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ORIGINAL PAPER

Outcome of elderly undergoing extracorporeal life support in refractory cardiogenic shock

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Abstract
Background The current study presents data from a real-world cohort of patients with refractory cardiogenic shock (CS) undergoing extracorporeal life support (ECLS) focusing on the comparison of elderly versus younger patients.
Methods and results One hundred consecutive patients with refractory CS underwent percutaneous ECLS implantation performed by interventional cardiologists. Follow-up was performed at hospital discharge as well as at a median of 18 months [interquartile range 15–36]. Patients were grouped according to median age (≤60 versus >60 years). ECLS could be weaned in more than half of the cohort ($n = 56$, 56%) with no differences between the age groups ($p = 1.00$). Despite similar rates of initial haemodynamic stabilisation, in-hospital mortality was higher in patients >60 years (82% versus 58%, $p = 0.02$). At mid-term follow-up, only three patients were alive in the group of patients >60 years. This resulted in a mortality rate of 94% in the elderly in comparison with 68% in patients aged ≤60 years ($p = 0.001$).
Conclusions Despite a high rate of initial successful ECLS weaning, mid-term prognosis of patients with CS undergoing ECLS above the age of 60 years is poor with superior results in patients aged ≤60 years.

Keywords Refractory cardiogenic shock · Active support device · Extracorporeal life support · Prognosis · Age

Introduction

Mortality of cardiogenic shock (CS) remains high despite modern treatment strategies [1–4]. Active support devices, such as extracorporeal life support (ECLS), are often the only option to achieve haemodynamic stability in patients with refractory CS. In recent years, ECLS use has risen considerably and found its way into clinical routine [5, 6]. Data on prognosis in patients treated with ECLS are scarce and limited to retrospective observational registry-based analyses, including fairly young patients [7–11]. However, the vast majority of CS patients are elderly and age has consistently been shown to have a high prognostic impact in CS [1, 3, 12, 13]. Thus, especially, elderly patients are at high risk for adverse clinical outcome. Implantation of active assist devices may also be an option to improve prognosis in this subset of high-risk patients. Despite the high proportion of elderly in CS and their poor outcome, prognosis of elderly patients undergoing ECLS has up to date not been specifically analysed. The aim of this analysis is to objectify complications and survival in elderly in comparison with younger patients with refractory CS undergoing ECLS.

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Methods

Patients

Data of all consecutive patients undergoing ECLS from January 2008 to January 2016 at two tertiary care centres were prospectively entered into electronic hospital registries. Additional data required for this analysis were retrospectively evaluated. Only patients with refractory CS were included, whereas patients undergoing ECLS implantation due to non-cardiac causes or post-operative CS were excluded. The analysis was approved by the local ethics committee.

The diagnosis of CS was made on established criteria, including (i) systolic blood pressure <90 mmHg for >30 min or vasopressors required to achieve a blood pressure ≥90 mmHg; (ii) pulmonary congestion or elevated left ventricular filling pressures; and (iii) signs of impaired organ perfusion with at least one of the following criteria: (a) altered mental status; (b) cold, clammy skin; (c) oliguria; and (d) increased serum lactate. All patients included in the current analysis underwent ECLS due to refractory CS defined as critical circulatory failure resulting in organ hypoperfusion unresponsive to conventional therapy with minimal chance of survival without ECLS. Thus, patients had an increasing demand of inotrope and vasopressor doses at increasing levels of serum lactate prior to ECLS implantation. The likelihood of death in the absence of ECLS was deemed to be extremely high. Possible outcomes had to be (i) ECLS weaning to recovery (bridge to recovery); (ii) heart transplantation (bridge to transplantation); or (iii) implantation of a permanent left ventricular assist device (bridge to bridge). Contraindications for ECLS implantation were severe co-morbidities, such as uncontrollable haemorrhage, irreversible brain damage, severe trauma, terminal multi-organ failure, or known terminal malignancies. The decision for ECLS implantation was performed by a team of cardiologists trained in intensive care medicine and interventional cardiology.

Detailed sets of clinical and functional parameters, such as the Simplified Acute Physiology Score-II, were repeatedly assessed [14]. Furthermore, all patients underwent continuous control of routine laboratory parameters, including serum lactate. Left ventricular ejection fraction was assessed by transthoracic echocardiography. Details on patients' previous medical diagnoses, such as history of symptomatic heart failure, chronic renal insufficiency (≥ stage 3), or peripheral artery disease, were based on the information provided by the treating physician or hospital charts in accordance with guideline definitions [15–17]. Patients were grouped according to median age (≤60 versus >60 years).

Procedure

ECLS implantation was exclusively performed in the catheterisation laboratory by experienced interventional cardiologists. The procedure was carried out independent of working hours or days of the week (24 h/7 days). All patients underwent coronary angiography prior to or at time of ECLS implantation. Additional procedures, such as percutaneous coronary intervention (PCI) or balloon valvuloplasty, were performed according to the standard clinical practice and guideline recommendations. All patients underwent ECLS implantation via a percutaneous femoro-femoral arterio-venous approach. Percutaneous cannulation using ~18 French arterial cannulae and ~22 French venous cannulae was performed using the Seldinger technique. To allow distal limb perfusion, a percutaneously introduced ~6 French antegrade sheath was obligatory. Unfractionated heparin (70 IU/kg body weight) was administered, and the pump blood flow was initially set at 3–4 l/min.

Intensive care treatment

All therapeutic measures (e.g. fluid management, renal replacement therapy, use of antibiotics, or administration of additional medication) were performed according to the standard clinical practice and guideline recommendations [18]. While on ECLS, patients underwent heparinisation with an activated clotting time of 160–180 s. In case of mechanical ventilation, lung protective ventilation was maintained. Although weaning of inotropes and vasopressors was targeted, additional dobutamine, norepinephrine, or epinephrine was administered if necessary for the shortest possible duration at the lowest possible dose to achieve a mean arterial blood pressure >60 mmHg. Transfusions of packed red blood cells, platelets, or fresh frozen plasma were restricted to the presence of clinically relevant bleeding problems.

In general, the therapeutic concept was (i) weaning from vasopressors and inotropes following ECLS implantation, (ii) optimisation of cardiopulmonary conditions while on ECLS (e.g., pulmonary decongestion), and (iii) ECLS weaning. Weaning was considered in case of stable clinical course for >24 h without vasopressor support at stable respiratory conditions (e.g., FiO_2 ≤40%, PEEP 8–10 mmHg). Blood flow was reduced gradually (~10 ml/kg/h) with concomitant reduction of gas flow. If needed, ventilator settings were adapted (e.g., increase in FiO_2) and moderate doses of inotropes were administered.

Physicians working at the intensive care unit were all specifically trained on the ECLS technique and management.

Outcome definitions

The primary outcome was mid-term mortality. Secondary outcomes included in-hospital mortality and mid-term survival with good functional outcome defined as a score of 1–2 based on Cerebral Performance Category (CPC) scale [19]. Clinical follow-up was conducted via a structured telephone questionnaire contacting the patient, the relatives, or the treating physician. All events were verified by hospital charts, direct contact with the treating physician, or contact with the local government registration. Data on the cause of death prior to discharge and occurrence of local and systemic complications were assessed using in-hospital documentation.

Statistical analysis

Each categorical variable is expressed as number and percentage of patients. Continuous variables are reported as medians with the corresponding interquartile range (IQR). Two-group comparisons for patients ≤60 versus >60 years were performed with Chi-square tests for categorical variables, Student *t* tests for normally distributed continuous variables, and Wilcoxon rank-sum tests for non-normally distributed continuous variables. For outcome analysis, Kaplan–Meier curves with log-rank comparison were computed. All statistical tests were two-sided with $p < 0.05$ and performed with the SPSS software, version 22.0 (SPSS Inc., Chicago, IL).

Results

Baseline characteristics

From January 2008 until January 2016, 100 patients underwent ECLS implantation due to refractory CS ($n = 83$ from Heart Centre Leipzig, $n = 17$ from University Heart Centre Lübeck). As displayed in Table 1, half of all patients were above the age of 60. The elderly had a higher prevalence of cardiovascular risk factors and co-morbidities in comparison with patients aged ≤60 years. With the exception of non-ischaemic cardiomyopathy, which was observed more frequently in younger patients, the aetiology of CS did not differ between groups. Younger patients were more likely to undergo cardiopulmonary resuscitation prior to ECLS insertion.

Procedure, treatment, and complications

ECLS implantation was successful in all patients. ECLS support lasted in median 5 days (IQR 3–8, range 1–54) and did not differ between groups [5 (IQR 3–7) versus 6 (IQR 3–8) days, $p = 0.91$].

The majority of patients were mechanically ventilated irrespective of age (88% versus 94%, $p = 0.49$). The rate of renal replacement therapy prior to or during ECLS support was numerically higher in elderly versus younger patients (46% versus 32%, $p = 0.22$). At a similar incidence of septic shock (16% versus 16%, $p = 1.00$), antibiotic therapy had to be initiated in most patients with an equal distribution in both groups (88% versus 78%, $p = 0.29$). Access site complications, including bleeding, ischaemia, and infections, did not differ (32% versus 36%, $p = 0.83$). Clinically relevant signs of haemolysis were not observed. Despite a relative strict transfusion regimen, the majority of patients ($n = 80$) required either packed red blood cells, platelets, or fresh frozen plasma without differences between patients ≤60 years in comparison with those >60 years (80% versus 80%, $p = 1.00$).

In-hospital outcome

ECLS could be weaned in more than half of the cohort (56%, $n = 56$) with no differences between the groups ($p = 0.53$; Fig. 1). All patients above the age of 75 years died prior to hospital discharge ($n = 14$). Causes of death were multi-organ failure due to prolonged or recurrent CS in the vast majority (71%; Table 2). No significant differences of causes of death in patients ≤60 versus >60 years were observed.

Mid-term outcome and predictors for adverse clinical outcome

Follow-up was completed in all patients alive at hospital discharge and was performed at 18 months (IQR 15–36). At the end of mid-term follow-up, only three patients were alive in the group of patients >60 years. These patients (age 71 years: $n = 2$; age 72 years: $n = 1$) had a good functional outcome with a CPC score ≤2. This resulted in a mortality rate of 94% in patients >60 years in comparison with 68% in patients younger than 60 years (Figs. 1, 2). The majority of patients aged ≤60 years surviving until hospital discharge ($n = 16/19$, 84%) remained event-free at mid-term follow-up (Figs. 1, 2).

Discussion

The main findings of the current study can be summarised as follows: (i) local and systemic complications under ECLS occurred frequently irrespective of patients' age and (ii) despite a high rate of initial haemodynamic stabilisation, mid-term prognosis of patients above the age of

Table 1 Baseline characteristics of the whole study cohort and according to age

	All patients ($n = 100$)	Age ≤60 years ($n = 50$)	Age >60 years ($n = 50$)	p value
Age, years	61 (50–71)	50 (44–55)	71 (68–76)	<0.001
Male gender, n (%)	72/100 (72)	38/40 (76)	34/50 (68)	0.50
Body mass index, kg/m^2	26 (24–29)	26 (24–29)	28 (25–32)	0.09
Cardiovascular risk factors, n (%)				
Arterial hypertension	60/88 (68)	18/40 (45)	42/48 (88)	<0.001
Hyperlipidaemia	38/85 (45)	10/39 (26)	28/46 (61)	0.001
Diabetes mellitus	29/87 (33)	6/41 (15)	23/46 (50)	0.001
Current smoking	39/88 (44)	25/42 (60)	14/46 (30)	0.010
Pre-existing co-morbidities, n (%)				
Coronary artery disease	24/89 (27)	3/43 (7)	21/46 (46)	<0.001
Prior PCI	20/87 (23)	2/42 (5)	18/45 (40)	<0.001
Prior CABG	10/87 (12)	3/42 (7)	7/45 (16)	0.32
Prior ICD/CRT	9/86 (11)	2/40 (5)	7/46 (15)	0.17
Known symptomatic heart failure	19/85 (22)	5/39 (13)	14/46 (30)	0.07
Peripheral artery disease	11/85 (13)	1/40 (3)	10/45 (22)	0.008
Chronic renal insufficiency	23/86 (27)	4/40 (10)	19/46 (41)	0.001
Aetiology of cardiogenic shock, n (%)				
Acute myocardial infarction	60/100 (60)	28/50 (56)	32/50 (64)	0.54
Ischaemic CMP	6/100 (6)	3/50 (6)	3/50 (6)	1.00
Non-ischaemic CMP	21/100 (21)	16/50 (32)	5/50 (10)	0.01
Valvular heart disease	9/100 (9)	2/50 (4)	7/50 (14)	0.16
Interventional complications	4/100 (4)	1/50 (2)	3/50 (6)	0.62
Functional parameters prior to ECLS				
LV ejection fraction, %	24 (15–37)	20 (10–32)	28 (20–45)	0.01
Maximum serum lactate, mmol/l	7 (3–11)	7 (2–11)	7 (3–11)	0.99
SAPS II score	51 (42–61)	45 (40–57)	58 (42–68)	0.06
ECLS at day 1 of shock, n (%)	63/100 (63)	35/50 (70)	28/50 (56)	0.47
Cardiopulmonary resuscitation prior to ECLS, n (%)				
OHCA + in-house	55/100 (55)	34/50 (68)	21/50 (42)	0.01
OHCA	18/100 (18)	16/50 (32)	2/50 (4)	<0.001
In-house	37/100 (37)	18/50 (36)	19/50 (38)	1.00

PCI percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *ICD/CRT* implantable cardiac defibrillator/cardiac resynchronization therapy, *CMP* cardiomyopathy, *ECLS* extracorporeal life support, *LV* left ventricular, *SAPS* Simplified Acute Physiology Score, OHCA out-of-hospital cardiac arrest

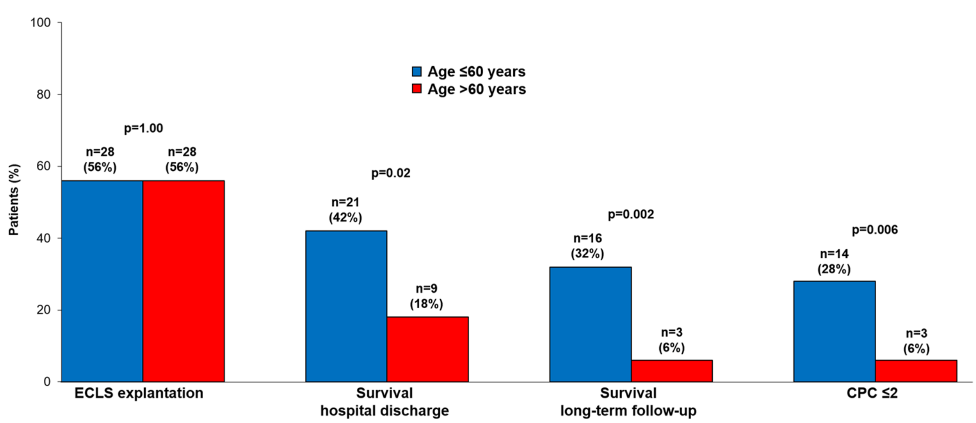

Fig. 1 Overview of outcome (*ECLS* extracorporeal life support, *CPC* cerebral performance category)

Table 2 Causes of in-hospital death

Cause of death, *n* (%)	All patients ($n = 70$)	Age ≤60 years ($n = 29$)	Age >60 years ($n = 41$)	*p* value
Cardiogenic shock	50 (71)	19 (66)	31 (76)	0.43
Septic shock	11 (16)	3 (10)	8 (20)	0.34
Major stroke	2 (3)	1 (3)	1 (2)	1.00
Anoxic brain injury	3 (4)	3 (10)	0 (0)	0.07
Haemorrhagic shock	4 (6)	3 (10)	1 (2)	0.30

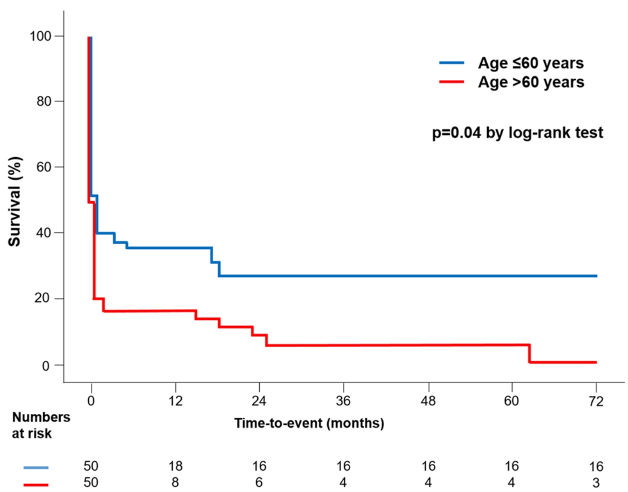

Fig. 2 Kaplan–Meier curve displaying mid-term mortality according to age ≤60 versus >60 years

60 years treated with ECLS due to refractory CS is very poor, whereas clinical outcome of younger patients appears to be good following the acute phase of CS.

Almost half of all patients with CS are older than 75 years. Even in prospective randomised trials traditionally enrolling rather young patients, the median age of patients was nearly 70 years [1–4]. Age has been demonstrated to be a strong independent predictor for mortality in CS [1, 3, 12, 13]. In recent years, mechanical circulatory support systems, such as ECLS, have been suggested to be an addition or even alternative to inotropic agents and vasopressors [20–22]. The increase of systemic blood flow while avoiding the potential cardiotoxicity and long-term morbidity of medical therapy creates the opportunity to reduce the high mortality rates currently associated with conventionally managed CS. Furthermore, mechanical support is often the only option to achieve haemodynamic stability in patients with refractory CS. As a consequence, mechanical circulatory support systems, such as ECLS, are increasingly used as part of clinical routine in tertiary care centres [5, 6]. In the absence of randomised trials, retrospective ECLS registries, including mostly younger patients, suggested that ECLS is a therapeutic option in the otherwise often futile situation of refractory CS [7–10]. Our trial is the largest that specifically examines the safety and efficacy of ECLS in the subset of high-risk elderly patients who are specifically prone to adverse outcome.

The present analysis confirms and expands the previous findings by demonstrating a very poor outcome in elderly patients undergoing ECLS for refractory CS. In the recently published results of the cardiac-RESCUE program, mean age of the 87 enrolled patients was 46 years. Notably, of the 12 patients, older than 62 years none survived [7]. In an analysis restricted to patients with ST-elevation myocardial infarction, age was again identified as an independent predictor of 30-day mortality [8]. This cohort, however, included only 46 patients undergoing ECLS and the reported survival rate was 61% which is astonishingly high. In a large international cohort of patients undergoing ECLS, younger age was associated with a higher likelihood of hospital survival [9]. Again, with a median age of 54 years, this cohort does not entirely reflect real-world CS patients. Furthermore, the aetiology of haemodynamic instability was inhomogeneous and included sepsis, pulmonary embolism, congenital heart disease, as well as shock in the setting of heart and lung transplantation. In contrast to these results, Combes et al. analysed data of 81 patients at a mean age of 46 years and did not identify age as a predictor for adverse clinical outcome [10]. However, it is worth mentioning that in this cohort, 32% of all patients were in postcardiotomy or posttransplantation CS and almost one-fifth of the patients underwent permanent assist device implantation or heart transplantation.

An important finding of the current analysis is that the rate of initially successful ECLS weaning did not differ between patients ≤60 versus >60 years. Furthermore, the incidence of complications and duration of ECLS support were similar in both groups. At hospital discharge and mid-term follow-up, however, the elderly had a significantly higher mortality in comparison with younger patients. Thus, patients at higher age appear to have a lower potential to permanently recover following ECLS explantation. This can most likely be explained by poor organ reserve and a lower intrinsic capability of functional improvement. Furthermore, elderly patients might be more susceptible to serious complications associated with ECLS due to a higher prevalence of co-morbidities [23]. Factors associated with ECLS, such as prolonged immobilisation, might be especially detrimental in older patients [24].

In the current analysis, all patients were in deep refractory CS with a likelihood of death deemed to be high in the absence of ECLS. Thus, one could argue that the three elderly patients were saved despite an apparent futile clinical situation. On the other hand, use of mechanical support devices might have led to complications with subsequent adverse clinical outcome in patients who still had non-invasive therapeutic options. As much as our analyses confirmed the hypothesis of inferior outcome in older patients, we believe that older patients should not be categorically denied aggressive care. Likewise, aggressive care and ECLS implantation should not be applied to all routinely, as previously concluded based on results of a subanalysis of the SHOCK trial registry [12]. Due to lacking randomised trials, the decision regarding ECLS implantation can only be performed individualised, especially in patients with higher age.

Finally, although mortality of elderly patients was very high, our data demonstrate that mid-term outcome of younger patients undergoing ECLS due to refractory CS is acceptable despite the initial extremely compromised clinical state. Notably, the vast majority of patients surviving the acute phase of CS remained event-free. This underlines the role of ECLS especially in the subset of younger patients.

Limitations

Some important limitations of the current analysis need to be mentioned. First, data are observational and thus prone to selection bias. Furthermore, the sample size is still too small to draw definitive conclusions. The current findings thus warrant additional investigation in larger cohorts. In addition, prior functional status was not recorded and biological age could be a more powerful predictor for outcome than chronological age. Nevertheless, objective parameters which can be assessed retrospectively in the acute setting of CS with the aim to assess functional state and biological age are currently not available. Finally, a large percentage of patients underwent cardiopulmonary resuscitation prior to ECLS implantation. Despite the lower mortality, patients aged ≤60 years were more likely to undergo cardiopulmonary resuscitation prior to ECLS insertion in comparison with those aged >60 years. Thus, it is unlikely that results would change substantially if only patients without prior cardiopulmonary resuscitation would be considered. Furthermore, prior cardiopulmonary resuscitation is very common in ECLS patients and exclusion of these patients could lead to a relevant selection bias with subsequent lower generalizability of the observed results.

Conclusion

In contrast to patients aged ≤60 years, mortality of elderly patients with refractory CS undergoing ECLS is extremely high. Next to the futile clinical state itself, this might also be partly explained by the high rate of local and systemic complications associated with ECLS potentially influencing clinical outcome especially in older patients with pronounced co-morbidities and less capacities to recover.

Compliance with ethical standards

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Conflict of interest The authors have no conflicts of interest to declare with respect to the current study.

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