What is the potential benefit of pre-hospital extracorporeal cardiopulmonary resuscitation for patients with an out-of-hospital cardiac arrest?

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Clinical paper

What is the potential benefit of pre-hospital extracorporeal cardiopulmonary resuscitation for patients with an out-of-hospital cardiac arrest? A predictive modelling study

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Abstract

Aim: In this predictive modelling study we aimed to investigate how many patients with an out-of-hospital cardiac arrest (OHCA) would benefit from pre-hospital as opposed to in-hospital initiation of extracorporeal cardiopulmonary resuscitation (ECPR).

Methods: A temporal spatial analysis of Utstein data was performed for all adult patients with a non-traumatic OHCA attended by three emergency medical services (EMS) covering the north of the Netherlands during a one-year period. Patients were considered potentially eligible for ECPR if they had a witnessed arrest with immediate bystander CPR, an initial shockable rhythm (or signs of life during resuscitation) and could be presented in an ECPR-centre within 45 minutes of the arrest. Endpoint of interest was defined as the hypothetical number of ECPR eligible patients after 10, 15 and 20 minutes of conventional CPR and upon (hypothetical) arrival in an ECPR-centre as a fraction of the total number of OHCA patients attended by EMS.

Results: During the study period 622 OHCA patients were attended, of which 200 (32%) met ECPR eligibility criteria upon EMS arrival. The optimal transition point between conventional CPR and ECPR was found to be after 15 minutes. Hypothetical intra-arrest transport of all patients in whom no return of spontaneous circulation (ROSC) was obtained after that point (n = 84) would have yielded 16/622 (2.5%) patients being potentially ECPR eligible upon hospital arrival (average low-flow time 52 minutes), whereas on-scene initiation of ECPR would have resulted in 84/622 (13.5%) potential candidates (average estimated low-flow time 24 minutes before cannulation).

Conclusion: Even in healthcare systems with relatively short transport distances to hospital, consideration should be given to pre-hospital initiation of ECPR for OHCA as it shortens low-flow time and increases the number of potentially eligible patients.

Keywords: Out-of-hospital cardiac arrest (OHCA), Extracorporeal cardiopulmonary resuscitation (ECPR), Pre-hospital

Introduction

Extracorporeal cardiopulmonary resuscitation (ECPR) is the application of venoarterial extracorporeal membrane oxygenation (VA-ECMO) during cardiac arrest. It is a complementary treatment to high-quality conventional cardiopulmonary resuscitation (cCPR) when return of spontaneous circulation (ROSC) cannot be obtained within a reasonable timeframe.[1] ECPR allows a retrograde flow of oxygenated blood through the aorta to vital organs, thereby

Abbreviations: ECPR, extracorporeal cardiopulmonary resuscitation, OHCA, out-of-hospital cardiac arrest, cCPR, conventional cardiopulmonary resuscitation, EMS, emergency medical service, ROSC, return of spontaneous circulation, VA-ECMO, veno-arterial extracorporeal membrane oxygenation, CPR, cardiopulmonary resuscitation, AED, automatic external defibrillator, VT, ventricular tachycardia, VF, ventricular fibrillation, SoL, signs of life, ADL, activities of daily living, DNR, do-not-resuscitate, BLS, basic life support, ALS, advanced life support, ED, emergency department, PCI, percutaneous coronary intervention, CI, confidence interval, IQR, interquartile range, SD, standard deviation, PEA, pulseless electrical activity. UMCG, University Medical Centre Groningen

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extending the time window to diagnose and treat the primary underlying cause of the arrest.[2]

Previous studies on the benefit of in-hospital ECPR for patients suffering from out-of-hospital cardiac arrest (OHCA) show conflicting results: although several observational studies have demonstrated that in-hospital ECPR can have a beneficial effect on survival to hospital discharge and neurological intact survival,[3,4] a recently published randomized controlled trial[5] could not demonstrate a benefit of early intra-arrest transport and initiation of ECPR on neurological outcome after 180 days compared to the same management without ECPR, although both arms of the trial had higher neurologically intact survival than the wider OHCA literature.

A shorter low-flow time (the time from the start of CPR to the moment of initiation of ECPR) has shown to be associated with a higher chance of neurological intact survival.[6] However, previous studies have demonstrated that it can be a challenge to minimise low-flow time and present patients with an OHCA in the hospital timely for initiation of ECPR.[7,8] This was recently emphasised by the INCEPTION-trial results.[9]

Pre-hospital initiation of ECPR can potentially reduce the low-flow time. A retrospective study in Paris comparing pre-hospital and in-hospital ECPR demonstrated greater odds of survival for pre-hospital initiation of ECPR.[10] However, pre-hospital ECPR is a resource-intensive treatment with significant logistical challenges. The potential societal benefit (compared to other interventions to improve outcome of OHCA) has not yet been fully established as it is currently unclear how many patients would potentially benefit from pre-hospital ECPR as a treatment option.

In the present study, we aim to determine how many patients may benefit (and to what extend) from pre-hospital initiation of ECPR for OHCA, by a temporal analysis of eligibility for ECPR in a large regional cohort of OHCA patients attended by three emergency medical services.

Methods

Study design

We performed a predictive modelling study based on a retrospective cohort of patients with an OHCA attended by emergency medical service (EMS) crews in the three northern provinces of the Netherlands during a one-year period (January 1st 2019 - January 1st 2020). By temporal spatial analysis we determined hypothetical eligibility for ECPR and low-flow times for various scenarios of pre-hospital and in-hospital ECPR.

Study setting

In the Netherlands, two EMS crews are dispatched to all patients with an OHCA. Each crew consists of a driver (basic life support (BLS) qualifications) and a specialised pre-hospital care nurse (advanced life support (ALS) qualifications). With backup of the national ambulance protocol, EMS nurses have the authority to not initiate or to cease resuscitation when efforts are deemed futile. No (national) redirection system however is in place to guide EMS staff on when patients with refractory OHCA should be transported to an ECPR-capable hospital.

In the North of the Netherlands, three emergency medical services together cover a population of 1.7 million people.[15] They attend on average 600 OHCA patients each year. The catchment area has fourteen hospitals with emergency departments (EDs). Four of these perform percutaneous coronary interventions (PCI), of which two hospitals have the capability to initiate extracorporeal membrane oxygenation for the purpose of ECPR (supplementary file 1), either in a trial setting[9] or as part of standard care.

Study population

Hypothetical eligibility for ECPR was determined in a population of adult patients (age $\geq$ 18 years) who had suffered a non-traumatic OHCA during the study period and were attended by EMS. Patients attended for interfacility transfers were excluded.

Patients were considered potentially eligible for ECPR in temporal spatial analysis when they[11–13]:

- Had a witnessed arrest with immediate bystander CPR or a confirmed no-flow time of less than 5 minutes AND;
- Had a pulseless ventricular tachycardia (VT) or ventricular fibrillation (VF) as the presenting rhythm (including patients who received an AED shock prior to EMS arrival), OR when they had signs of life (SoL) during resuscitation (gasping, limb movements, pupil reactivity) AND;
- Had no ROSC at the moment of determining eligibility.

In addition to this, for the scenario's where hypothetical in-hospital ECPR was analysed, the (actual- or hypothetical) arrival time in the hospital had to be no later than 45 minutes after the arrest time. This would allow 15 minutes of cannulation on arrival to facilitate full support on VA-ECMO by 60 minutes, as outcome is often poor with low-flow times exceeding 60 minutes.[6,14]

Age, baseline functional status, comorbidities, quality of life, cognition and activity of daily living dependency were not considered for determination of potential eligibility, as on many occasions little information is available in the pre-hospital setting to guide EMS in this respect. Patients with do-not-resuscitate (DNR) declarations were considered ineligible for ECPR.

Clinical endpoints

Primary endpoint

The primary endpoint was defined as the hypothetical number of ECPR eligible patients after 10, 15 and 20 minutes of conventional CPR as a fraction of the total number of OHCA patients attended by EMS.

Secondary endpoints

- The number of ECPR eligible patients upon arrival in an ECPR-centre based on the current EMS workflow;
- The hypothetical number of ECPR eligible patients upon arrival in hospital would a dedicated redirection protocol (with intra-arrest transport to the nearest ECPR-centre after 10, 15 or 20 minutes of unsuccessful conventional CPR by EMS providers on-scene) have been used;[1]

[1] Intervals are arbitrary numbers chosen as potential reasonable times for a minimal amount of on-scene resuscitation to get ROSC before potentially inferior resuscitation during transport and chosen to identify if there was a particular time interval that delivered the most amount of ROSC on-scene prior to hypothetical transport.

– The number of patients who regained ROSC prior to EMS arrival or during EMS treatment on-scene;
– The number-needed-to-dispatch, defined as the number of patients eligible for pre-hospital ECPR divided by the total number of witnessed OHCA with bystander CPR.

Data acquisition

Data were collected from the electronic patient records of the three emergency medical services (January 1st 2019–January 1st 2020). Collected data included patient characteristics (age, sex, medical history, advanced directives), cardiac arrest characteristics (location of arrest, witnessed arrest, bystander CPR, AED use, AED shocks, initial cardiac rhythm on EMS arrival, ROSC on-scene after 10, 15 or 20 minutes, presumed arrest aetiology), pre-hospital interventions (type and dose of administered medication, number of defibrillators, airway management, vascular access), timing (EMS dispatch time, arrival on-scene, leaving scene, hospital arrival), and disposition (transport, CPR during transport, destination hospital, closest hospital, facilities of the destination hospital).

Temporal-spatial data

Timing taken from the electronic patient records from the EMS represent timings as registered in real-time (and not post-hoc) by the dispatch centre and by ambulance crews on scene. For patients transported to an ECPR-centre, true transport times were used. When patients were not transported or transported to a non-ECPR-centre, the theoretical most favourable transport times to the closest ECPR-centre were calculated. Calculations were performed with Google Maps[16] based on the location of arrest and the nearest ECPR-centre, accounting for blue-light driving by reducing the transport times by 25%.

Ethical considerations

The study was determined to be exempt research by the institutional medical ethical review board of the University Medical Centre Groningen (UMCG) (METc UMCG, nr M19.242374). As only routinely collected pseudonymized data were analysed, deferred consent was not obtained from patients and/or relatives (LTC IGK UMCG, nr 201900757). Data sharing agreements were signed between UMCG and EMS services prior to data transfer and analysis.

Statistical analysis

Continuous variables are expressed as mean (95% CI). Categorical data are expressed as absolute numbers and percentages. Percentages are based on the total study cohort unless otherwise specified. Differences between means were analysed using Student's t-test or the Mann-Whitney U-test where appropriate. Differences between categorical data have been analysed with the Chi-squared test. A two-sided *P*-value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS 26.0 software (Inc., Chicago, IL, USA).

Results

Study population

During the study period, 810 OHCA entries were registered by EMS crews in the electronic patient records, of which 622 met our inclusion criteria (Fig. 1).

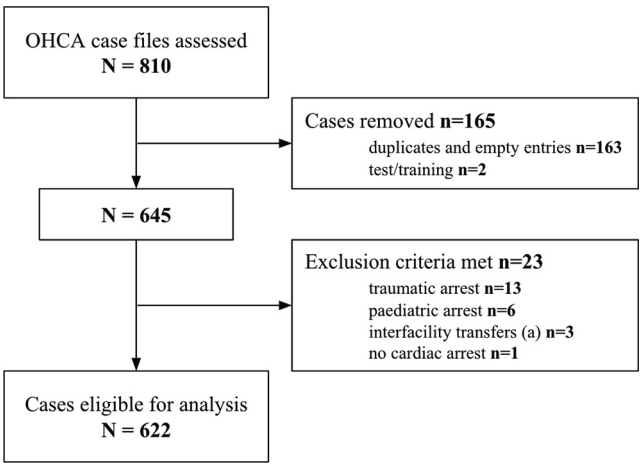

Fig. 1 – Derivation of study population. OHCA, out-of-hospital cardiac arrest. (a) transport of patients with spontaneous circulation between two different hospitals.

The main demographics and characteristics of the study cohort are presented in Table 1. The majority of the arrests were witnessed (419/622, 67.4%), of which 58 (9.3%) were witnessed by EMS crews. Bystanders initiated CPR in 384 (61.6%) cases and an AED was applied before the arrival of the first ambulance in 164 patients (26.4%), delivering a shock in 68 patients (10.9%). Twenty-three patients (3.7%) obtained ROSC prior to EMS arrival, of which 11/23 (47.8%) went into cardiac arrest again later. In 65 patients (10.5%), resuscitation efforts were deemed futile upon arrival of the EMS crew, and resuscitation efforts were not continued by EMS personnel in accordance with the ambulance protocol.

Primary and secondary outcomes

Of the 622 patients in the study population, 200 patients were potentially eligible for ECPR at the moment of initiation of conventional CPR (cCPR) by the EMS crews (32.2% of the study population) (Fig. 2).

Eligibility for in-hospital ECPR based on current workflow

Of the 200 potentially eligible patients in whom cCPR was started, ROSC was obtained in 51 patients, whereas in 46 patients resuscitation efforts were ceased on-scene after an average cCPR duration of 22.9 [SD 8.0], minutes in accordance with Dutch Resuscitation Council guidance (asystole > 20 minutes). Characteristics of this latter population compared to patients transported to hospital are represented in Supplementary file 2. The remainder of the patients were transported intra-arrest to a hospital with ongoing CPR: 13 to an ECPR-centre and 88 to a non-ECPR hospital. Only three patients (0.5%) were presented in an ECPR-centre within the pre-specified timeframe of 45 minutes (Fig. 2). All were male (aged 47, 57 and 75 years) and received immediate bystander CPR and AED shocks. On hospital arrival, one presented with asystole and two with PEA. ROSC was obtained in one patient in-hospital. None of them were treated with ECPR, and all three died before hospital discharge.

Hypothetical eligibility for in-hospital ECPR would a pre-hospital redirection system have been in place

Mean (SD) EMS on-scene time in our cohort of 200 patients was 28.8 (10.1) minutes. Fig. 3 shows the hypothetical effect of the imple-

Table 1 – Baseline patient- and cardiac arrest characteristics (n = 622).

Characteristics	No (%)	Available datapoints, *N* (%)
Age, median (IQR), years	69 (59–77)	612 (98.4)
Sex		
Male	428 (68.8)	618 (99.4)
Female	190 (30.5)	
Location of arrest		
Home	377 (60.6)	584 (93.9)
Public	207 (33.3)	
Witnessed arrest	419 (67.4)	587 (94.4)
Bystander witnessed	361 (58.0)	
EMS witnessed	58 (9.3)	
Unwitnessed	167 (26.8)	620 (99.7)
No-flow < 5 mins	8 (1.3)	
No-flow > 5 mins	159 (25.6)	
Bystander CPR	384 (61.6)	563 (89.5)
Bystander AED on-scene	164 (26.4)	527 (83.2)
AED defibrillation delivered	68 (10.9)	613 (98.4)
EMS response time, mean (SD), minutes	8.6 (3.4)	580 (93.2)
Resuscitation deemed futile by EMS	65 (10.5)	612 (98.4)
Initial cardiac rhythm		
Pulseless VT	15 (2.4)	538 (86.5)
VF	169 (27.2)	
PEA	119 (19.1)	
Asystole	235 (37.8)	
ROSC obtained		
Prior to EMS arrival	23 (4.1*)	595 (95.2)
On-scene	230 (37.0)	577 (92.8)
On hospital arrival	188 (30.2)	585 (94.1)
HEMS on-scene	49 (7.9)	
Care terminated on-scene	332 (53.4)	618 (99.4)
Transported to hospital	284 (45.7)	
ECPR-centre	115 (18.5)	617 (99.2)
Non-ECPR-centre	168 (27.0)	
Transport time to closest appropriate hospital, mean (sd), minutes	15.4 (7.9)	245 (39.4)
Estimated transport distance to closest ECPR-centre, mean (sd), kilometres	47.1 (24.0)	612 (98.4)
Estimated transport time to closest ECPR-centre, mean (sd), minutes	29.0 (11.6)	

Values are represented as (%) and proportions of the total cohort unless stated otherwise. IQR, interquartile range; CPR, cardiopulmonary resuscitation; AED, automatic external defibrillator; VT, ventricular tachycardia; VF, ventricular fibrillation; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; HEMS, helicopter emergency medical service; ECPR, extracorporeal cardiopulmonary resuscitation; EMS, emergency medical service; SD, standard deviation.
* Given as proportion of all non-EMS witnessed arrests (n = 564).

mentation of a strict pre-hospital redirection protocol, wherein all potentially eligible ECPR candidates are transported intra-arrest to ECPR-centres after 10, 15 or 20 minutes of unsuccessful conventional CPR on-scene. When EMS crews would have started transport after 10 minutes of cCPR, 22/98 (22.4%) potentially eligible patients would have regained ROSC at or before the moment of presentation in an ECPR-centre. At least 42 patients would no longer be eligible for ECPR, as their arrival in an ECPR-centre would be beyond the pre-specified 45-minutes mark. For 8/98 patients (8.2%), EMS response times were not recorded. This leaves 26 patients potentially eligible for ECPR upon hospital arrival. Would 15 or 20 minutes of unsuccessful cCPR have been used as a cut-off to initiate transport, this would have respectively left 16 and 12 patients (Fig. 3). Eligible patients would have an average low-flow time of respectively 48, 52, and 57 minutes plus the time needed for cannulation, if ECPR would be initiated directly upon arrival in hospital.

Hypothetical eligibility for pre-hospital ECPR

After 10 minutes of cCPR on-scene, ROSC status was unknown for 27 patients, whereas 75/200 patients (37.5%) had regained a stable ROSC, leaving 98/200 patients (49.0%) being eligible for pre-hospital ECPR after 10 minutes of cCPR. An additional 14 patients regained ROSC in the subsequent 5 minutes of cCPR, whereas after more than 15 minutes of CPR only four patients got ROSC (Fig. 3). Therefore, 15 minutes of cCPR was found to be the optimal transition point for initiation of pre-hospital ECPR. At this point, 84 of the initial 622 patients (13.5%) met eligibility criteria, which is a 10.9% absolute increase (95% CI [8.0 to 13.9], $p < 0.001$) compared to the 16/622 patients (2.6%) that would be eligible for in-hospital ECPR if transport intra-arrest to the nearest ECPR-centre would have been initiated at that moment. Average low-flow time for these 84 patients would be 24 minutes plus the time needed for cannulation, if ECPR could be directly provided by a critical care teamon-scene by that time.

In an attempt to reach all eligible patients, an ECPR resource will have to be dispatched to all patients with a witnessed cardiac arrest with immediate bystander CPR who do not have a DNR (311/622, 50.0%). Therefore, the number-needed-to-dispatch in our population would have been 3.7 (311/84).

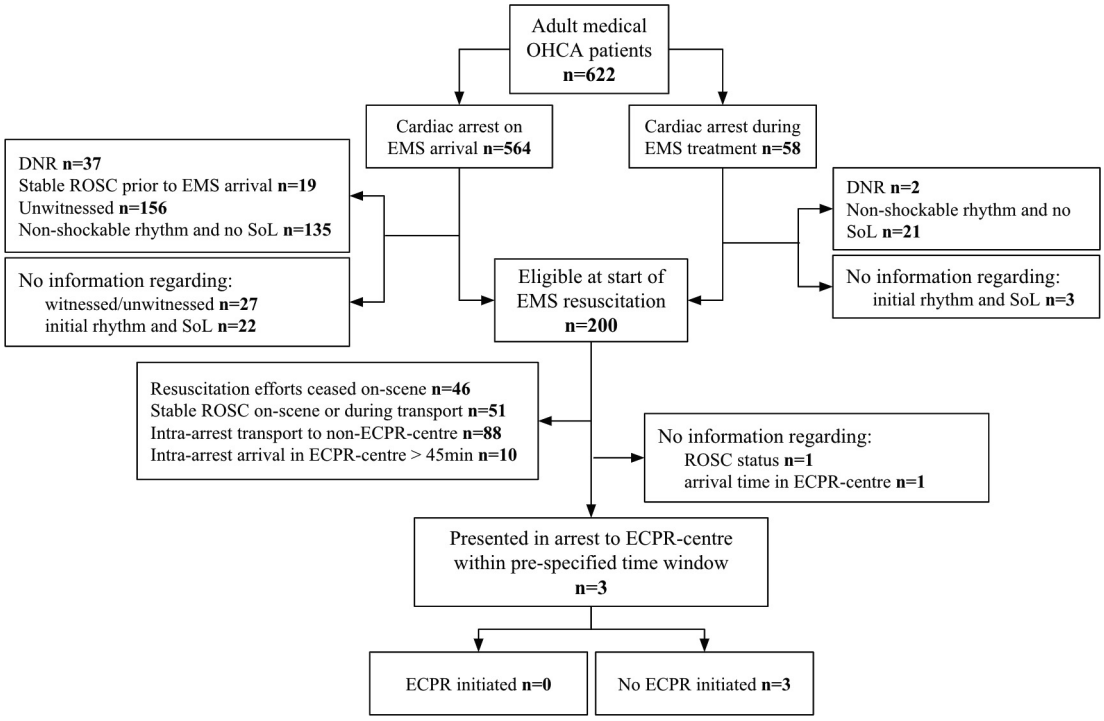

Fig. 2 – ECPR eligibility at the moment of initiation of conventional CPR by EMS. OHCA, out-of-hospital cardiac arrest; SoL, signs of life; DNR, do-not-resuscitate; ECPR, extracorporeal cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; EMS, emergency medical service.

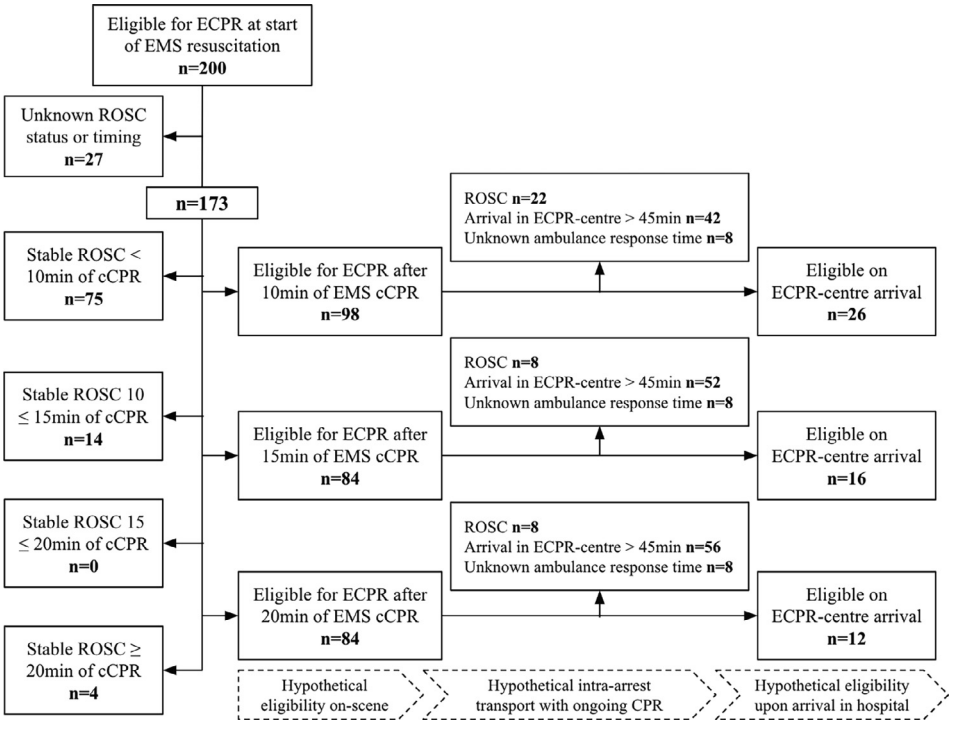

Fig. 3 – Flowchart of hypothetical eligibility for pre-hospital ECPR based on a time spatial analysis of ROSC rates (n = 200). ECPR, extracorporeal cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; EMS, emergency medical service; cCPR, conventional cardiopulmonary resuscitation.

Discussion

In the present study, we demonstrate that pre-hospital initiation of ECPR may increase the number of potentially eligible patients more than 5-fold compared to in-hospital ECPR, mainly by significantly shortening the low-flow times.

Previous studies have reported that the number of OHCA patients who may benefit from in-hospital ECPR for OHCA is low.[17,18] As in our study, this comes down to the fact that the time to deliver patients to an ECPR-centre is prohibitively long when combining times normally spent resuscitating on-scene and the distance to travel to reach ECPR-centres. Implementation of a strict pre-hospital redirection protocol, wherein potentially eligible ECPR candidates are directed to ECPR-centres intra-arrest after 15 minutes of unsuccessful cCPR may increase the number of eligible patients.[19–21] This is in line with our predictions: in the first 15 minutes, EMS crews would be able to regain a stable ROSC in 89 of the 200 (44.5%) patients meeting ECPR eligibility criteria at the time of arrival of EMS. Thereafter however, the number of patients in whom a stable ROSC could be obtained was small, and hence either pre-hospital ECPR or expedited intra-arrest transport to the nearest ECPR-centre should be considered.

If in our population this 15-minute optimal transition point would have been used in a pre-hospital EMS redirection protocol with the intent of performing in-hospital ECPR, this could have increased the percentage of potentially eligible patients upon arrival in hospital from 0.5% to 2.6% (95% CI [0.7–3.4], $p = 0.003$). However, even then, many patients still would not have made it into the ECPR-centre within the predefined 45-minute time window. This is in line with findings from the recently published INCEPTION trial, also carried out in the Netherlands, where the average time from arrest to start of cannulation for eligible patients was 58 minutes.[9]

Pre-hospital instead of in-hospital cannulation not only increases the number of eligible patients, it mainly does so by reducing the time taken to get onto VA-ECMO. Predictive modelling studies previously have estimated a difference in low-flow interval of around 35 minutes between in-hospital and pre-hospital initiation of ECPR in an urban environment.[22] This is in line with our findings, wherein we demonstrate a reduction in low-flow time of 28.3 minutes. As there is compelling evidence that low-flow duration is related to neurological outcome,[23–26] this may have important prognostic implications.

For mobile ECPR teams to reach all these patients quick enough to initiate ECPR early after the 15-minute transition point, early dispatch is warranted. Our findings demonstrate that this is feasible, as the amount of overtriage needed at dispatch to reach all potential ECPR eligible patients would be relatively limited with a number-needed-to-dispatch of 3.7.

In some systems (urban, high ECPR availability and integrated EMS systems) a quick transport to hospital will work well at delivering a high number of ECPR candidates and avoiding the challenging logistics of pre-hospital provision.[27] In most areas however, as demonstrated by this paper, transport intra-arrest to an ECPR-centre will not deliver most potential ECPR candidates to hospital in time, and pre-hospital ECPR delivery will allow a greater patient population to benefit.

The ultimate potential of pre-hospital ECPR depends on many variables including geography, population density, rate of bystander CPR, AED availability, dispatch criteria, availability of a dedicated team, ECPR-team transport mode and patient selection criteria. The EuReCa TWO study showed that bystander CPR rates in Europe range from 13% to 82% between countries with an average of 58%.[28] A lower rate of bystander CPR may result in less ROSC before arrival of EMS, but also in a lower percentage of patients who still have a shockable rhythm by the time of arrival of EMS.[29] Our findings should therefore not simply be extrapolated to other regions or healthcare systems, but rather be regarded as an example of how potential benefit of a pre-hospital ECPR program can be quantified before feasibility and cost-effectiveness of pre-hospital ECPR are explored.

We acknowledge that our study has several limitations. First, as we used previously collected data for our modelling study, there was a significant amount of missing data regarding ROSC rates and timing. However, as we classified patients with missing data as non-eligible, hypothetical eligibility rates are rather an under- than an overrepresentation of true rates. Further, patients who obtained ROSC on-scene, subsequently lost output, and then regained ROSC prior to transportation to hospital were considered as non-eligible. This may have contributed to an underestimation of eligibility as they potentially may have benefitted from pre-hospital initiation of ECPR to avoid a (second) low-flow period. Second, in our study we report numbers of *potentially* eligible patients based on information immediately available to pre-hospital care providers. Numbers of *actually* eligible patients are likely lower, as prognostic indicators to help guide ECPR decision making, such as $ETCO_2$, lactate, pO2, as well as age and frailty have not been taken into account. Third, we used hypothetical transport times to estimate ECPR eligibility when a dedicated redirection protocol would have been used. These transport times were calculated using Google Maps with an estimated 25% subtraction for blue-light driving.[30,31] However, cross-referencing time benefits from our estimates with true recorded transport times for those patients who were actually transported to an ECPR-centre demonstrated that this was an accurate estimation. Further, our study did not investigate how prehospital ECPR can best be delivered: the moment of dispatch, the number of available ECPR -teams (in relation to travel distances), team composition and team training are all factors that have to be considered. From our data however, it seems that ECPR-teams to be effective, should benefit from early dispatch and reasonably short travel distances to reach the patient within reasonable timing.. Finally, studies currently underway should answer the question whether the potential for pre-hospital ECPR as found in this study also translates into a survival benefit with good neurological outcome.[32–34] Low-flow times are only one aspect of prognosis and patient outcome. ECPR is part of a bundle of care, and should be implemented in a pre-established pathway, whether it is initiated in hospital or pre-hospital.

Conclusion

Even in healthcare systems with relatively short transport distances to hospital, consideration should be given to pre-hospital initiation of ECPR for OHCA as it shortens low-flow time and increases the number of potentially eligible patients.

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None.

CRediT Author Contribution Statement

EtA: conceptualization, methodology, supervision, and writing - orginal draft. IV: formal analysis, visualization, and writing- original draft. ED: data curation, project administration, investigation and writing- review & editing. MK, BD, RP and EMFJ: Investigation, Resources and writing- review & editing. JCtM, MMRFS, BS, BWJB investigation writing- review & editing.All authors gave final approval of the version to be submitted and agreed to be accountable for all aspects of the work.

Declaration of Competing Interest

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.

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.resuscitation.2023.109825.

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