptable complication rate even after thrombolysis.

Key words: pulmonary embolism, extracorporeal life support system, cardiopulmonary resuscitation, thrombolysis, right heart failure

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Introduction

Fulminant pulmonary embolism (PE) is a potential hazardous disease. Pulmonary artery occlusion by thromboembolism may lead to oxygenation and/or right heart failure. Patients with PE suffering from cardiogenic shock or cardiac arrest have high mortality rates (65%) [1, 2].

Treatment options range from simple anticoagulation to definitive treatment options such as local or systemic thrombolysis, surgical embolectomy and catheter-based therapies. In cases with severe cardiogenic shock or cardiac arrest, immediate thrombolysis is often performed. Since 1995, only a few cases were reported in which extracorporeal membrane oxygenation (ECMO)/ /extracorporeal life support (ECLS) were applied either in combination with the above mentioned treatment options or alone [3].

However, in some patients who do not respond to the definitive treatment options mentioned above, ECLS might be the only life-saving therapy. In these patients, ECLS can be used as a bridge to right heart recovery. Data on the use of ECLS after treatment of PE with thrombolysis, surgical embolectomy or catheter based techniques are rare [4]. The recently updated ESC (European Society of Cardiology) guidelines from 2019

Address for correspondence: Sven Kaese, Department of Cardiology and Intensive Care Medicine, Johannes Wesling University Hospital, Ruhr University Bochum, Minden, Germany; e-mail: sven.kaese@gmx.de
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for the treatment of PE recommend that "ECMO may be considered, in combination with surgical embolectomy or catheter-directed treatment, in patients with PE and refractory circulatory collapse or cardiac arrest" [5]. This recommendation is classified as class IIb and level C [5]. The use of ECLS in high-risk PE patients as a stand-alone technique with anticoagulation is deemed to be controversial and as such, the ESC guidelines suggest considering additional therapies, such as surgical embolectomy or catheter-directed treatment [5].

We conducted a study in high-risk patients suffering from cardiogenic shock due to PE despite thrombolysis with subsequent need for ECLS therapy.

Material and methods

Our study was performed according to the Declarations of Helsinki. Due to the retrospective nature of the study, a full review by the local Ethics Committee was not required.

We retrospectively enrolled 12 consecutive patients that were admitted to the ICU of the University Hospital of Muenster with fulminant pulmonary embolism who did not respond to thrombolysis and were treated with ECLS.

ECLS was implanted if return of spontaneous circulation (ROSC) could not be achieved during CPR after systemic thrombolysis, if shock symptoms and hypotension did not recede after thrombolysis, and in one patient due to severe shock and progressive lactic acidosis with a rapidly rising need for vasopressors.

For ECLS we used Rotaflow or Cardiohelp systems (Maquet, Rastatt, Germany). Cannulas (Novalung, Heilbronn, Germany and Maquet, Rastatt, Germany) were sized 15F–23F, if appropriate. Cannulas were placed via the femoral vein and femoral artery in most cases. In two cases, the subclavian artery was used via surgically implanted patches.

Thrombolysis was performed using either 8000 IU tenecteplase or 100mg of rtPA with prior application of 5000 IU heparin.

We analyzed demographic parameters of the study cohort as well as the following data: duration of ICU treatment, duration of ECLS treatment, need for cardiopulmonary resuscitation, circumstances of ECLS implantation (during CPR or emergency setting), ECLS associated complications, mode of ICU admission, and survival.

Study cohort characteristics

Our study cohort involved 12 patients (3 females) with a mean age of 44.2 ± 11.9 years (Table 1).

With regard to pre-existing diseases, one patient had a congenital heart defect with a hypoplastic right ventricle, pulmonary valve stenosis and a secundum atrial septal defect which was previously treated with a modified Fontan operation. Another patient suffered from dilative cardiomyopathy. One patient had a factor V Leiden mutation with recurrent deep vein thrombosis and former oral anticoagulation therapy. Lastly, one patient had a myeloproliferative disease.

Table 1. Study cohort characteristics. Summary of study cohort characteristics concerning gender, age, duration of stay on intensive care unit (ICU), duration of extracorporeal life support (ECLS) treatment, need for cardiopulmonary resuscitation (CPR), complications after thrombolysis and ECLS implantation, time point of thrombolysis and survival

Patients (n)	12
Male	9 (75%)
Age (years)	44.2 ± 11.9
ICU duration (days)	22.4 ± 23
ECLS duration (days)	5.6 ± 6.5
CPR before ECLS implantation	11 (92%), 7 in-hospital, 4 out-of-hospital
CPR during ECLS implantation	3 (25%)
ECLS associated complications	5 (42%)
Time of thrombolysis	4 out-of-hospital, 6 in-hospital, 2 local *via* catheter into pulmonary artery
Overall survival	6 (50%)

CPR — cardiopulmonary resuscitation; ECLS — extracorporeal life support; ICU — intensive care unit

Confirmation of diagnosis

Assumed admission diagnosis of all 12 patients was severe pulmonary embolism. In 7 patients, pulmonary embolism was confirmed by contrast-enhanced computed tomography (CT). In the remaining 5 patients, PE was assumed due to clinical presentation and severe right heart dilatation detected by echocardiography.

In one of these five patients, echocardiography detected a large thrombus in the right atrium protruding into the right ventricle.

Circumstances of admission and ECLS implantation

6 patients were admitted to the ICU by the emergency medical service. Further, 5 patients were subsequently transferred to our ICU from other hospitals. One patient presented at our emergency department by herself.

11 of 12 patients suffered from cardiac arrest and received CPR of different duration prior to ECLS implantation (Table 1). Seven of these 11 patients suffered from in-hospital cardiac arrest and four had an out-of-hospital cardiac arrest (OHCA) (Table 1). In one of the four OHCA patients, the emergency medical service team achieved out of hospital return of spontaneous circulation (ROSC). The remaining three OHCA patients were transported under ongoing CPR. In two of these three patients, ECLS was implemented during continuous CPR in our ICU. One of the three patients had intra-hospital ROSC and received ECLS subsequently due to persistent hemodynamic instability.

In total, three of the ECLS systems were implanted during ongoing cardiopulmonary resuscitation and the remaining nine ECLS systems were implanted during emergency conditions in critically hemodynamically unstable patients. Only one patient received ECLS without prior resuscitation due to progressive shock.

ICU and drug treatment

All patients received systemic or local thrombolysis before implementation of ECLS (Table 1). Four patients received systemic thrombolysis out-of-hospital and six patients received systemic thrombolysis intra-hospital. Two patients received local thrombolysis via pulmonary artery catheterization. In addition, two of the 12 patients were additionally treated with pulmonary catheter fragmentation.

During ECLS implantation, 11 patients were intubated and mechanically ventilated. One patient not requiring CPR was awake during ECLS implementation and received analgosedation.

The venous cannula was inserted into the vena femoralis in all patients. The arterial cannula was placed in the arteria femoralis in 10 patients. In 2 patients, the arterial cannula was placed surgically into the arteria subclavia dextra.

ICU course and complications

Mean duration of ICU treatment was 22.4 ± 23.0 days. ECLS therapy was performed with a mean duration of 5.6 ± 6.5 days.

After thrombolysis and subsequent implementation of ECLS, bleeding complications occurred in four patients. One patient showed minor bleeding at the arterial cannula placed in the arteria subclavia. Further, two patients had minor bleedings at the cannulas as well as gastrointestinal bleeding. During ECLS treatment, one patient showed major bleeding with subsequent femoral compartment syndrome. One of these patients also suffered from initially accidental misplacement of the venous cannula into the arteria femoralis during ECLS implantation with need for immediate surgical revision. Additionally, one patient developed an arteriovenous fistula with need for surgical therapy in the further course (Table 1).

In all surviving patients, ECLS was extracted without need for re-implantation.

Outcome

6 of 12 patients (50%) died during treatment. 5 patients died due to multi-organ failure and lactic acidosis after prolonged CPR. Three of these five patients had out-of-hospital cardiac arrest with CPR during transport to the hospital. In addition, one patient died during long-term ICU stay due to sclerosing cholangitis. This patient had presented herself at the emergency department and did not require CPR. The other 6 of 12 patients (50%) were discharged from hospital (Table 1).

Discussion

For prognostic reasons and therapeutic decision making, PE is often classified as high risk, intermediate risk, and low risk PE [5, 6]. Patients with low and intermediate risk PE should receive anticoagulation only. Patients with cardiac arrest

or severe shock due to pulmonary embolism should be treated with thrombolysis with adherence to individual contraindications such as recent intracerebral bleeding. The PEITHO study showed that patients with even an intermediate risk PE had a lower risk of hemodynamic decompensation when treated with thrombolysis. However, they had an elevated risk of major hemorrhage or stroke [7].

Due to advances regarding ECLS therapy (i.e. improved pump technology and coated tubes), ECLS systems have been developed that can be rapidly applied even in patients in severe shock or during CPR via femoral vein and artery access [8]. ECLS has already been reported as a supportive measure in patients undergoing surgical thrombectomy [9]. During the last few years, implementation of ECLS due to refractory cardiac arrest is increasingly used. This procedure is so far called eCPR (extracorporeal cardiopulmonary resuscitation) and is known to increase survival rates in selected patients [10]. Therefore, in patients with massive PE and severe shock despite definitive treatment by thrombolysis and catheter fragmentation, ECLS can be used as a bailout strategy. A review by Yusuff *et al.* reported 43 patients receiving ECLS for refractory cardiac arrest due to PE with an overall survival of 51.2% [3]. In a subgroup of 21 patients treated with ECLS and thrombolysis or catheter embolectomy, survival rate was 43%. Another study reported 17 patients treated with fibrinolysis and ECMO having a 30 day survival rate of 23.5% [11]. In addition, a study by Corsi *et al.* [12] reported thrombolysis in 8 of 17 patients with fulminant PE before ECLS was implemented. Overall, 90 day survival of the 17 PE patients treated with ECLS was 47% [12]. In our study, patients pretreated with thrombolysis and subsequent ECLS therapy had a survival rate of 50% until hospital discharge. In our university hospital, we perform around 50 ECMO/ECLS implantations per year. Around 10 percent of ECMO/ECLS are implanted during ongoing CPR. A trained ECMO/ECLS team for implantation is permanently available. Due to these conditions, the experience of our center might also contribute to the improved survival rate in our study cohort.

In comparison, other studies showed a range of survival rates between 35–52% in patients with PE and cardiogenic shock or cardiac arrest treated with fibrinolysis or embolectomy but without ECLS treatment [1, 2, 11]. When comparing these studies to our study, ECLS therapy may be useful and points to improved survival in a subgroup of patients with high risk PE and failure of thrombolysis and embolectomy.

Further, the review by Yusuff *et al.* found an ECLS related complication rate of 37% (16/43 patients) [3]. Another study with 52 patients being treated with only ECLS therapy or ECLS therapy in combination with thrombolysis and embolectomy found that major bleeding events occurred in 20 patients (38.5%) [11]. In addition, Corsi *et al.* [12] found severe hemorrhages with no impact on survival in 15 of 17 patients (88%) with a median of 4 packed red-cell and 5 fresh -frozen plasma units transfused. Surgical wound infections are reported in 9.6% of PE patients treated with ECLS [11]. In our study, we had a complication rate of 17% directly related to the ECLS (misplacement of one cannula and arteriovenous fistula, 2/12 patients). One of these two patients and an additional three other patients had bleeding complications after thrombolysis and ECLS implantation, which is a typical side effect after thrombolysis. By summarizing the complications due to thrombolysis and ECLS implantation, we observed a complication rate of 42% which is comparable to the reported complication rate by other studies [3, 11, 12]. Therefore, ECLS implantation seems to be feasible in the subgroup of high-risk PE patients pretreated with thrombolysis.

In our study, the mean duration of ICU stay was 22.5 ± 23 days, which is comparable to another study with 19 ± 14.6 days [3]. Duration of ECLS treatment in our patient cohort was relatively short with 5.6 ± 6.5 days and is in a similar range when comparing with other reports (2.5–4.5 days) [3, 11, 12]. Duration of ECLS therapy in patients with severe PE seems to be briefer in relation to patients treated with ECMO due to severe acute respiratory distress syndrome (ARDS) within 9–15 days of ECMO support [13]. This relatively short ECLS treatment duration in PE patients may be due to thrombus dissolution by continuous heparin application together with spontaneous thrombolysis [12].

In our study, as expected, the main cause of death in non-survivors (5/12 patients) was multi -organ failure, which was similarly the cause of death found in other studies [3, 11, 12]. In our study more than half of the patients were resuscitated outside of the hospital, which is a patient subgroup with a known worse outcome.

Conclusions

We therefore postulate that ECLS should be considered as a bailout therapy in PE patients not responding to prior definitive treatment such

as thrombolysis. Further, ECLS therapy seems to be feasible with an acceptable complication rate even after thrombolysis against the background of lacking therapy alternatives in this subgroup of patients. Our results may indicate an improved survival rate in this subgroup of PE patients. Therefore, further studies and randomized controlled trials are required to confirm the usefulness of ECLS therapy in patients with severe PE even without definitive treatment such as thrombolysis but instead, only anticoagulation.

Conflicts of interest

None declared.

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