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# Extracorporeal life support in cardiovascular patients with observed refractory in-hospital cardiac arrest is associated with favourable short and long-term outcomes: A propensity-matched analysis

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## Abstract

**Aims:** Extracorporeal life support (ECLS) has shown encouraging survival rates in patients with in-hospital cardiac arrest; however, its routine use is still controversial. We compared the survival of patients with in-hospital cardiac arrest receiving conventional cardiopulmonary resuscitation (CCPR) to that of patients with ECLS as an adjunct to cardiopulmonary resuscitation (ECPR).

**Methods:** A total of 353 patients with in-hospital cardiac arrest (272 CCPR and 52 ECPR) were included in this retrospective, propensity score-adjusted (1:1 matched), single-centre study. Primary endpoints were survival at 30 days, long-term survival and neurological outcome defined by the cerebral performance categories score.

**Results:** In the unmatched groups patients undergoing ECPR initially had significantly higher APACHE II scores ($P$=0.03), increased norepinephrine dosages ($P$=0.03) and elevated levels of creatine kinase ($P$<0.0001), creatinine ($P$=0.04) and lactate ($P$=0.02) before cardiopulmonary resuscitation compared with those undergoing CCPR. After equalising these parameters significant differences were observed in short and long-term survival, favouring ECPR over CCPR (27% vs. 17%; $P$=0.01 (short-term) and 23.1% vs. 11.5%; $P$=0.008 (long-term); median follow-up duration after discharge 1136 days (interquartile range 823–1416)). There was no significant difference in the incidence of a cerebral performance categories score of 1 or 2 between the matched groups (CCPR 66.7% vs. ECPR 83.3%; $P$=0.77). ECLS implantation was the only significant and independent predictor of mortality in multivariate Cox regression analysis (hazard ratio 0.57, 95% confidence interval 0.35–0.90; $P$=0.02).

**Conclusion:** In our cohort of cardiovascular patients ECPR was associated with better short- and long-term survival over CCPR, with a good neurological outcome in the majority of the patients with refractory in-hospital cardiac arrest.

## Keywords

Cardiopulmonary resuscitation, extracorporeal life support, in-hospital cardiac arrest, neurological outcome

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## Introduction

Cardiopulmonary resuscitation (CPR) is associated with low success rates and high variability in survival. The estimated incidence of in-hospital cardiac arrest (IHCA) is one to six per 1000 admissions.[1,2] Data regarding the survival to hospital discharge after IHCA are scant but estimates vary between 15% and 40%.[2–4] Several factors are related to the outcome, including immediate recognition of cardiac arrest (CA), early CPR, rapid defibrillation, initial rhythm, underlying cause of CA, duration of CPR and initial resuscitation effort as well as integrated post-CA care.[2] To improve survival by enhancing perfusion during resuscitation, a variety of alternatives to conventional cardiopulmonary resuscitation (CCPR) have been developed.[5]

Extracorporeal life support (ECLS) systems using extracorporeal membrane oxygenation have been proposed as a therapeutic option for refractory CA when other means of resuscitation have failed.[5–8] ECLS can be implanted within 10–15 minutes while the patient is undergoing resuscitation.[6] This has been shown even for prehospital implantation by non-surgeons to have promising results.[9] Rapid ECLS treatment in refractory CA is sufficient for organ support, cerebral and myocardial perfusion and oxygenation, and expeditiously improves the metabolic state after circulatory arrest.[6,7,10] It may also offer a prolonged timespan for diagnostic work-up such as coronary angiography and subsequent percutaneous coronary intervention. Cardiogenic shock occurs in 5–10% of patients with acute coronary syndrome and remains the leading cause of in-hospital mortality in these patients. Previous studies have shown that early revascularisation improves the clinical outcome of patients who present with cardiogenic shock as well as those who are resuscitated after CA.[7,11,12] The current guidelines for CPR and emergency cardiovascular care recommend that ECLS should be considered in CPR when the patient's time without blood flow is short and the condition leading to CA is deemed reversible or amenable to heart transplantation or revascularisation (class IIb, LOE C).[5]

Published data illustrate the ease of ECLS application with encouraging survival rates in patients with refractory IHCA, ranging from 23% to 42%.[6,13–16] In contrast, ECLS implantation during CPR has been described as an independent predictor of in-hospital mortality and there is little evidence concerning the benefit of the procedure compared with CCPR.[6,17] ECLS treatment might also increase the rate of complications in post-resuscitation care.[8,17,18] Therefore, identifying patients with IHCA who might benefit from ECLS while undergoing CPR or while in cardiogenic shock represents a clinical challenge. Consequently, the routine use of ECLS for haemodynamic stabilisation is still under scrutiny. The aim of the present study was to compare the survival and neurological outcome of patients receiving CCPR to those receiving ECLS during CPR (ECPR).

## Methods

### *Study population and data collection*

We retrospectively analysed data from 353 patients who had undergone CPR for IHCA. Data were collected in a highly specialised centre for cardiovascular medicine that included departments of cardiology, cardiothoracic surgery and pulmonary medicine specialised in the treatment of chronic pulmonary hypertension. All patients were admitted to hospital due to cardiovascular reasons. Data were collected retrospectively from the coding system as well as from patients' charts. As all patients were monitored after cardiac surgery or percutaneous interventions using wireless telemetry on intensive and intermediate care units and on normal wards, all included patients had witnessed IHCA. All patients with an index date between January 2009 and January 2013 were included. The follow-up was completed in January 2014 so that there was at least a one-year follow-up period for all patients. Those who received ECLS with CPR were assigned to the ECPR group, and those who did not have ECLS were assigned to the CCPR group.

All included patients had witnessed IHCA and were initially treated by a medical emergency team trained in the technique and management of advanced life support according to the current guidelines.[2] After receiving notification of an ongoing CPR by the medical emergency team, the ECLS team was activated and prepared for ECLS implantation. The ECLS team was available at all times (24/7) and consisted of an interventional cardiologist, a cardiac surgeon and a perfusionist. ECLS implantation was implemented in adult patients who experienced witnessed IHCA and in whom CCPR for more than 10 minutes did not result in return of spontaneous circulation (ROSC) (Figure 1). There was no age limit for inclusion. An arrest was presumed to be of cardiac aetiology unless it was known or likely to have been caused by trauma, drug overdose, or any other non-cardiac cause as best determined by the ECLS team. CA with post-cardiotomy bleeding was also classified as being of cardiac origin. CPR duration was defined as the interval between initiation of CPR and ROSC or death in the CCPR group, and as the interval between initiation of CPR and ECLS implantation in the ECPR group. Return of spontaneous heartbeat was identified by echocardiography in the ECPR group and by palpable central pulse in the CCPR group.

ECLS was set up if the following criteria were met:

- Witnessed IHCA;
- Refractory CA, defined as the absence of ROSC after conventional CPR;
- Absence of severe co-morbidities that would have precluded ICU treatment;
- Condition leading to CA presumed to be reversible or eligible for revascularisation or heart transplantation.

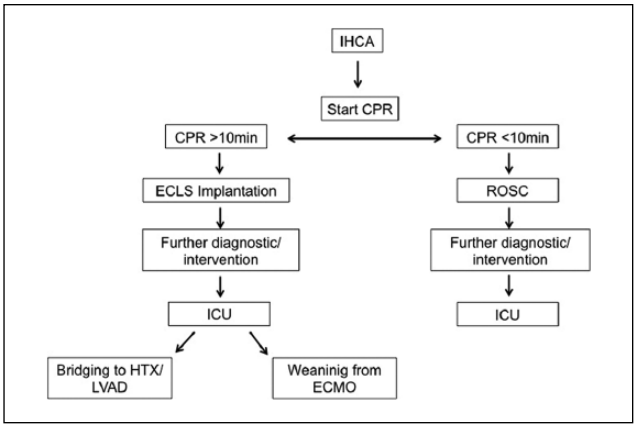


**Figure 1.** Flowchart of patient care after in-hospital cardiac arrest.
CPR: cardiopulmonary resuscitation; ICU: intensive care unit; HTX: heart transplantation; LVAD: left ventricular assist device; ROSC: return of spontaneous circulation.

Contraindications for ECLS implantation were known terminal malignancies, severe trauma, aortic dissection, severe aortic failure, coagulation disorders, uncontrollable haemorrhage, irreversible brain damage and signed consent for 'do not resuscitate'.

ECLS implantation was performed by percutaneous vessel cannulation or by surgical cut-down cannulation. The decision about the implantation technique was left to the ECLS team.

None of the patients received CPR with a chest compression device. None of the patients in the ECPR group received an intra-aortic balloon pump (IABP). In the CCPR group 29/301 patients received an IABP. In order to keep the focus of this study on comparing the outcome of ECPR and CCPR and to allow a meaningful comparison of the groups, all patients who received an IABP in the CCPR group were excluded. The post-CA treatment regimen as well as the decision to induce therapeutic hypothermia after ROSC in the absence of contraindications (class IIb, LOE B)[2] was left to the intensive care unit (ICU) physicians.

The initial rhythm and the different time points (duration of CPR) as well as procedural characteristics and the clinical course of post-CA care were taken from the hospital records. In all patients, the baseline left ventricular ejection fraction (LVEF) was determined at the time of hospital admission. Assessment of the LVEF was performed using the biplane method of discs (modified Simpson's rule).

Routine laboratory parameters, including estimated glomerular filtration rate, pH, serum creatinine, creatine kinase, lactate dehydrogenase, aspartate transaminase and lactate levels were measured on admission (pre-resuscitation) and immediately after CPR as well as during the post-CA care using standardised methods. Biomarker levels were included to classify the severity of illness with regard to a prognostic value.

The duration of survival was designated as the time from CPR to death or survival and was assessed at 30 days, one year and in the long-term follow-up. The follow-up was performed by telephone interview. Neurological status was assessed by using the cerebral performance categories (CPC) score.[19] The performance categories are defined as follows: CPC 1, conscious and alert with normal function or only slight disability; CPC 2, conscious and alert with moderate disability; CPC 3, conscious with severe disability; CPC 4, comatose or in a persistently vegetative state; and CPC 5, certified brain death or dead by traditional criteria. Good neurological outcome was defined by a score of 1 or 2. The CPC score was calculated on the basis of discharge summary abstracts, medical records and the telephone call during the follow-up assessment. Good neurological outcome was defined by a score of 1 (good recovery) or 2 (moderate disability). The CPC score was calculated on the basis of discharge summary abstracts, medical records and the results of the telephone interview.

The local ethics committee of the Justus Liebig University of Giessen Medical School approved this study (file number 23/14) according to the principles of the Declaration of Helsinki. The requirement for individual patient consent was waived because of the study's retrospective design.

## *ECLS system and procedure*

Details of the ECLS technique and management have been described previously.[6,7] In brief, ECLS support consisted of a Rotaflow Maquet centrifugal pump (MAQUET Cardiopulmonary AG, Hirrlingen, Germany) and a polymethylpentene fibre oxygenator module (EUROSETS, ECMO mini-bypass set, Corm. D, Medolla, Italy). Percutaneous cannulation of the femoral artery and vein was performed using the Seldinger technique or by surgical cut-down cannulation with size 16–18 French catheters for arterial cannulation (Edwards Lifesciences, Unterschleissheim, Germany) and size 22 French catheters for venous cannulation (Avalon Elite, Rancho Dominguez, USA). Tubing, pump, and oxygenator were all coated with Bioline coating (MAQUET Cardiopulmonary AG).

To reduce the risk of limb ischaemia, an anterograde reperfusion catheter (8 French) was inserted for distal limb perfusion. During the procedure, unfractionated heparin was administered to avoid coagulation in the membrane oxygenator with an activated clotting time of 160–180 seconds. Pump blood flow was initially set at 3–4 L/minute. Additional fluids, blood transfusion, and/or catecholamines were administered, if necessary, to achieve an arterial blood pressure >60 mmHg, oxygen partial pressure >100 mmHg and normocapnia to optimise organ perfusion. If possible, beating heart circulation was maintained to reduce the risk of left ventricular over-tension and intra-cardiac thrombus formation. To avoid pulmonary collapse during ECLS,

minimal lung ventilation was maintained. Invasive blood pressure was routinely measured in the right radial artery. The ECLS-related complications were defined as cannula site complication (bleeding requiring transfusion of at least 2 units and ECLS), retroperitoneal haemorrhage and lower limb ischaemia.

In patients with assumed myocardial ischaemia as a cause of IHCA, coronary angiography was performed immediately after ECLS implantation and percutaneous coronary intervention was carried out if deemed necessary. According to the current CPR guidelines, all patients underwent mild therapeutic hypothermia (32–34 °C) for 24 hours. If the patient's haemodynamic status remained stable with low levels of inotropes and vasopressors and a $PaO_2/FiO_2$ index >200, weaning was attempted by a stepwise reduction of the ECLS pump flow. ECLS was surgically removed upon continued haemodynamic stability. Further transthoracic echocardiographic evaluation was routinely performed as a part of the weaning process. In all patients, baseline LVEF was determined directly after ECLS implantation in the catheter laboratory and then every 24 hours as part of the weaning protocol as well as after successful weaning from the ECLS. Left ventricular volumes were measured from the apical four and two-chamber views.

### *Statistical analysis*

All data were analysed retrospectively. Data for categorical variables are expressed as numbers and percentages. For continuous variables, data are reported as the mean ± standard deviation (SD) or as the median with interquartile range (IQR) where appropriate. After testing for normal distribution, differences were compared with unpaired Student's t tests or with the Mann–Whitney test. Fisher's exact test or the chi-square test was used for categorical variables with nominal scales.

A propensity score analysis was performed to reduce the effects of selection bias and potential confounding factors. The propensity score, which was the predicted probability of receiving ECPR with the covariates, was derived using multiple logistic regression analysis. All of the covariates such as age, gender, LVEF and all parameters revealed in the univariate analysis to be predictive of mortality were used in the propensity score. Propensity score-matched 1:1 pairs were derived from a next-neighbour approach using cluster analysis. CPR duration was additionally adjusted during the matching process using the propensity score. After the propensity score matching was performed, we again compared the covariates between the two groups.[20]

Univariate Cox regression analyses were performed with mortality as the outcome variable. The following predictors were tested: age, APACHE II score, obesity, CPR duration, glomerular filtration rate (pre-CPR), creatinine (pre-CPR), creatine kinase, pH (pre-CPR), lactate (pre-CPR), LVEF (pre-CPR), treatment duration in the ICU before CA, acute myocardial infarction, ECLS, intubation before CA and location of CPR. The impact of discrete variables was tested using Kaplan–Meier survival analysis. Predictors with $P \leqslant 0.10$ were entered into multivariate Cox regression analysis.

Statistical tests were performed with SPSS software version 20.0. A two-tailed $P$ value <0.05 was considered statistically significant.

## Results

In summary missing values of all variables were <20% except of baseline lactate concentration. Baseline lactate concentration was missing in 30% of the cases. The baseline characteristics of all patients are shown in Table 1. The unmatched groups (CCPR vs. ECPR) showed several significant differences in variables such as age, APACHE II score and norepinephrine dosage. Aside from the proportion of patients with coronary artery disease, which was higher in the CCPR group ($P$=0.01), there were no significant differences between the groups in the main diagnoses at the time of admission. Median CPR duration in patients in whom ECLS was applied was also significantly longer compared with patients with CCPR.

After equalising these parameters in the propensity score 1:1 matching process there were no significant differences in baseline characteristics, main diagnosis at time of admission, procedures, and pre-resuscitation biomarker levels between the matched CCPR (M-CCPR) and ECPR (M-ECPR) groups (Table 2). The proportion of patients who were intubated before CA occurred was significantly higher in patients in whom ECLS was applied. Pre-resuscitation treatment duration in the ICU was significantly longer in patients with M-CCPR compared with those with M-ECPR. CA occurred more frequently in the ICU in patients with M-CCPR. CA in the catheter laboratory/operating room was more frequent in the M-ECPR group compared with the M-CCPR group. There were no differences between the groups regarding the first documented rhythm by the medical emergency team (Table 3). There were also no significant differences in the rate of therapeutic hypothermia ($P$=0.16) or in the maximum norepinephrine dosage during post-CA care between the groups ($P$=0.62). During post-CA care ischaemia of the access site leg was significantly more frequent in patients with M-ECPR as were bleeding complications necessitating transfusions. A total of three patients from the M-ECPR group were bridged to left ventricular assist device or heart transplantation.

The median follow-up duration after hospital discharge was 1136 days (IQR 823–1416). No significant differences were observed in long-term survival between the unmatched groups (CCPR: 37.5% vs. ECPR 23.1%; $P$=0.15). In the propensity score 1:1 matched groups significant differences

**Table 1.** Comparison of baseline clinical characteristics of unmatched CCPR and ECPR groups.

| Variable | CCPR (n=272) | ECPR (n=52) | *P* value |
|---|---|---|---|
| Male gender, n (%) | 167 (61.4) | 28 (53.8) | 0.69 |
| Age in years, median (IQR) | 75.29 (67.4–79.1) | 72 (55–77.9) | **0.02** |
| Pre-resuscitation APACHE II score | 16.0 (12.5–19.0) | 21.0 (18–24.0) | **0.03** |
| Pre-resuscitation LVEF in %, median (IQR) | 47.5 (30.5–60.0) | 44.0 (25.0–60.0) | 0.13 |
| CPR duration in min, median (IQR) | 20.0 (5.5–40.0) | 33.0 (19.0–47.0) | **0.001** |
| History, n (%) | | | |
| Hypertension | 174 (64.0) | 38 (73.1) | 0.27 |
| Current smoker | 30 (11.0) | 9 (17.3) | 0.24 |
| Diabetes | 82 (30.2) | 14 (26.9) | 0.74 |
| Obesity (body mass index >30kg/m²) | 163 (59.9) | 24 (46.2) | 0.07 |
| Dyslipidemia | 109 (40.1) | 28 (53.9) | 0.07 |
| Family history of CAD | 16 (5.9) | 5 (9.6) | 0.35 |
| Main diagnoses at admission, n (%) | | | |
| AMI | 58 (21.3) | 15 (28.9) | 0.28 |
| CAD (non-AMI) | 103 (37.9) | 8 (15.4) | **0.01** |
| Valvular heart disease | 68 (25.0) | 16 (30.8) | 0.39 |
| Dilated cardiomyopathy | 17 (6.3) | 6 (11.5) | 0.17 |
| Tako Tsubo cardiomyopathy | 2 (0.7) | 0 (0) | 0.54 |
| Heart transplantation waiting list | 1 (0.4) | 1 (1.9) | 0.30 |
| Pulmonary embolism | 7 (2.6) | 3 (5.8) | 0.21 |
| Other | 16 (5.9) | 3 (5.8) | 1.0 |
| Pre-resuscitation biomarker levels, median (IQR) | | | |
| pH | 7.39 (7.31–7.44) | 7.38 (7.31–7.46) | 0.85 |
| Lactate in mmol/L | 2.0 (1.2–4.0) | 3.6 (1.6–8.4) | **0.02** |
| Creatine kinase in U/L | 143 (69–426) | 162 (64–596) | **0.001** |
| Estimated glomerular filtration rate in ml/min/1.73 m³ | 66.21 (42.3–90.8) | 54.4 (28.8–79.3) | **0.04** |
| Creatinine in mg/dL | 1.16 (0.88–1.67) | 1.22 (0.82–2.20) | **0.04** |
| Location of cardiac arrest | | | |
| Normal care unit | 5 (1.8) | 0 (0) | 1.0 |
| Emergency room | 4 (1.5) | 0 (0) | 0.63 |
| Intensive care unit | 189 (69.5) | 17 (32.7) | **0.0001** |
| Catheter laboratory | 47 (17.3) | 13 (25.0) | 0.17 |
| Operating room | 19 (7.0) | 20 (38.5) | **0.0001** |
| Other | 1 (0.4) | 0 | 1.0 |
| Not reported | 7 (2.6) | 2 (3.8) | n.a. |
| First documented rhythm by the MET, n (%) | | | |
| Sinus rhythm without atrioventricular block II–III | 174 (64.0) | 32 (61.5) | 1.0 |
| Arrhythmia absoluta | 57 (21.0) | 15 (28.9) | 0.21 |
| Atrioventricular block III | 14 (5.2) | 1 (1.9) | 0.48 |
| Ventricular tachycardia | 8 (2.9) | 1 (1.9) | 1.0 |
| Asystole | 14 (5.2) | 0 (0) | 0.14 |
| Pulseless electrical activity | 5 (1.8) | 0 (0) | 1.0 |
| Not reported | 0 (0) | 3 (5.8) | n.a. |
| Pre-resuscitation dosage of catecholamines | | | |
| Norepinephrine in µg/kg/min, median (IQR) | 0.09 (0.04–0.17) | 0.17 (0.06–0.65) | **0.03** |
| Epinephrine in µg/kg/min, median (IQR) | 0.16 (0.06–0.39) | 0.33 (0.22–0.39) | 0.73 |
| Dobutamine in µg/kg/min, median (IQR) | 4.61 (3.70–7.82) | 5.05 (3.45–7.53) | 0.60 |

Data are shown as n (%) and median (IQR). Numbers in bold are statistically relevant.
AMI: acute myocardial infarction; CAD: coronary artery disease; CCPR: conventional cardiopulmonary resuscitation; ECPR: extracorporeal life support in cardiopulmonary resuscitation; MET: medical emergency team; LVEF: left ventricular ejection fraction; IQR: interquartile range.

were observed in short-term, one-year, and long-term survival (Figure 2; Table 3), favouring M-ECPR over M-CCPR (14 out of 52 (27.0%) vs. nine out of 52 (17.3%); *P*=0.01 (short-term), 12 out of 52 (23.1%) vs. seven out of 52 (13.5%); *P*=0.007 (one-year) and 12 out of 52 (23.1%) vs. six out of 52 (11.5%); *P*=0.008 (long-term)). Refractory

**Table 2.** Comparison of baseline clinical characteristics of matched CCPR and ECPR groups.

| Variable | Matched CCPR (n=52) | Matched ECPR (n=52) | *P* value |
|---|---|---|---|
| Male gender, n (%) | 31 (59.62) | 28 (53.9) | 0.69 |
| Age in years, median (IQR) | 73 (68–78) | 72 (55–77.9) | 0.28 |
| Pre-resuscitation APACHE II score | 18.0 (15–22.0) | 21 (18–24.0) | 0.14 |
| Pre-resuscitation LVEF in %, median (IQR) | 50 (31–63.0) | 44 (25–60.0) | 0.77 |
| History, n (%) | | | |
| Hypertension | 31 (59.2) | 38 (73.1) | 0.21 |
| Current smoker | 6 (11.5) | 9 (17.3) | 0.58 |
| Diabetes | 17 (32.7) | 14 (26.9) | 0.67 |
| Obesity (body mass index >30kg/m²) | 29 (55.8) | 24 (46.2) | 0.43 |
| Dyslipidemia | 25 (48.1) | 28 (53.9) | 0.7 |
| Family history of CAD | 5 (9.6) | 5 (9.6) | 1.0 |
| Main diagnoses at admission, n (%) | | | |
| AMI | 19 (36.6) | 15 (28.9) | 0.53 |
| CAD (non-AMI) | 7 (13.5) | 8 (15.4) | 1.0 |
| Valvular heart disease | 11 (21.2) | 16 (30.8) | 0.37 |
| Dilated cardiomyopathy | 7 (13.5) | 6 (11.5) | 1.0 |
| Heart transplantation waiting list | 0 (0) | 1 (1.9) | 1.0 |
| Pulmonary embolism | 2 (3.9) | 3 (5.8) | 1.0 |
| Other | 6 (11.5) | 3 (5.8) | 0.49 |
| Procedures, n (%) | | | |
| Primary coronary intervention | 17 (32.7) | 9 (17.3) | 0.11 |
| CABG | 10 (19.2) | 10 (19.2) | 1.0 |
| CABG + other procedures | 5 (9.6) | 6 (11.5) | 1.0 |
| Aortic valve replacement | 8 (15.4) | 13 (25) | 0.33 |
| Mitral valve replacement | 4 (7.7) | 4 (7.7) | 1.0 |
| Pulmonary endarterectomy | 0 (0) | 2 (3.9) | 0.5 |
| Heart transplantation | 0 (0) | 3 (5.8) | 0.2 |
| Other procedures | 13 (25) | 5 (9.6) | 0.07 |
| Frequency of procedures, mean (SD) | 1.1 (0.63) | 1.0 (0.39) | 0.5 |
| Pre-resuscitation biomarker levels, median (IQR) | | | |
| pH | 7.39 (7.28–7.44) | 7.38 (7.31–7.46) | 0.40 |
| Lactate in mmol/L | 2.4 (1.4–8.5) | 3.6 (1.6–8.4) | 0.74 |
| Creatine kinase in U/L | 110 (70–402) | 162 (64–596) | 0.07 |
| Lactate dehydrogenase in U/L | 230 (196–313) | 269 (191–341) | 0.41 |
| Aspartate transaminase in U/L | 30 (23–46) | 33.5 (24–93) | 0.38 |
| Estimated glomerular filtration rate in ml/min/1.73 m³ | 55.04 (35.9–81) | 54.4 (28.8–79.3) | 0.83 |
| Creatinine in mg/dL | 1.1 (0.9–2.2) | 1.2 (0.8–2.2) | 0.81 |

Data are shown as n (%), mean (SD) and median (IQR).
AMI: acute myocardial infarction; CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; CCPR: conventional cardiopulmonary resuscitation; ECPR: extracorporeal life support in cardiopulmonary resuscitation; LVEF: left ventricular ejection fraction; IQR: interquartile range.

cardiogenic shock was the main cause of death in both groups (M-ECPR: 25 out of 52 (48.1%) vs. M-CCPR: 35 out of 52 (67.3%); *P*=0.07). Further causes of death were multiple organ failure (M-ECPR: seven out of 52 (13.5%) vs. M-CCPR: three out of 52 (5.8%); *P*=0.32), refractory ventricular fibrillation (M-ECPR: one out of 52 (1.9%) vs. M-CCPR: three out of 52 (5.8%); *P*=0.62) and ventricular perforation (M-ECPR: one out of 52 (1.9%) vs. M-CCPR: two out of 52 (3.9%); *P*=1.0). Brain death occurred in one patient of the M-CCPR group. In two patients of the M-CCPR group and six patients of the M-ECPR group the cause of death was not reported.

No significant differences were observed in the incidence of a CPC score of 1 or 2 in short-term, one-year and long-term follow-up periods (Table 3). In the long-term follow-up four out of six (66.7%) of the long-term survivors in the M-CCPR group and 10 out of 12 (83.3%) of the long-term survivors in the M-ECPR group had a CPC score of 1 or 2 (*P*=0.77).

In univariate Cox regression analysis the following factors were associated with mortality: age, APACHE II score, ECLS implantation, intubation before CA and diagnosis of an acute myocardial infarction (Supplementary Table 1). For further clarification, multivariate Cox regression analysis was carried out for the factors associated with mortality.

**Table 3.** Comparison of the resuscitation and post-resuscitation characteristics of the matched CCPR and ECPR group.

| Variable | Matched CCPR (n=52) | Matched ECPR (n=52) | *P* value |
|---|---|---|---|
| CPR characteristics | | | |
| CPR duration in min, median (IQR) | 37.0 (30.0–45.0) | 33.0 (19.0–47.0) | 0.4 |
| Therapeutic hypothermia, n (%) | 2 (3.8) | 7 (13.5) | 0.16 |
| Location of cardiac arrest, n (%) | | | |
| General ward | 1 (1.9) | 0 (0) | 1.0 |
| Intensive care unit | 34 (65.4) | 17 (32.7) | **0.02** |
| Catheter laboratory/cardiac surgery room | 15 (28.9) | 35 (67.3) | **0.001** |
| Other | 2 (3.9) | 0 (0) | n.a. |
| First documented rhythm by the MET, n (%) | | | |
| Sinus rhythm without atrioventriuclar block II–III | 29 (55.8) | 32 (61.5) | 1.0 |
| Arrhythmia absoluta | 13 (25.0) | 15 (28.9) | 0.83 |
| Atrioventricular block III | 3 (5.8) | 1 (1.9) | 0.36 |
| Ventricular tachycardia | 2 (3.9) | 1 (1.9) | 1.0 |
| Asystole | 2 (3.9) | 0 (0) | 0.5 |
| Pulseless electrical activity | 3 (5.8) | 0 (0) | 0.24 |
| Not reported | 0 (0) | 3 (5.8) | n.a. |
| Complications during post-CA care, n (%) | | | |
| Malperfusion of the leg | 1 (1.9) | 9 (17.3) | **0.02** |
| Bleeding or haematoma with need for transfusion | 7 (13.5) | 17 (32.7) | **0.03** |
| Sepsis/systemic inflammatory response syndrome | 5 (9.6) | 4 (7.7) | 0.87 |
| Acute kidney failure | 5 (9.6) | 1 (1.9) | 0.2 |
| CPC score in 30-day survivors, n (%) | Survivors n=9 (17.3) | Survivors n=14 (26.9) | |
| CPC score 1 and 2 | 7 (77.8) | 11 (78.6) | 0.53 |
| CPC score in one-year survivors, n (%) | Survivors n=7 (13.5) | Survivors n=12 (23.1) | |
| CPC score 1 and 2 | 6 (85.6) | 10 (83.3) | 0.56 |
| CPC score in long-term follow-up, n (%) | Survivors n=6 (11.5) | Survivors n=12 (23.1) | |
| CPC score 1 and 2 | 4 (66.7) | 10 (83.3) | 0.77 |

Data are shown as n (%) and median (IQR). Numbers in bold are statistically relevant.
CA: cardiac arrest; CAD: coronary artery disease; CPR: cardiopulmonary resuscitation; CCPR: conventional cardiopulmonary resuscitation; CPC: cerebral performance scale; ECPR: extracorporeal life support in cardiopulmonary resuscitation; ICU: intensive care unit; MET: medical emergency team; IQR: interquartile range.

ECLS remained the only significant and independent predictor of long-term mortality in the multivariate Cox regression analysis. Subgroup survival analysis of the M-ECPR group revealed no significant differences between survivors and non-survivors regarding bleeding complications and the frequency of limb ischaemia. (See Supplementary Material Table 1, available online).

## Discussion

During IHCA prolonged CPR is associated with poor outcomes. Only a few of the patients in whom ROSC can be achieved are able to return to their former lives without complications.[2,3,7,16] In a large database of 64,339 patients with IHCA 49% achieved ROSC and 15% survived to discharge.[3] However, in nearly half of the patients in whom ROSC was achieved it occurred within 10 minutes after the onset of CA, in one quarter during the subsequent 10 minutes, and in only 6% after a CPR duration of more than 30 minutes.[3,21] ECLS during CPR to restore blood flow in patients with IHCA not responding to CCPR has been reported to enhance survival.[6,8,13–17,22,23] Reports about survival to discharge for patients with IHCA and ECPR are inconsistent, however, and vary from 15% to 42%.[6,8,13–17,23,24] Few of these studies report long-term survival (defined by survival for at least one year after CA), which ranges from 19% to 26%.[6,15,16]

The aim of the present study was to provide detailed data about short and long-term survival as well as the neurological outcome in patients with ECPR and CCPR in a propensity-matched patient cohort. The results demonstrate that short and long-term survival was significantly better in patients undergoing ECPR compared with CCPR, with the majority of the patients exhibiting a good neurological outcome.

Shin and colleagues performed an observational study of adults with IHCA who received CPR for more than 10 minutes.[25,26] Although the study was not randomised, propensity score matching was performed to eliminate confounding factors. As in the present study, their data demonstrated a benefit of ECPR over CCPR with regard to short and long-term survival as well as neurological outcome.[25,26] In contrast to Shin and colleagues we collected

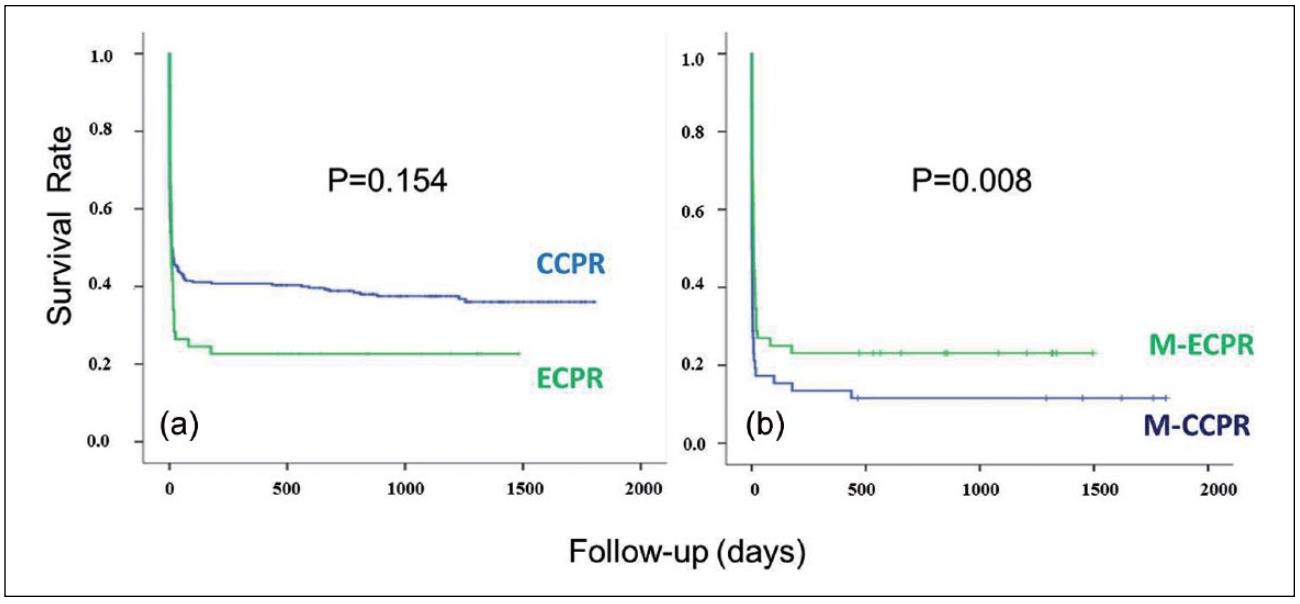


**Figure 2.** (a) Kaplan–Meier survival analysis for the unmatched ECPR and CCPR group; (b) Kaplan–Meier survival analysis for the matched ECPR and CCPR group.

data of patients at a specialised heart centre. All patients who were included were admitted to hospital due to cardiac issues. Therefore, our data most likely represent a more homogeneous patient cohort. Data were collected concerning the frequency of access-related complications, which was considered to be a prognostic factor in recent publications. In addition, our study presents a more up-to-date patient cohort as the latest technology in extracorporeal membrane oxygenation (ECMO) devices, including cannulas and the ICU standards, was used. Especially with regard to device-related complications such as major bleeding or leg ischaemia, this seems to play an important role. Thus, we present an acceptable rate of device-related complications such as malperfusion of the access site, information that is absent in the data of Shin and colleagues.

In our unmatched study cohort, patients who received extracorporeal haemodynamic support were younger and initially had a higher dosage of vasopressor agents, impaired renal function, elevated lactate and creatine kinase levels, and higher APACHE II scores. The most important finding of our study is that after equalising these parameters significant differences were observed in short and long-term survival, favouring M-ECPR over M-CCPR. In addition, a good neurological outcome (defined by a CPC score of 1 or 2) was observed in 83% of the M-ECPR survivors during the one-year and long-term follow-up periods. In recent studies a good neurological outcome after ECPR varies between 23.6% and 93% compared with 16% and 81% in patients with CCPR.[3,6,14,19,27] The reported rates of good neurological survival in patients with ECPR, however, are based on single-centre experiences and small patient numbers.[6,7,14,27] The observations in our M-ECPR cohort might be attributed to the sufficient perfusion of vital organs provided by ECLS during treatment of the cause of CA and/or while waiting for recovery of the injured myocardium. In addition, in experimental animal models a sufficient brain and peripheral organ saturation after ECLS initiation as well as a significant increase in coronary perfusion pressure, which is a cornerstone of ROSC after CA, was demonstrated.[10,28,29]

Several studies have reported that ECLS implantation during CPR increases the risk of death in patients with cardiogenic shock.[17,23] Beurtheret and colleagues noted a survival rate in patients with ECPR of 8% (one out of 13) and identified ECLS initiation during CPR as a factor associated with in-hospital mortality in their cardiac RESCUE programme.[17] The devastating outcome for patients in whom ECLS was implanted under ongoing CPR reported in the RESCUE programme might be explained by the additional delay of at least 30 minutes to reach the patients.[17] In comparison, in our study cohort the median CPR duration in patients with ECPR was 33 minutes. Several studies demonstrated that the longer the time interval before ECLS implantation, the poorer the outcome;[7,8,16,23,24] therefore, rapid ECLS implantation might have great potential for decreasing the mortality rate of patients with IHCA. If ECLS is considered, all efforts should be made to minimise the time from CA to ECLS flow.

ECLS-related complications including leg ischaemia and major bleeding are common and have been reported to influence morbidity and mortality rates negatively for emergency ECLS.[8,14,17,18,24,30] Complications reported in the literature range from 33% to 84%, depending on the different definitions.[14,18,30] We observed malperfusion of the access site leg in 17% and bleeding complications with the need for transfusion in 33% of the ECLS patients. Belle et al. reported

a combined complication rate of 84% pertaining to a combination of access site and ECLS treatment complications, which makes it difficult to compare the results with other observational studies.[18] However, they reported a lower limb ischaemia of nearly 18%, which is similar to our results.[18] A meta-analysis of 1763 patients with variable criteria for applying ECLS revealed a bleeding rate up to 33%, also in line with our results.[30] Nevertheless, in patients in whom conditions apply that are usually associated with a high risk of death the survival benefit clearly outweighs potential complications. This is especially evident from the results of the multivariate Cox regression analysis, which demonstrated that ECLS was the only significant and independent predictor of long-term mortality in our cohort. In addition, an association between complications and mortality was ruled out in the subgroup analysis of the survivors and non-survivors in the M-ECPR group.

These data demonstrate that ECLS implantation during CPR is associated with a higher survival rate in patients with IHCA and prolonged CPR in whom ROSC could not be achieved. Furthermore, a good neurological outcome was documented in the majority of the patients. Despite these promising results, ECLS should not be considered in cases in which the risks and use of hospital resources outweigh the chance of success. Whether determining an upper limit of CPR duration before deploying ECLS results in better survival and neurological outcome than CCPR remains unknown.[21]

### *Limitations*

One of the major limitations to our study is the small number of patients from a single centre and the retrospective study design.

The propensity score approach was used to reduce selection bias and confounding factors. A key limitation in our propensity score-adjusted analysis, however, is that bias could remain if there are unmeasured or unknown confounders that are not incorporated into the propensity score. Hence, we were able to demonstrate an association between the use of ECPR and a better outcome, but we cannot conclude that ECPR is the cause of the better outcome because we cannot rule out that other unknown factors may have played a role.

Due to the fact that nearly all patients had CA in a monitored zone, no-flow times were not reported. Furthermore, the levels of biomarkers we analysed were not available for all patients at the same time points, and in some patients pre-resuscitation and post-CA laboratory measurements were incomplete.

Data were collected in a highly specialised centre for cardiovascular medicine. The organisation of the ECLS team was well structured and timeframes and distances were very short. The ECLS team members, including an interventional cardiologist, a cardiac surgeon and a perfusionist, were available at all times (24/7), which is not common in smaller hospitals. Most importantly, cardiologists are trained to implant the ECLS without the support of surgeons if necessary. These factors have to be taken into account in interpreting the results.

## Conclusion

In cardiovascular patients with observed refractory IHCA we observed significant differences in short and long-term survival, favouring ECPR over CCPR, with a good neurological outcome in the majority of the patients.

### Conflict of interest

The authors declare that they have no conflict of interest.

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