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Clinical paper

Outcome in refractory out-of-hospital cardiac arrest before and after implementation of an ECPR protocol

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Abstract

Aim: To compare the outcomes in patients with refractory out-of-hospital cardiac arrest (OHCA) fulfilling the criteria for extracorporeal cardiopulmonary resuscitation (ECPR) before and after implementation of an ECPR protocol, whether the patient received ECPR or not.

Methods: We compared cardiac arrest registry data before (2014–2015) and after (2016–2019) implementation of the ECPR protocol. The ECPR criteria were presumed cardiac origin, witnessed arrest with ventricular fibrillation, bystander CPR, age 18–65, advanced life support (ALS) within 15 min and ALS > 10 min without return of spontaneous circulation (ROSC). The primary outcome was 30-day survival; the secondary outcomes were sustained ROSC, neurological outcome and the proportion of patients transported with ongoing ALS.

Results: There were 1086 and 3135 patients in the pre- and post-implementation sample; 48 (4%) and 100 (3%) met the ECPR criteria, respectively. Of these, 21 (44%) vs. 37 (37%) were alive after 30 days, p = 0.4, and 30 (63%) vs. 50 (50%) achieved sustained ROSC, p = 0.2. All survivors in the pre-implementation sample had cerebral performance category 1–2 vs. 30 (81%) in the post-implementation sample, p = 0.03. Of the patients fulfilling the ECPR criteria, 7 (15%) and 26 (26%), p = 0.1, were transported with ongoing ALS in the pre- and post-implementation sample, respectively.

Conclusions: There were no differences in 30-day survival or prehospital ROSC in patients with refractory OHCA before and after initiation of an ECPR protocol.

Keywords: Out-of hospital cardiac arrest, Refractory cardiac arrest, Extracorporeal cardiopulmonary resuscitation, Advanced life support

Introduction

There is growing interest worldwide in extracorporeal cardiopulmonary resuscitation (ECPR) using veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in patients with refractory out-of-hospital cardiac arrest (OHCA) of cardiac origin. Several studies have demonstrated its feasibility,[1,2] and even improved outcomes in propensity-score-matched patients treated with ECPR compared to conventional advanced life support (ALS).[3,4] However, meta-

Abbreviations: ALS, advanced life support; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; EMS, Emergency Management System; OHCA, out-of-hospital cardiac arrest; PRE, patients in the pre- implementation sample; POST, patients in the post-implementation sample; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.

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https://doi.org/10.1016/j.resuscitation.2021.01.038
Received 24 September 2020; Received in revised form 26 January 2021; Accepted 28 January 2021

analyses and systematic reviews with pooled results find insufficient evidence to support ECPR over conventional resuscitation in refractory OHCA patients.[5–9] The first randomised controlled trial (RCT) comparing standard ALS with early ECPR, found that ECPR improved survival to hospital discharge. This was a single centre study with 15 patients in each group, with randomization and inclusion after arrival to the emergency department.[10]

To survive cardiac arrest, patients must have a reversible cause, the means to reverse the cause must be within reasonable proximity, and minimum circulation must be maintained until and after the cause has been corrected. ECPR can be a bridge to this treatment, but will fail to increase survival unless all the requirements are met. Most ECPR programmes have operationalised this with criteria selecting patients with presumed acute ischaemic cause of arrest, favourable conditions around the collapse, proximity to an ECPR-capable hospital and minimal comorbidities. These criteria also select patients with the best chances for survival with conventional treatment.[11]

The balance between deciding to continue on-scene ALS vs. transport to hospital for timely access to ECPR most likely depends on capabilities in the system. As we await more RCTs, services performing ECPR should evaluate its effects within their system.

The aim of this study was to compare outcomes for ECPR-eligible patients before and after introduction of an ECPR protocol promoting transport with ongoing ALS. The comparison was performed regardless of whether ECPR was provided or not.

Methods

Setting

The study took place at Oslo University Hospital and Oslo and Akershus Emergency Medical Services (EMS), Norway. The hospital has two centres with ECMO capacity (Ullevål and Rikshospitalet). ECMO treatment has been performed at the hospital for cardiac and pulmonary support since 1990 but without an established ECPR protocol until 2016. The population have about 1.2 million and an area of 5555 km^2. We identified the study population through the local cardiac arrest registry. The inclusion criteria to the registry are victims who have received any resuscitation effort, regardless of who provided the resuscitation. All patients in the registry have been included from both periods. The incidence of registered OHCA, receiving any form of resuscitation, was 44–70/100 000 per year.[12,13]

ECPR protocol

Our protocol was developed by a pre- and intra-hospital multidisciplinary team based primarily on the criteria from Fagnoul et al.[14,15] and a mini-health technology assessment.[16,17] This included evaluation of organisational, economic and ethical consequences.[18] In addition to defining potential candidates, and describe the inhospital treatment, the protocol enables prehospital anaesthesiologists, if inclusion and exclusion criteria are met, to activate in-hospital ECMO team (Table 1). Initiation of transport was at the discretion of the prehospital anaesthesiologist. Distance to hospital was part of this assessment and the patient had to arrive to the hospital within 40 min after arrest. The protocol has remained unchanged after implementation in January 2016.

If OHCA was suspected or occurred after arrival of the first ambulance, a second ambulance and a physician-staffed unit were dispatched. This included an helicopter or a rapid response car with anaesthesiology-trained medical doctors. The helicopter crew members and paramedics are ALS-trained. Mechanical chest compression devices (LUCAS2™, Jolife AB, Lund Sweden) are available in physician-manned units and some regular ambulances.

If cardiac cause is suspected, coronary angiography is performed immediately after arrival at hospital followed by percutaneous coronary intervention (PCI) if appropriate.[19] Patients are treated in multi-disciplinary intensive care units (intensivists, cardiologists, cardiac surgeons, and critical care nurses) with standardised treatment protocols, including targeted temperature management between 33 °C and 36 °C for 24 h.[20] For ECPR patients, cannulation is performed percutaneously at the coronary angiography lab by an interventional cardiologist or, if complicated, by a cardiac surgeon using cut down. Staff experienced in ECMO treatment treated these patients during intensive care.

Patients

Before implementation of the ECPR protocol, ALS was performed on scene until return of spontaneous circulation (ROSC), termination of resuscitation, or transport with ongoing mechanical CPR to hospital to treat possible reversible causes of arrest or provide more definitive care. Transportation to hospital or termination of resuscitation was at the discretion of the prehospital physician (Fig. 1).

In 2016, OHCA patients with specified inclusion criteria could be considered for prehospital activation of the in-hospital ECMO team.[14]

Table 1 – ECPR criteria for patients with refractory cardiac arrest of presumed cardiac cause.

Inclusion criteria	Exclusion criteria
Presumed cardiac cause	CA due to uncontrolled haemorrhage
Witnessed arrest	Long-term oxygen therapy
Bystander resuscitation	Dialysis
Shockable first rhythm (VF or VT)	Diabetes with severe secondary complications
Age 18–65	Expected life span <1 year
Paramedic CPR within 15 min	Known low compliance with treatment
>10 min of ALS without ROSC	Ongoing chemotherapy
<60 min from CA to ECMO cannulation*	Substantial existing CNS deterioration
	Terminal stage of pulmonary disease

CA—Cardiac arrest, VF—ventricular fibrillation, VT—ventricular tachycardia, ALS—advanced life support, ROSC—return of spontaneous circulation, ECMO—extracorporeal membrane oxygenation, ECMO—extracorporeal membrane oxygenation, CNS—central nervous system.

* <60 min from CA to ECMO cannulation is a criterion in the ECPR protocol but did not exclude patients from being part of the sample.

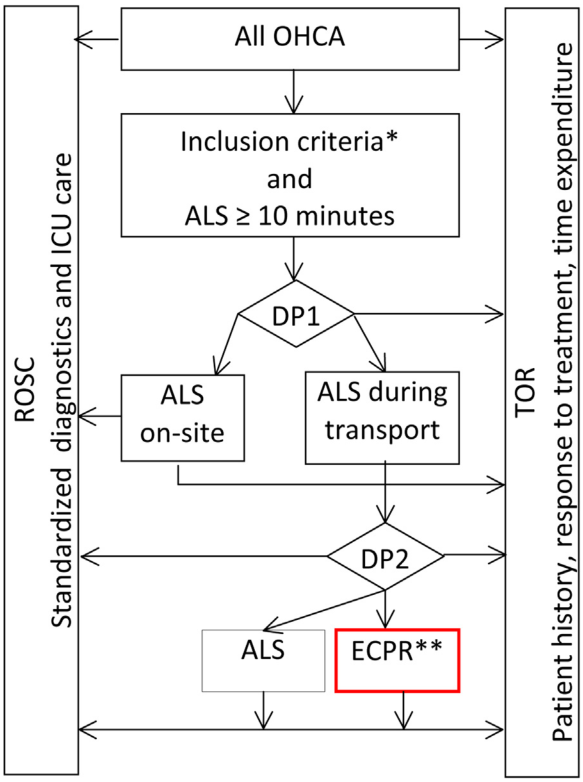

Fig. 1 – Flow diagram for selection of patients eligible for ECPR. *Inclusion criteria see Table 1. **ECPR was only available to selected patients after protocol implementation. DP1—prehospital anesthesiologist decides if patient meets criteria, and decide further treatment based on patient history, response to treatment and expected evacuation time.
DP2—Emergency room team reconsider if patient still meets criteria, supported by patient journal, response to treatment and time expenditure. ROSC—return of spontaneous circulation, ICU—intensive care unit, OHCA—out-of-hospital cardiac arrest, ALS—advanced life support, DP—decision point, ECPR—extracorporeal cardiopulmonary resuscitation, TOR—Termination of resuscitation.

The exclusion criteria consisted of factors associated with low survival and reduced life span (Table 1 and Fig. 1).

The sample of ECPR-eligible patients in this study was limited to the Oslo and Akershus area. This was a pragmatic approach to the criterion of a maximum delay of 60 min from collapse until established ECMO circulation. The protocolled aim was to establish the (VA)-ECMO circuit within 20 min of arrival at hospital. When the prehospital anaesthesiologist activated the ECMO team, patients were transported with ongoing mechanical chest compressions and continued ALS with defibrillation and drug administration as appropriate. If stable ROSC was achieved during transport or prior to the establishment of the ECMO circuit, the patient would not be treated with ECMO, and would instead receive standardised post-resuscitation care.

Data set

The pre-implementation sample (PRE) comprised patients who received conventional ALS from 2014 to 2015, and the post-implementation sample (POST) that could receive ALS and ECPR, from 2016 until 2019. We have applied the same criteria for ECPR eligibility for the entire study sample, without any form for pre-selection (Table 1).

Primary outcome was the proportion of patients alive after 30 days. Secondary outcomes were the proportion of patients with sustained ROSC, 24-h survival and favourable neurologic outcome, as well as the proportion of patients transported with ongoing ALS. For transported patients, we describe time interval from cardiac arrest until arrival at hospital.

Sustained ROSC was defined as ROSC for at least 20 min in the prehospital phase or ROSC until transfer of care to hospital staff. Good neurological outcome was defined as cerebral performance category (CPC) scores 1 or 2 after 30 days or at the time of hospital discharge.

Statistics

Categorical variables are summarised with frequencies and percentages and compared with chi-squared tests. Continuous data is presented as medians with quartiles for variables not normally distributed and compared with the Mann–Whitney U test. As this was a retrospective review of actual practice, no formal power calculation was performed.

Ethics

In Norway, data collection to the cardiac arrest registry is mandatory by law, without the need for consent. The regional ethics committee (2017/1255) and the local data protection officer (2017/14604) approved the use of collected data. Data disclosure was approved by the steering committee for the registry.

Results

Between 2014 and 2019, 4221 patients were resuscitated in the Oslo and Akershus area. In PRE, there were 1086 OHCAs, of which 48 (4%) met the ECPR criteria. In POST, there were 3135 OHCAs, including 100 (3%) patients meeting the criteria for ECPR (Fig. 2). ECMO was deployed in 14 of 26 patients transported with on-going ALS. Of the remaining ECPR candidates, 50 had prehospital ROSC and treatment was discontinued for the last 24 patients. The patients and their cardiac arrest characteristics are described in Table 2.

Survival, sustained ROSC and CPC for potential ECPR candidates

In PRE, 21 (44%) of the patients were alive after 30 days vs. POST with 37 (37%), $p = 0.4$. Sustained ROSC was achieved in 30/48 patients (63%) vs. 50/100 (50%), $p = 0.2$ in PRE and POST, respectively. After 24 h, 29 (60%) vs. 52 (52%), $p = 0.3$, were alive in PRE and POST, respectively. All survivors (100%) in PRE had good neurologic outcomes vs. 30 (81%) in POST, $p = 0.03$ (Table 3).

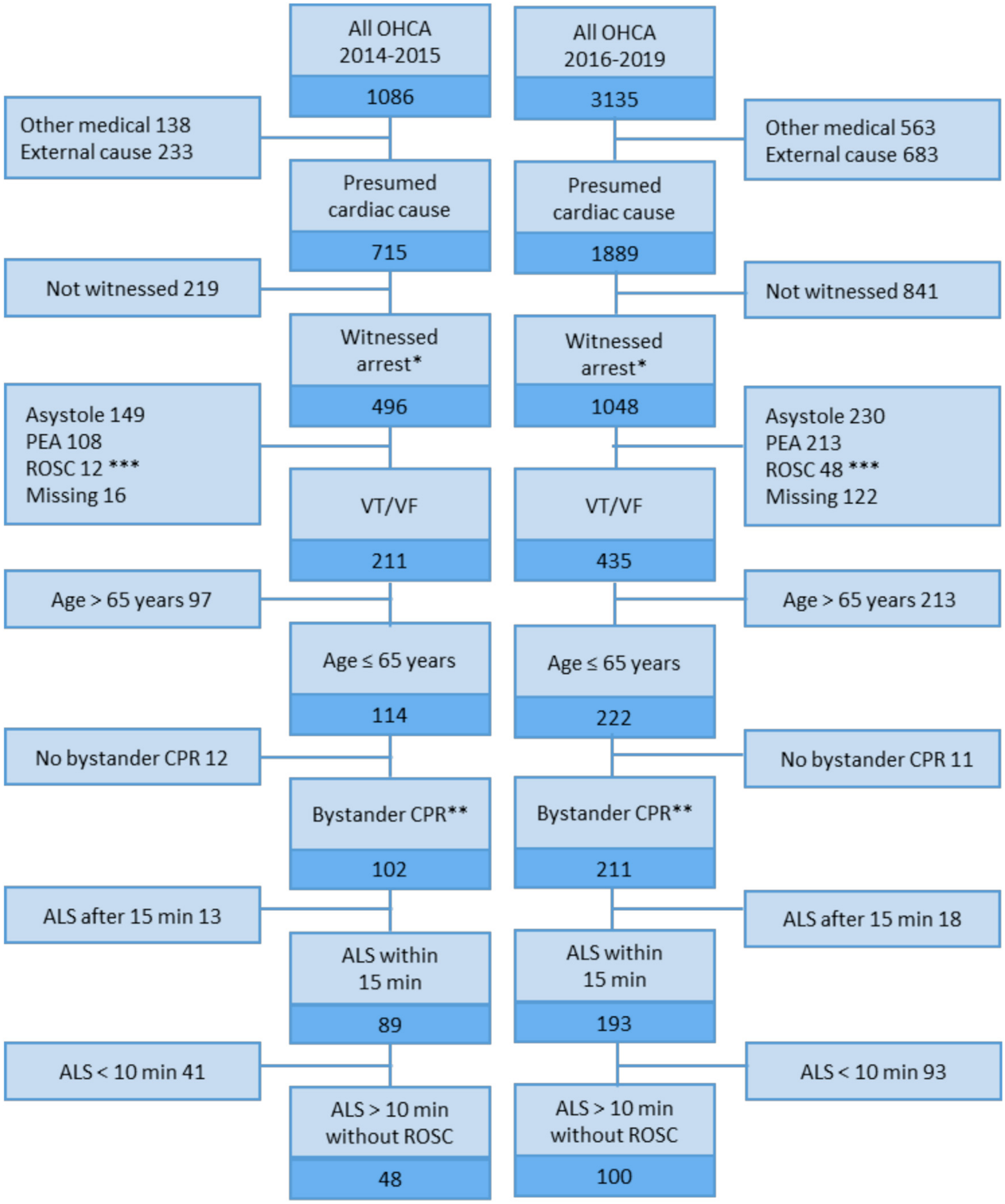

Fig. 2 – Number of patients meeting the criteria for extracorporeal cardiopulmonary resuscitation before and after introduction of the procedure for transport with ongoing advanced life support to promote in-hospital extracorporeal membrane oxygenation treatment. To be registered in the Norwegian Cardiac Arrest Registry, the patient must have received chest compressions or an automated external defibrillation shock. All patients were 18 years or older. OHCA—out-of-hospital cardiac arrest, PEA—pulseless electrical activity, ROSC—return of spontaneous circulation, VT—ventricular tachycardia, VF—ventricular fibrillation, CPR—cardiopulmonary resuscitation, ALS—advanced life support. *Witnessed by bystander, first responder or ambulance staff. **Either cardiopulmonary resuscitation by bystander or ambulance staff-witnessed arrest. ***ROSC means that the patient had spontaneous circulation upon arrival of the emergency management service crew. Time to ALS means time to paramedic initiated CPR.

Table 2 – Baseline and cardiac arrest characteristics for all patients and potential ECPR candidates before (2014–2015) and after (2016–2019) introduction of the ECPR protocol for refractory cardiac arrests outside hospital.

	All patients			ECPR candidates		
Characteristics	Before n = 1086	After n = 3135	p-value	Before n = 48	After n = 100	p-value
Patient and scene characteristics						
Women, n (%)	337 (31)	1128 (36)	0.003	7 (15)	16 (16)	0.8
Age, median (25th and 75th percentile)	68 (54,79)	67 (52,79)	0.2	58 (52,63)	57 (49,61)	0.6
OHCA in private home (%)	671 (62)	1923 (61)^	0.7	26 (54)	48 (48)	0.5
Resuscitation factors						
Witnessed (%)	699 (64)	1906 (61)	0.04	48 (100)	100 (100)	*
Presumed cardiac cause (%)	715 (66)	1889 (60)	0.001	48 (100)	100 (100)	*
Bystander CPR (%)	906 (83)	2786 (89)^^	< 0.001	38 (79)	84 (84)	0.5**
Initial shockable rhythm (%)	262 (24)	547 (17)	<0.001	48 (100)	100 (100)	*

OHCA—out-of-hospital cardiac arrest, CPR—cardiopulmonary resuscitation. ^Two patients were missing information on location of arrest. ^^33 patients had missing information as they received bystander CPR. *This factor is mandatory to become an ECPR candidate. **The remaining patients were CA witnessed by ambulance staff.

Table 3 – Primary and secondary outcomes for all patients and potential ECPR candidates before and after the ECPR protocol for refractory cardiac arrest outside of hospital.

	All patients				ECPR candidates	
Outcome	Before n = 1086	After n = 3135	p-value	Before n = 48	After n = 100	p-value
Sustained ROSC* (%)	351 (32)	747 (24)	< 0.001	30 (63)	50 (50)	0.2
24-h survival (%)	278 (26)	743 (24)	0.2	29 (60)	52 (52)	0.3
30 days survival (%)	167 (15)	464 (15)	0.6	21 (44)	37 (37)	0.4
CPC score 1–2** (%)				21 (100)	30 (81)	0.03
ALS during transport and on arrival to hospital (%)	56 (5)	121 (4)	0.7	7 (15)	26 (26)	0.1
Time from CA to arrival at hospital						0.3
≤40 min				2	14	
41–59 min				2	8	
≥60 min				3	4	

ECPR—extracorporeal pulmonary resuscitation, ROSC—return of spontaneous circulation.
* Sustained ROSC is prehospital ROSC for 20 min or more, or ROSC upon arrival to hospital. The difference between sustained ROSC and 24-h survival is due to ROSC after arrival to hospital.

** Percentage of patients alive at 30 days after the event; numbers from all patients were not available for the complete study period. The difference between number of ECPR candidates and patients with ALS during transport reflects on delayed ROSC on-scene or during transport, or termination of resuscitation.

Table 4 – The distribution and survival for all out of hospital cardiac arrest patients treated wtih ECPR from the Oslo-Akershus EMS system 2014–2019. The patients are divided in groups whether they were treated within or outside the criteria in the ECPR protocol.

	2014–2015	2016–2019	
	Outside criteria n = 5	Inside criteria n = 14	Outside criteria n = 18
Cardiac cause	0	14	8
Non-cardiac cause	5	–	10
CPC 1	3	1	2
CPC 2	–	–	5
CPC 3	–	–	1
Dead	2	13	10

ECPR—extracorporeal pulmonary resuscitation, EMS —emergency medical system, CPC —cerebral performance category.

Transport with ongoing ALS

We found no increase in patients transported with ongoing ALS amongst the general OHCA population; 56 (5%) patients PRE and 121 (4%) POST, p = 0.7. Of ECPR-eligible candidates, 7 (15%) were transported with ongoing ALS before the procedure and 26 (26%) after; this difference did not reach statistical significance. In PRE, 2 of 7 patients arrived in hospital within 40 min from cardiac arrest vs. 14 of

26 in POST, p = 0.3, (Table 3). Details for distribution and survival, including CPC score for all ECPR treated OHCA, Table 4. Details for inhospital ECPR treatment after OHCA with cardiac cause, supplemental Table 1.

Discussion

In this registry-based study of patients potentially eligible for ECPR, we compared patient outcomes and number of patients transported with ongoing ALS, before and after implementation of an ECPR protocol. We compared groups of patients filling inclusion criteria, whether ECPR was provided or not. We found no difference in overall 30-day survival between the two periods, but the proportion of survivors with good neurological outcome, was higher in the period before initiation of the ECPR protocol. The proportion of potential candidates transported to hospital with ongoing ALS before and after the protocol was unchanged. Based on promising results from other studies, our results were surprising and disappointing. There could be several explanations for the unchanged 30-day survival and worsening in neurological function among the survivors after initiation of the ECPR protocol.

Cardiac arrest may be considered refractory, unavailable for treatment, after three failed defibrillations.[1] In our protocol based on previous studies,[14] this was operationalized as lack of ROSC after ten minutes of ALS. Most inclusion criteria in our protocol could be applied to the registry to identify comparable sub-groups before and after ECPR-implementation. Several sites have performed studies to calculate the potential load of ECPR patients, and found between 3% and 11% potential ECPR candidates with similar criteria as our protocol.[21–23] In agreement with these results, we found that 3%–4% of our OHCA patients met the criteria. This corresponds to about two patients per month. Considering our two locations with ECMO capacity, this new ECPR treatment poses a minor extra workload to the hospital.

The ten-minute mark was implemented as a minimum duration of on-scene ALS. Decision to continue on-scene ALS or initiate transport with on-going ALS was at the discretion of the prehospital anesthesiologist. The decision was informed by knowledge of preexisting co-morbidities not registered in our registry, and most importantly, on-scene estimates of evacuation duration and thus total time expenditure before ECPR could be applied.

Criteria for ECPR-eligibility were met by 100 patients in POST. Only one fourth of eligible patients arrived at hospital with on-going ALS. More than half of the potential candidates achieved prehospital ROSC after more than ten minutes of ALS and before transport to hospital. We demonstrated in a previous study that, although time to ROSC was a predictor of adverse outcome, 29% of OHCA patients survived with good outcome with time to ROSC exceeding 25 min.[24] Stub and colleagues found that in their EMS system, which provided ALS on-scene, much like our system, patients without ROSC in the field transported with ALS had poor outcome.[25] Several studies have reported a high proportion of ROSC (between 47% and 75%) within samples of ECPR candidates with comparable definitions as in our study.[23,26,27]

This demonstrates the paradox that a promising new treatment necessitates new strategies that might put patients, who already have good chances for survival, to a disadvantage. Balancing early evacuation for ECMO or prolonged ALS on-scene remains the major dilemma of ECPR for OHCA. We found that 63% of PRE- and 50% of POST-cohorts achieved sustained ROSC in the prehospital setting. The change was not statistically significant, but it is worrying if a reduction in number is due to a shift in focus towards early evacuation to arrive at hospital in time for ECPR. Eastin and colleagues demonstrated that changing focus from early transport and mandating EMS personnel to perform longer on-scene ALS, from 19 to 30 minutes, increased the rate of ROSC from 27% to 40%.[28] Another study found that intra-arrest transport was found to be associated with a lower probability of survival and a worse neurologic outcome.[29] Several studies have considered the balance of on-site ALS and transport, finding that 90% of survivors achieved ROSC within 16 min[26] to 24 min,[27] and Kim et al. concluded that 21 min was the best time to initiate transport to the hospital.[30] It may not be possible within a group of patients to predict who might benefit from prolonged on-scene ALS or transport with ongoing ALS.

For the potential ECPR candidates, there was a numeric increase in transport with ALS, this did not reach statistical significance. There was no increase in transport with ALS for the overall group of OHCA patients, suggesting good adherence to protocols for these patients. For ECPR candidates transported with ALS, there was a trend towards earlier admission to hospital after the arrest. Transport to hospital is associated with interruptions in chest compressions,[31] and impaired quality of resuscitation.[32] However, in our system, chest compression devices are available and remain a prerequisite for these transports. In order to prepare for the ECPR protocol and a potential increase in transport with ALS, all involved crewmembers trained specifically for transport with ALS.

Only half of potential ECPR patients arriving at hospital with on-going ALS got ECPR. The decision to proceed with ECPR was reconsidered upon arrival to hospital, based on protocol criteria. The most important criteria that could not be met were time from cardiac arrest to initiation of ECMO < 60 min. We found long time intervals "from cardiac arrest until arrival at hospital", and "from hospital arrival until cannulation". This may indicate delays both in the prehospital and in-hospital phase, also long transport distances. We are unable to characterize these time intervals further based on registry data. Only 14 patients were treated within the ECPR inclusion criteria during four years. However, the total volume of ECPR at our hospital was higher, including both OHCA outside the current criteria and in-hospital cardiac arrests. But, better outcomes have been seen in other systems with higher volumes.[2,10,33] The fraction of patients ending up with ECPR varies between studies, but most considered ECMO possibilities after arrival to hospital. Yannopoulos et al. initiated ECMO in 15 of 18 (83%) patients meeting their inclusion and exclusion criteria at arrival to hospital.[1] Patricio et al. and Maekawa et al. initiated ECPR in 70 of 351 (20%) and 53 of 162 (33%) of their OHCA patients transported to the hospital, respectively.[3,4] Noteworthy, the denominator in these studies is *not* the same, due to differences in organization and capacities.

Systematic reviews that tried to pool the evidence for ECPR treatment have not been able to support or refute ECPR for refractory OHCA,[8,9] some of the reason are the heterogeneity of the studies. While we lack more RCTs to determine this question, it is important for each system to evaluate the effect of ECPR within their system, both effects on the selected group of patients eligible for ECPR and on the general OHCA population. It is likely that outcome after ECPR depends on a cluster of variables and differences within EMS systems and in-hospital care; this will continue to make the results of ECPR studies difficult to generalise. We found in PRE that the rate of prehospital ROSC was already very high for the selected group. We

attribute this to the level of care provided in the prehospital phase in our system. Most of the potential ECPR candidates who achieved sustained ROSC were alive after 24 h and 30 days. We speculate that for the candidates who were unresponsive to prehospital treatment, prolonged resuscitation during transport and after arrival at hospital might have contributed to fewer survivors, and reduced CPC scores. The proportion of ROSC and survival in our study provides optimism for patients fulfilling ECPR criteria, even if predicted evacuation duration precludes this treatment.

Limitations

Our findings are limited by the observational design, as this was a retrospective study of registry data. In addition, we compare time periods where other changes than introduction of ECPR might have affected our results. We found differences between the total OHCA populations before and after implementation (lower proportion of presumed cardiac cause and initial shockable rhythm, and higher proportion of bystander CPR). Yet, for the ECPR eligible cases, all these factors were part of the inclusion criteria, thus resulting in comparable cohorts.

Increased incidence of OHCA over the total study period relates to a registry under development. Potential missing registrations in the registry might have influenced the results, even if the incidence of survival was stable within the increased incidence in OHCA. The study was performed using all available patients in the registry, and the sample was limited in order to detect significant differences between the groups.

Our dataset did not contain the possibility to calculate time spent on-scene. This limits examination of how this aspect may have influenced results. In order to inform the discussion on why ECPR has failed to improve outcome for our OHCA patients, it is necessary to look further into details of treatment and timeliness both prehospitally and inhospitally. Due to the complexity of prehospital and in-hospital factors influencing the outcome of refractory OHCA patients, this study may not be generalizable to other systems.

Conclusions

The implementation of the ECPR protocol did not increase survival after OHCA in our system. Quality in the chain of survival might be equally important to increase the chance of ROSC and survival even in patients with prolonged cardiac arrest duration.

Funding

No financial support has been received to conduct this study.

Authors' contributions

KAK, GS, SAO, KS, BB, GØA, AF, OAH and JKJ contributed to conception and/or design of the study. KAK and GS involved in data acquisition; KAK and JKJ were involved in the data analysis and interpretation. KAK and JKJ drafted the manuscript. GS, SAO, KS, BB, GØA, AF, OH and JKJ critically revised the manuscript. All authors read and approved the final manuscript.

Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Kristin Alm-Kruse: Conceptualization, Data curation, Investigation, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Gro Sørensen:** Data curation, Investigation, Writing - review & editing. **Svein Are Osbakk:** Conceptualization, Methodology, Writing - review & editing. **Kjetil Sunde:** Conceptualization, Methodology, Writing - review & editing. **Bjørn Bendz:** Conceptualization, Methodology, Writing - review & editing. **Geir Øystein Andersen:** Conceptualization, Methodology, Writing - review & editing. **Arnt Fiane:** Conceptualization, Methodology, Writing - review & editing. **Ove Andreas Hagen:** Conceptualization, Methodology, Writing - review & editing. **Jo Kramer-Johansen:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Visualization, Writing - original draft, Writing - review & editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2021.01.038.

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