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Potential candidates for ECPR in the catchment area of the University hospital in North Norway

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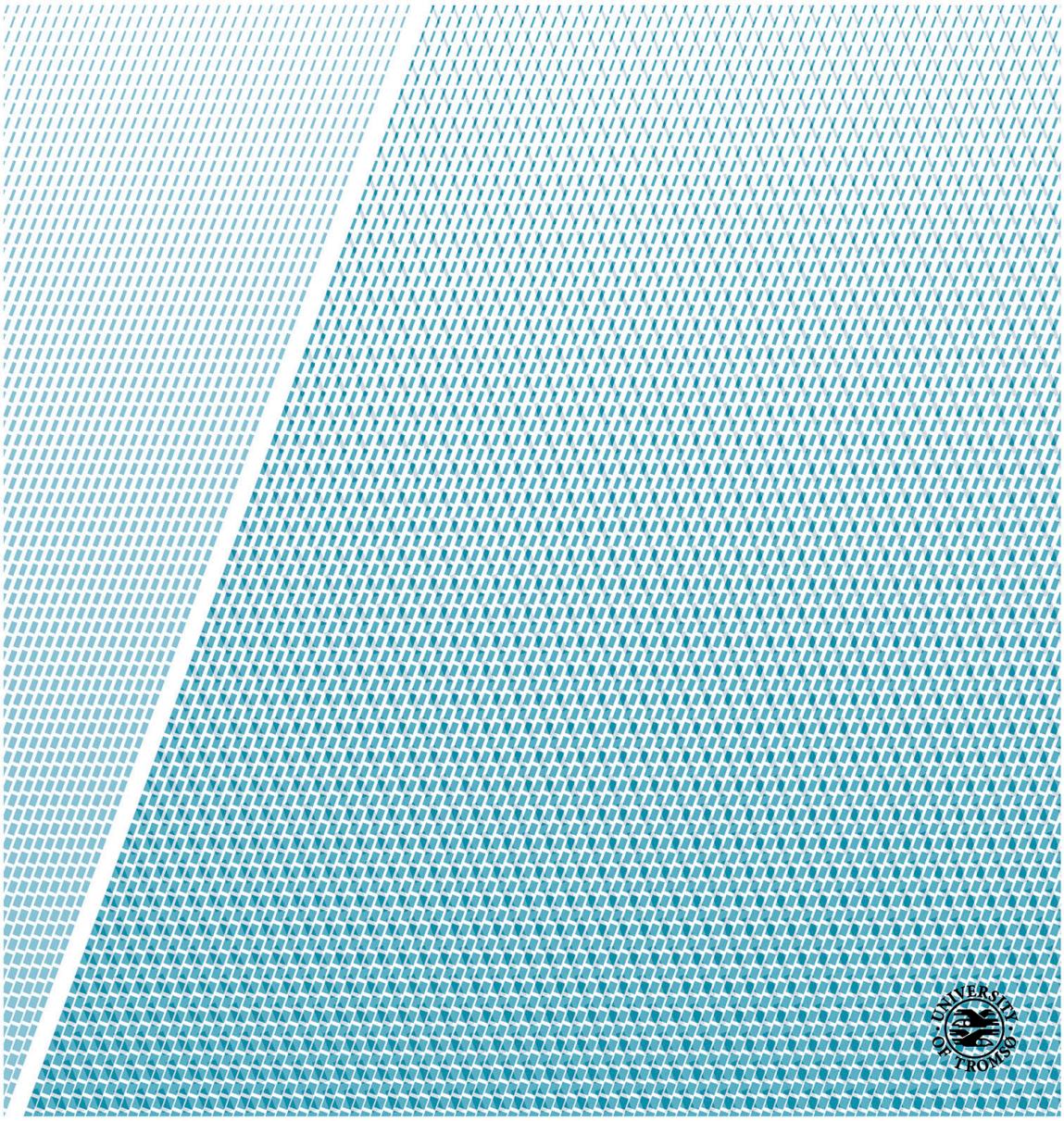

Preface

Ever since I was a small child my dream has been to work with emergency medicine at one of Norway's helicopter emergency medical services. When I started medical school in 2014 the dream was getting closer, and I got the chance to get to know associate professor Knut Fredriksen because of our common interest in acute care medicine thru Tromsø´s Acute Care Fraternity (TAMS). Dr. Fredriksen has been pivotal for my entire work ever since he accepted my request as supervisor for this project. He has been a very engaging supervisor, and has spent countless hours helping me with my thesis. I´m very grateful for all the help, guidance, discussions and supervision he has given me. His encouragement, professional knowledge and interest for this field of work is beyond limits, and has made this journey very interesting and educational.

I also want to thank Torvind Næsheim who is an pioneer in the University Hospital of North Norway's ECMO program. Thanks for all the help with selection of the right patients and the expert guidance.

I also want to thank Rod Wolstenholme at the UiT for designing the figure in this thesis. Thanks to Ståle Bratland at the Department of Clinical Medicine for assistance with collecting data from The Norwegian Cardiac Arrest Registry, and thanks to Tommy Kraknes (pilot with Norwegian Air Ambulance Foundation) for the discussion about estimated flight times for the HEMS.

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Abstract

Introduction: Some studies report increased survival from out of hospital cardiac arrest (OHCA) with extracorporeal cardiopulmonary resuscitation (ECPR), but the survival rates vary and heterogeneous study populations complicate comparison between studies.

Aim: The purpose of this study was to find potential ECPR candidates among all OHCA cases in the catchment area of the University Hospital of North Norway (UNN).

Material and methods: In a case series design, we analyzed retrospectively patient record data from the local UNN OHCA registry from January 1 2015 to December 31 2017. Patients were included in the study if they fulfilled the UNN ECPR protocol criteria: Age $\leq$ 80 years, witnessed OHCA with bystander CPR, no-flow time < 5 min, initial VF, VT or PEA and a refractory cardiac arrest. However, we omitted the time limitation of CPR time of maximum 40 min in order to also include the cases that theoretically would have been excluded solely due to distance from the center. Geographical position at the time of arrest was recorded and travel time to the center was estimated.

Results: There were 321 cases of OHCA during the study period. Following the ECPR inclusion criteria 138 cases (43%) were included, of which 22 (7%) did not have an exclusion criterium, and were considered eligible for ECPR, but only five had actually been treated with ECPR.

Conclusion: Approximately 7 % of OHCA in the UNN area fulfilled the ECPR criteria, and may theoretically have benefited from ECPR treatment. However, with the current requirements of low flow time, only nine would have access to the treatment. Integration of an OHCA-ECPR program may have a small but clinically important effect in selected patients. Our results encourage further investigation of wider application of ECPR, which in the future also should focus on options for the OHCA patients that occurred outside the current geographical limits for this therapy.

Key words: *Out-of-hospital cardiac arrest, Extracorporeal membrane oxygenation, Cardiopulmonary resuscitation*

Abbreviations

ACLS = Advanced Cardiovascular Life Support

AED = Automatic Electric Defibrillators

AHA = The American Heart Association

ALS = Advanced Life Support

AMIS = The UNN Emergency Medical Communication Centre´s Electronic Record

CPR = Cardiopulmonary-resuscitation

DC = Direct-Current

ECMO = Extracorporeal Membrane Oxygenation

ECPR = ECMO-CPR

EMS = Emergency Medical Services

EPR = Electronic Patient Record

ERC = European Resuscitation Council

HEMS = Helicopter Emergency Medical Services

IHCA = In-Hospital-Cardiac-Arrest

OHCA = Out-of-Hospital-Cardiac-Arrest

PEA = Pulseless Electrical Activity

REK = Regional Ethical Committee

ROSC = Return of Spontaneous Circulation

UNN = University Hospital of North Norway

VF = Ventricular Fibrillation

VT = Ventricular Tachycardia

1. Introduction

1.1 Out of hospital cardiac arrest

Out-of-hospital-cardiac arrest (OHCA) is a major cause of death, especially as a consequence of cardiac disease(1, 2). The prevalence and incidence of the condition has been reported with widely different figures from different sources, but the recently established Norwegian Cardiac Arrest Registry has shed some light on the missing key epidemiological data for cardiac arrest. The registry was established by the Norwegian National Advisory Unit on Prehospital Emergency Medicine in 2002, and received status as a mandatory national health registry in 2013. It´s main objective is to monitor the quality of the healthcare given in OHCA(3). Only patients with cardiac arrest that has received bystander or emergency medical services (EMS) treatment are included in the registry, in order to distinguish treatable OHCA from other causes of sudden death. Currently, more than 80% of OHCA cases in Norway are included in the registry, and it is a limited variation between the regions completeness of data(4). The main epidemiological figures for OHCA in Norway are shown in Box 1. The incidence is comparable to other parts in the world, and are in the order of 53-61/100,000 inhabitants per year, and the frequency of bystander efforts to start resuscitation is clearly increasing(3-6).

1.2 Etiology

Cardiac disease represents the most frequent presumed etiology for OHCA, followed by respiratory disease(1, 4, 7, 8), but also other mechanisms, like trauma, intoxications, neurological conditions and hypothermia are involved in a limited number of the cases (Box 1 and 2).

1.3 Cardiac rhythm

The presenting arrhythmia divides cardiac arrest into two main categories, the shockable and the non-shockable arrests, based on the fact ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) may be treated with cardiac defibrillation. All treatment of cardiac arrest is described in widely distributed algorithms published by the main resuscitation science bodies, like the European Resuscitation Council (ERC) and the American Heart Association (AHA)(9, 10). The advanced life support (ALS) treatment algorithms differ slightly for the two main categories, as does also the prognosis, as patients with a shockable

rhythm have a higher portion of return of spontaneous circulation (ROSC) and survival(11-15). This fact is, however, is depending on quick access to defibrillation(16-18).

1.4 Cardiopulmonary resuscitation (CPR)

Both groups need basic life-support like cardiopulmonary resuscitation (mouth to mouth rescue ventilations and chest compressions). This may be performed by bystanders in the public following a short training in simple CPR. Advanced life support is based on medically trained providers, like ambulance staff (emergency medical services, EMS) that may defibrillate, use technical adjuncts for both chest compressions and airway management and use drug in order to treat the patient. However, even defibrillation has become increasingly accessible to laypersons with a minimal amount of training, as modern automatic electric defibrillators (AED) may be positioned within the reach of the public, and may therefore be used before the EMS arrives on the scene. Karlson et al., found tripled bystander defibrillations and nearly a doubling of 30-days survival when accessible AED´s for bystanders compared to no-accessible AED`s(16).

1.5 Prognosis

The prognosis of OHCA has been considered dismal with only 2-16 % survival(15, 19-22), and there is significant differences in survival between different countries and regions(2, 23). However, the prognosis is better in subsets of patients. This increase in survival is attributed e.g. to implementation of standardized treatment guidelines, increase in bystander-observed arrest, and bystander CPR with early access to defibrillation, if the presenting rhythm is possible to defibrillate, and in the case of a reversible cause of the arrest(21, 24, 25). The last decade has shown rising survival after OHCA, and Lilja et al., found that the majority of the patients in working age came back to work after OHCA in Denmark, tough had the survivors a more restricted societal participation 6 months past arrest(26). Another study in Norway by Ørbo et al., assessed the possibility of neurological damage and neuropsychological issues after OHCA and found normal cognitive outcome in more than half of the survivors(27).

1.6 Advanced Cardiovascular Life Support (ACLS)

Over the last years it has been increasingly feasible to offer temporary extracorporeal circulatory support to selected OHCA patients, particularly to those with a reversible cause of arrest. This contrasts earlier studies that have failed to reveal improved patient outcome

from advanced pre-hospital services, like physician-manned ambulances, air ambulance services, or from advanced treatment like advanced airway management or use of drugs(15, 18). However, early institution of basic bystander CPR has on the contrary proven most effective, and recent publications have demonstrated that population based education of laypersons correlates with significantly increased bystander CPR rates(28, 29), and this even relates to increased survival from OHCA(21, 30). In addition, shortened EMS response intervals, access to early defibrillation has also contributed to improved survival rates(18, 20, 21, 24, 25). In the intra-hospital setting the focus has for years been on optimal post-resuscitation treatment, however limited to patients with ROSC, e.g. temperature control and therapeutically hypothermia. The impact of this treatment has been modest, at best(31), but more recently intriguing and promising results have been demonstrated with extracorporeal membrane oxygenation (ECMO) for OHCA (ECPR) even without return of spontaneous circulation (ROSC)(17, 32-35).

1.7 Extracorporeal membrane oxygenation (ECMO)

Extracorporeal cardiopulmonary resuscitation is in principle a veno-arterial cardiopulmonary bypass that oxygenates and circulates blood externally through cannulation of large arteries and veins(19, 36). The ECMO technique has been utilized for several indications, for instance: respiratory failure, sepsis, trauma, cardiac arrests and many other. The technology was developed in the 1960s, at that time to replace heart and lung function until heart surgery could be performed. Kennedy JH., suggested already in 1966 that heart-lung machines should be considered for use as an extended form of cardiopulmonary resuscitation in selected patients(37), and ECPR has since the 1990s been developed as rescue therapy in patients with cardiac arrest(14, 38, 39). If ECMO is established in time after cardiac arrest, adequate perfusion of vital organs may be secured whilst the underlying etiology for arrest is diagnosed and specific treatment is initiated.

According to international consensus ECPR should be initiated within 60 minutes of onset of OHCA to keep the low-flow period (conventional CPR) at a minimum to achieve an acceptable neurological outcome if the patient survives(7, 19, 39-41). Transport from the scene to the ECMO-center has to be considered early, in order to reach this goal. Between 8 to 24 minutes has been suggested as an ideal timing for considering transport, with 16 minutes as a midpoint balancing the risks and benefits of early and later transport where

earlier transport is preferred for non-shockable rhythm if the quality of CPR can still be maintained(11, 19, 42). However, Kim et al., claims that 21 minutes is an optimal timing of to switch from conventional CPR strategy, to go for ECPR(43). Selection of patients to ECMO must therefore follow a strict protocol, based on inclusion and exclusion criteria that allow the EMS crew to identify the right candidates within a very short time after arrival on scene. However, the time frames described above, are probably impossible to achieve in most places of the world, except the larger cities, as the distance from the scene to the nearest ECMO center will be too big. This is also true in Norway, in spite of a modern and advanced health care system, and especially in North Norway, with only one single ECMO facility covering the entire region.

Only a few recent studies have addressed how many patients could be potential candidates for ECPR, and all of these were undertaken in urban settings. Poppe et al., found that 6% of the OHCA-patients in Vienna without ROSC fulfilled the criteria for ECPR(44), while the OHCA patients in Vancouver fulfilled the criteria in approximately 10% of the cases(22).

1.8 Rural North Norway

The University Hospital of North Norway in Tromsø (UNN Tromsø) is the only ECMO center in North Norway. The last years an ECPR protocol has been established, based on clear inclusion and exclusion criteria. The time limits of the protocol for the most part limits the treatment to patients in the urban areas of the city, with some exceptions being a limited number of patients that have been resuscitated with intermittent periods of ROSC during air ambulance transport to the UNN Tromsø.

To our knowledge, no studies from a rural setting have addressed OHCA patients that could theoretically be included, especially not using the UNN Tromsø ECPR protocol. Thus, we investigated the geographical distribution, with ensuing transport times from the scene of cardiac arrest to the ECMO center, for OHCA patients without ROSC in the catchment area of the UNN. Our main research question was how many patients should theoretically have been included if their geographical position had allowed a timely transport into the ECMO facilities according to the ECPR protocol, and how far in time were these patients from being eligible for ECPR. We wanted to assess the hypothesis that most patient with cardiac arrest in our area are too far away from the University Hospital (UNN) in Tromsø in time and distance for being eligible for extracorporeal membrane oxygenation as a rescue therapy.

2. Material and methods

2.1 Study design

This study is a case series based on retrospective patient record data, based on data recorded at the UNN for the Norwegian Cardiac Arrest Registry.

2.2 Study setting

The study is limited to the catchment area of the UNN. The UNN has department hospitals in the cities of Tromsø, Narvik and Harstad. The area has a population of approximately 183,500 inhabitants distributed over an area of ca 30, 000 sq.km(45). Outside the cities, the majority of the population is located in rural areas, and ground ambulance times are normally between 1-4 hours of driving time to hospital. Widespread use of helicopter emergency medical services (HEMS) cover the area with two HEMS bases that may reach the majority of the patients within 25 min. The UNN in Tromsø is the only ECMO capable facility in the region.

2.3 Data acquisition

We extracted all EMS-treated OHCA cases reported to the healthcare trusts database of reports to the Norwegian Cardiac Arrest Registry in the catchment area of the UNN in the period January 1, 2015, to December 31, 2017. The national registry collects variables according to the Utstein reporting template(46). All patients are deidentified in the registry, and it´s only possible to identificate the patients through an link key.

Data reported to the national registry were supplemented with necessary data from the in-hospital electronic patient record (EPR), the UNN Emergency Medical Communication Centre's electronic record AMIS® and the HEMS database system LABAS® (Table 1). Especially demographic information were collected from AMIS and LABAS. All obtained data were compared to the UNN ECPR protocol inclusion and exclusion criteria (Table 2), and screening for ECPR eligible patients followed this protocols inclusion and exclusion criteria's. An association between age and favorable outcome has to our understanding not yet been established in other ECPR observational studies for OHCA´s, and therefore we sat the upper age limit to $\leq$ 80 years in our inclusion criteria which were higher than most other studies. Age was calculated from the National Cardiac Arrest Registry. According to the study protocol, some patient's records were not included for analysis because of criteria being

impossible to determine or missing. If notes were missing in the ambulance records or in the cardiac arrest registry, it was counted as absent, and the patient was excluded. The initial rhythm was determined using the first reported rhythm after arrest. Information from the scene were collected from the ambulance records or LABAS® and AMIS®. In case that were initially indeterminate, a panel of an experienced anesthesiologist and cardiothoracic surgeon (both part of the UNN ECMO team) concluded what would have been the most plausible decision about ECMO treatment or not, and the patients were included or excluded accordingly. Only patients that met all criteria were included as potential ECPR-candidates.

The distance and time from the included OHCA´s to the nearest ECMO performing hospital, UNN Tromsø, were calculated by air distance, and timetable for the air ambulance and for ambulance by road was taken from earlier established timetables and estimates based on an average speed of 70km/h by ground ambulance (Table 4). Specific timetable from the two HEMS-bases to the location of cardiac arrest is different due to their different geographical location in Tromsø and at Evenes. In the time estimates it is calculated with optimal weather conditions which means it´s possible to take optimal routes, and with zero head wind. The average speed is different for the helicopters; HEMS1 = 150knots (≈ 278kph) and HEMS 2 = 120knots (≈ 222kph), and they will therefore have different response times to the different locations. In some cases the HEMS is not relevant due to faster response times by ground ambulance, like in the city of Tromsø.

Transport times for ground and HEMS were recorded from a database of normal transport times from alarm, to the scene of arrest, and to the UNN Tromsø. In addition we added 15 minutes as necessary ground time for both the EMS and HEMS at the location to imitate realistic ground effort before an evacuation can be possible.

2.4 Statistical analysis

All data were registered and analyzed in a Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, USA) worksheet. Descriptive statistics were used. Data are reported as mean value and median [range], while categorical values are reported as number (%).

2.5 Endpoints

The main endpoint of the study were to find how many OHCA patients in our catchment area who possibly met all inclusion-criteria for ECPR despite their geographical location at

the time of cardiac arrest (Table 4). Further, we wanted to assess the geographical location of the patients at the time of arrest, and calculated the transport time by ground and air ambulance from this location and to the UNN Tromsø for the included patients, and calculated if they would have been offered ECPR if their location had been closer to UNN Tromsø.

2.6 Ethics

The project is a quality improvement project and is approved by the UNN's Data Protection Officer (ref. no. 2018/1514). No ethical improvement were required for this retrospective registry study, and there were therefore no need of approval from the Regional Ethical Committee (REK).

3. Results

3.1 OHCA in the UNN catchment area

The UNN EMS treated 321 patients suffering out-of-hospital cardiac arrest in the catchment area of the UNN in the study period between 2015 and 2017. 88 (27,4%) of the cases were females. Mean age 64,9 years [0-93] (median age 69 years). All included patients had to fulfill the inclusion-criteria to be ECPR eligible. Of 321 patients, 22 (6,9%) patients fulfilled our hypothetical ECPR criteria and were included in the study (50% were females) (Table 5: Patients characteristics). The mean age of the included patients were 58,3 [19-76] (median age 60 years). The study flow are listed in Figure 1.

3.2 Epidemiology

Presumed causes of the cardiac arrests had a cardiac cause in approximately 70 % of the cases, and presumed respiratory cause in about 7,8 % of the cases. The Norwegian Cardiac Arrest Registry lack complete information about the survival rates, and it is missing in 55 cases. Despite missing data on survival, 42 patients (13,1%) is recorded with 30 days survival. The reported survival of 42 patients gives an estimate of 279 deceased patients, which gives a 30 days survival rate of 13,1%.

3.3 Excluded by the ECPR protocol

Exclusion of patients followed the UNN ECPR protocol´s inclusion and exclusion criteria. Several patients was excluded on more than one point. 64 patients (19,9%) were excluded due to age > 80 years. 106 (33%) were excluded due to non-witnessed cardiac arrest and 117 (36%) because of no-bystander CPR. The largest exclusion criteria was initial asystole which excluded 149 patients (46%). Because of missing data or indeterminable data 23 patients was excluded. The reason of exclusion are listed in Table 3.

3.4 Distance and time to UNN Tromsø

The mean distance from location of cardiac arrest to UNN Tromsø by road were 123,6km [4-301], (median 111 kilometers). Estimated mean time by road from location of cardiac arrest too UNN Tromsø were 107 minutes [3-265] (median 107,5 minutes). While the estimated mean time by HEMS were 53,5 minutes [10-100] (median 50 minutes) for HEMS1, and 64 minutes [54-87] (median 60 minutes) for HEMS 2 in feasible cases. HEMS services was not recommended as feasible in 7 cases due to ground ambulance was the absolute fastest alternative. The distribution of all OHCA´s in our region are plotted in figure 2.

3.5 ECMO-patients

Of the 321 patients, only 5 were reported as ECMO patients in the Norwegian Cardiac Arrest Registry (the number is probably higher in reality), and of the 22 included patients in the study, only 5 cases were treated with ECPR during the study period (3 men, 60%). Mean duration of ECMO were 74,4 hours [12-168], only one survived to hospital discharge. Of the included patients, 17 died without ECPR therapy. Based on the international consensus of initiating ECPR within 60 minutes of onset of OHCA, only 10 of the included patients fulfilled the current time criteria when transported by ground ambulance and not calculating for 15 min pitstop time (the time the ambulance or HEMS use at the scene of OHCA before evacuation is possible). When calculating pitstop time of 15 minutes in addition to transport time, one case of transport by ground ambulance would have been excluded due to exceedance of time limits, which gives us 9 realistic ECPR candidates by current requirements of low flow time. In some of the mentioned cases, the HEMS would have been a more feasible alternative. HEMS1 from Tromsø could have reached the location of OHCA and back to the UNN in Tromsø by under 60 minutes in 7 of the cases, and HEMS 2 from Evenes could have been feasible in zero cases due to long transportation from actual

locations and would therefore not be capable to reach the UNN by 60 minutes. In cases of intermittent periods of ROSC during transport, the time is reset and both HEMS and EMS could be a reasonable transport in selected cases.

4. Discussion

A total of 321 patients were treated for OHCA during the study period, with approximately 13% of 30 days survival. Of the 321 OHCA´s only 22 (6,9%) fulfilled our hypothetical ECPR criteria. Only one (4,5%) of the included patients survived to hospital discharge. The largest exclusion criteria were asystole (46%), followed by no-bystander CPR 36% and age > 80 years 33%. Among the included patients were the mean distance from location of CA to the UNN in Tromsø 123,6 km, and estimated mean time by road to the UNN were 107 minutes. Estimated mean time by HEMS1 were 53,6 minutes, and 64,3 minutes for HEMS2. In 7 cases were ground ambulance considered as the fastest alternative of transportation. Of the 22 cases, only 5 patients were treated with ECPR, and 17 patients died without ECPR therapy. Only 9 patients fulfilled the current time criteria for consideration of ECPR, all of them were located in or around the city of Tromsø at the time of cardiac arrest.

OHCA has generally a poor prognosis (15, 19-22), but the survival is increasing in subsets of patients, especially in bystander-observed cases and in cases where early bystander CRP has been initiated and when defibrillation is given before EMS arrival(21, 24, 25). Studies have failed to reveal improved patient outcome after advanced pre-hospital life support measurements instead of basic bystander CPR, early defibrillation and early EMS response(15, 18). The increase in early bystander CPR and defibrillations may contribute to an increased survival rate by maintaining a certain cerebral perfusion while waiting for the EMS and in some cases by achieving ROSC before EMS arrival. In cases of no bystander CPR the arrival of EMS and HEMS would have been useless. Bystander CPR obviously gives the EMS a better starting point of the resuscitation, and CPR training of laypersons and in schools may be a great contributor to the tendency of increased survival rates(28, 29).

During the last decade it has been more normal and feasible to offer ECPR-treatment to selected OHCA-patients in urban areas. Earlier studies has shown variable outcome on survival after ECPR therapy, but recent studies has demonstrated promising results on

survival in highly selected patients with ECPR(14, 17). The variability in ECPR results and outcome may be due to the limitations in availability, local resources, cost-efficacy and especially ethical limitations at subgroups at CA patients. Patients with a reversible cause of CA which can be treated whilst maintaining perfusion of critical organs, e.g. cerebral perfusion has shown good results. A good example of well used ECMO therapy is the study done in 2014 by Hilmo, Naesheim and Gilbert. They concluded with "Nobody is dead until warm and dead", and they found that pre-hospital EMS and hospital emergency teams couldn't be sure of which patients who would survive resuscitation attempt after hypothermic cardiac arrests until extracorporeal rewarming was performed(47).

Both the AHA and ERC guidelines from 2015 are addressing ECPR as a possible rescue therapy in selected cases when conventional CPR is failing and to facilitate specific interventions(10, 48), but the technique is preliminary though only reserved to selected patients in urban areas with rapid access to a ECMO facility(32-35). The ECPR therapy in Norway are limited to the heart surgery center at the university hospitals in Oslo, Trondheim, Bergen and Tromsø. The latter is the only one in North Norway, and is in principle covering one third of Norway's land area from the counties of Nordland to Finnmark. Because of the long distances and short interval of optimal window for initiating ECPR, the therapy is therefore limited to the area in or around the city of Tromsø. The ECMO teams in Norway consist of heart anesthesiologist, perfusionist and a heart surgeon. Their competence has to be maintained by regularly use of heart lung machine and invasive circulation control. The UNN has ECMO procedures which is made to select the "right patients" in the right occasions, but the low-flow time is still the crucial limiting factor in offering ECPR-therapy. In this study we looked away from geographical limitations, which means we excluded the utopic time factor. The purpose was to determine how many patients which is possible to save if we can maintain the perfusion whilst the reversible cause is being treated, e.g. with PCI, thrombectomy, transfusions and bleeding control, dialysis of intoxications etc.

We found that the majority of the patients who fulfilled our inclusion criteria lived in the most urban areas of our region, and especially in or around the city of Tromsø. Our findings of approximately 7% of hypothetically ECPR eligible patients lies between the findings of Poppe et al., with 6% in Paris and Granau et al., with 10% in Vancouver(22, 44). There may

though be a bias in inclusion of the patients in the cardiac arrest registry which leads to our findings, but it´s the same department at UNN who register all the OHCA´s for the entire region, and all of the EMS in the study area belongs to the same department at the university hospital. The EMS are dispatched at almost 100% of all OHCA´s in the area and there are strict routines of delivering Utstein data after each OHCA. In cases of OHCA´s far away from public roads, on mountains, islands etc. The HEMS are dispatched to the scene, and in those cases the HEMS doctor is responsible to register the OHCA. The HEMS is part of another division of the same department as the EMS, and due to good collaboration between the department, divisions, emergency physicians and field supervisors we believe that we have complete results for all of the OHCA´s in our area, and there is nothing which leads to think there could be systematic geographical errors in our data. The complete dataset is probably tough too small to draw valid conclusions regarding ECPR candidates. Only patients with clear notes were enrolled in the study, and therefore it´s still a possibility that only a minimum of ECPR candidates were discovered.

There has been shown a difference between survival in intra-hospital-cardiac arrest (IHCA) and OHCA after ECPR treatment, where IHCA has shown survival rates between 20 to 35% (49, 50), while OHCA´s still have pessima prognosis up to 15% in highly selected patients(51), the survival rates is tough similar after adjustments for the low-flow time(19). Better outcomes after IHCA may be due to more effective and rapid resuscitation with early access to ECPR treatment and less low-flow time. Hutin et al., addresses the difference between low-flow time at IHCA and OHCA as a key difference in survival(7), and that longer intervals of conventional resuscitation preceding ECPR are associated with poor outcome(19). Less low-flow time could be possible for OHCA´s in urban areas with minimal distance to nearest ECPR center and optimal conditions. Some organizations employ mechanical chest compression machines (e.g. LUCAS2) and a rapid transport to initiate ECPR at the hospital. Other places like the cities of Paris and Düsseldorf even offer mobile ECPR treatment were specialized teams initiate ECMO treatment in the pre-hospital setting, and studies from these cities shows promising results(40, 52). The logistics around pre-hospital ECPR is probably most suited for urban areas where those specialized ECPR units can be dispatched shortly after arrest. Singer et al., discussed that the ECPR team should have a target response time within 10 minutes, which limits most rural and even metropolitan regions to

initiate ECPR(19). In Norway, the national target response time for the EMS are to reach 90% of the cases by 12 minutes. Our geographical distances and terrain would most likely limit an initiation of a pre-hospital ECPR program, especially in North Norway.

Including the suburbs, the city of Tromsø has a population of approximately 76 700. In comparison; Oslo has approximately 1 million while Paris has a population of approximately 2,2 million residents and a influence area of more than 12 million residents. The population density in Tromsø and the rest of North Norway is extremely different from the European big-cities. Lamhut, L et al., reported 156 actual cases from Paris over a 4 year period, while we found 22 potential candidates for ECPR in our region over a 3 years period. Of whom, only 9 of them would have been realistic candidates due to their location of the arrest. This gives us 3 ECPR cases per year, and we have to assume that this would enable a pre-hospital ECPR system at the UNN since the ECMO team would have had under one case per team member each year, all of which must have been available for dispatch 24/7.

The future may give us technological devices which can solve our challenge when it comes to engaging pre-hospital ECPR, but right now there´s nothing that suggests that will happen. There is also a great ethical challenge within critical ill ECPR patients and the relationship between cost efficacy and the quality of life, and this is an important issue to evaluate since the treatment is differentiated, the mortality is high and the prognosis is poor despite advanced modern therapy. So far, the residents in the region's largest city, Tromsø, has an acute care offer that the other residents in our region don't have. The differentiated access to heart surgeon and anesthesiologic competence, hence the ECMO team available 24/7.

To our knowledge, there is no published RCT´s assessing the use of pre-hospital ECPR, either no studies which has addressed ECPR in rural settings. Perhaps due to the minimal time available and long distance to a ECPR facility.

Of the 22 patients which were included in our study, only 5 of them were treated with ECPR. A total of 9 patients located in Tromsø at the time of arrest were found as potential candidates for ECPR, only 4 of them were treated with ECPR therapy, while the last patient which were given ECPR was resuscitated with intermittent periods of ROSC during HEMS transport to the UNN Tromsø. The remaining 17 patients was either transported to UNN with temporary ROSC, transported under ongoing CPR with mechanical compression

devices, or terminated in the pre-hospital setting. All of them deceased without ECPR therapy.

The mean distance from location of cardiac arrest to the UNN in Troms was 123,6km [4-301], with estimated time by road on 107 minutes [3-265] which gives us an estimate over our challenging reality when it comes to time and distance. Our two different HEMS has an estimated mean flight time of 53,5 [10-100] and 64 [54-87] minutes to the location of the included patients. The HEMS are in many cases a necessary resource when in need of rapid transportation. But does this mean that all OHCA´s in our region should lead to alert of the HEMS to facilitate transport of all OHCA´s to the UNN in Tromsø? It´s a theory that may and should be evaluated. It may be better to alert the HEMS and eventually it could be possible to terminate the resuscitation effort when identification of patients who wouldn't be a candidate for ECPR is detected. Most OHCA patients will not be candidates for pre-hospital ECMO, but a dispatch of both the EMS and the HEMS to all cases of OHCA could give the team necessary time and resources for choosing the "right patients" for rapid transportation of those with refractory ROSC/arrest, and at the same time be able to reach ECPR initiation when arriving the UNN in Tromsø. All patients in our area can be reached within approximately 30 minutes by the HEMS, but it can take up to over an hour from location to the UNN in Tromsø, which is a long time with hemodynamic instability. Mechanical compression devices is a necessity for transportation in ground ambulance, HEMS and winged aircraft, both for ensuring good compressions but also for safety reasons for the EMS personnel. Some studies shows better flow compared to conventional compression, but the difference is marginal, and the flow is probably still too low to compensate for the time and distance if the patient don't shows signs of life during the transport. If so happens, the time would have been reset in relation to the UNN ECPR protocol. Preliminary data of ECPR from the ECMO team at the UNN gives an estimate of survival around 30 %. It is still tough too early to estimate validated cerebral outcomes after ECPR. It is still a small number of cases, but the estimates is promising.

An important strength with this study, is that it is not only discussing the results of which patients who actually was given ECPR therapy, but it´s also discussing a hypothetical issue about potential candidates for ECPR therapy. It strengthens this study by assessing the issues

at an early stage, and there are few other studies as we are aware of that assesses the same problems. This is an interesting new and original way of addressing relevant issues.

This thesis has several limitations. The patients were small in numbers and highly selected from one single center in North Norway. The inclusion criteria was taken from the UNN ECMO protocol which consist of variables that there is some kind of international consensus about, but it is still unsure if there might be other variables that could give us better prognostic factors that would help us choose the "right patients". All reported data were collected from the Norwegian Cardiac Arrest Registry, electronical patient records, local HEMS and EMS journals. It is a possibility of some survival-bias in databases like the cardiac arrest registry, but we believe that this don't affect the results due to our understanding and knowledge about the complete registration of the cases described above. This study is also an subjective retrospective case series, where we are totally dependent of accuracy and quality in the registration of the data, and this point leads to the studies maybe biggest limitation and that was the lack of information about "signs of life" during resuscitation. The EMS personnel at the UNN has no strict system of reporting the "signs of life" during resuscitation, and the Norwegian Cardiac Arrest Registry has no point of which they assess "signs of life during resuscitation" in their template. There was also an subjective interpretation of our ECMO team in cases of doubt. Due to the reasons mentioned above, this should lead to an prospective collection of relevant ECMO registry data, and an update in the collection of the registry data. International guidelines should continuously be updated and evaluated, and local adjustments made when reasonable. The treatment with ECPR will in some way or another, be a part of the CPR guidelines in the future, and rural districts should not be forgotten.

We can see a great ethical challenge within critical ill ECPR patients and the relationship between cost efficacy and the quality of life. This is an important issue to evaluate since the mortality is high and the prognosis is poor despite advanced modern therapy.

5. Conclusion

We believe that we have found which patient who potential would have been ECPR candidates in the catchment area of the UNN. 22 of 321 (6,9%) EMS treated OHCA patients fulfilled our theoretically set of ECPR criteria when ignoring their geographical position at the

time of cardiac arrest, and they could potentially have taken benefit of rapid transportation with ongoing CPR to the ECPR facility at the University Hospital of North Norway in Tromsø. However, with the current requirements of low flow time, only 9 would have access to the treatment. Integration of an OHCA-ECPR program may have a small but clinically important effect in selected patients. Our results encourage further investigation of wider application of ECPR, which in the future also should focus on options for the OHCA patients that occurred outside the current geographical limits for this therapy.

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7. Figures and Tables

Box 1: Data from the Norwegian Cardiac Arrest Registry

Epidemiological figures of OHCA in Norway

	2015	2016	2017
Incidence	53	61	60
30-day survival	15%	14%	7%
Bystander CPR rate	75%	78%	81%

Assumed causes of OHCA in Norway

	2015		2016		2017	
	Number (n)	%	Number (n)	%	Number (n)	%
Cardiac cause	1702	67%	2184	69%	2180	69%
Respiratory failure	267	10,6%	292	9%	315	10%
Overdose & intoxications	145	5,7%	204	6%	169	5%
Trauma	93	3,7%	108	3%	88	3%
Drowning	40	1,6%	47	1%	44	1,4%
Other	290	11,4%	328	12%	376	11,6%
Total	2537		3163		3172	

Other incudes: neurological conditions, suffocating, SIDS etc

Box 2: Local data from the Norwegian Cardiac Arrest Registry

Assumed causes of OHCA in UNN´s catchment area 2015-2017

	2015		**2016**		**2017**	
	Number (n)	%	Number (n)	%	Number (n)	%
Cardiac cause	63	64,9%	91	72,2%	71	72,4%
Respiratory failure	10	10,3%	9	7,1%	6	6,1%
Overdose & intoxications	3	3,1%	6	4,8%	0	-
Trauma	5	5,2%	10	7,9%	1	1%
Drowning	2	2,1%	-	-	-	-
Other	14	14,4%	10	7,9%	20	20,4%
Total	97		126		98	

Other incudes: neurological conditions, suffocating, SIDS etc

Initial rhythm in UNN´s catchment area 2015-2017

	2015		**2016**		**2017**	
	Number (n)	%	Number (n)	%	Number (n)	%
VF	23	23,7%	26	20,6%	20	20,4
VT	1	1%	2	1,6%	2	2%
Asystole	41	42,3%	66	52,4%	42	42,9%
PEA	14	14,4%	18	14,3%	20	20,4%
Other/ unkown	18	18,6%	14	11,1%	14	14,3%
Total	97		126		98	

VF ventricular fibrillation, *VT* ventricular tachycardia, *PEA* pulseless electrical activity

Table 1: Data & Sources

DATA	SOURCE
LOCATION	AMIS®, LABAS®, EPR
MUNICIPALITY	AMIS®, LABAS®, EPR
AGE	NCAR
WITNESSED ARREST	NCAR
BYSTANDER CPR	NCAR
TIME OF ARREST	NCAR, EPR
ON-SCENE INFORMATION	NCAR, EPR, LABAS®
SIGNS OF LIFE DURING CPR	EPR
INITIAL RHYTHM	NCAR, EPR
NUMBER OF DC	NCAR
REFRACTORY ARREST	NCAR, EPR
KNOWN COMORBIDITY	EPR
MECHANICAL COMPRESSION MACHINE	NCAR, EPR
IN-FLIGHT CARDIAC ARREST	LABAS®
DISTANCE AND TIME BY ROAD TO UNN TROMSØ	Location + database
DISTANCE AND TIME BY AIR TO UNN TROMSØ	Location + LABAS®/database

AMIS® = the UNN Emergency Medical Communication Centre's electronic record, *LABAS®* = HEMS database system, *EPR* = Electronical Patient Record, *NCAR* = Norwegian Cardiac Arrest Registry, *DC* = Direct-Current, *CPR* = Cardiopulmonary resuscitation

Table 2: UNN ECPR protocol inclusion and exclusion criteria

Inclusion Criteria for Consideration of Pre-hospital ECPR 1. Age ≤ 80 years 2. Witnessed CA with bystander CPR 3. No-flow time < 5 min 4. Initial VF, VT or PEA 5. Refractory CA
Exclusion Criteria 1. Age > 80 years 2. Non-witnessed CA and/or no bystander CPR 3. No-flow time > 5 min 4. Initial asystole **5.** No refractory CA
ECPR = extracorporeal cardiopulmonary resuscitation, *CPR =* cardiopulmonary resuscitation, *CA =* cardiac arrest, *VF* = Ventricular Fibrillation, *VT = V*entricular Tachycardia

Table 3 Excluded by:

	2015	**2016**	**2017**
Age > 80years	27	22	15
Non-witnessed arrest	35	39	32
No bystander CPR	39	36	42
Initial asystole	41	66	42
Comorbidity (e.g HLR -)	9	8	9

Table 4: Time and distance table for the included patients

No.	Distance (kilometers)	Time by road (min)	Time HEMS1 based in Tromsø (min)			Time HEMS2 based in Evenes (min)		
	From location of CA to the UNN	From location	To location	Ground time	From location	To location	Ground time	From location
1.	135	115	25	15	25	35	15	28
2.	24	20	5	15	5	-	15	
3.	159	136	22	15	22	60	15	24
4.	87	100	15	15	15	70	15	17
5.	7,6	6	-	15		-	15	
6.	238	203	40	15	40	18	15	50
7.	163	139	18	15	18	35	15	22
8.	6	5	-	15		-	15	
9.	4	3	-	15		-	15	
10.	6,7	5	-	15		-	15	
11.	7	6	-	15		-	15	
12.	12,4	10	5	15	5	-	15	
13.	301	265	33	15	33	10	15	45
14.	277	237	50	15	50	7	15	60
15.	253	216	45	15	45	10	15	50
16.	53	45	8	15	8	-	15	
17.	5	4	-	15		-	15	
18.	12	10	-	15		-	15	
19.	255	218	40	15	40	4	15	50
20.	292	250	35	15	35	10	15	45
21.	185	158	15	15	15	37	15	20
22.	236	202	45	15	45	10	15	50

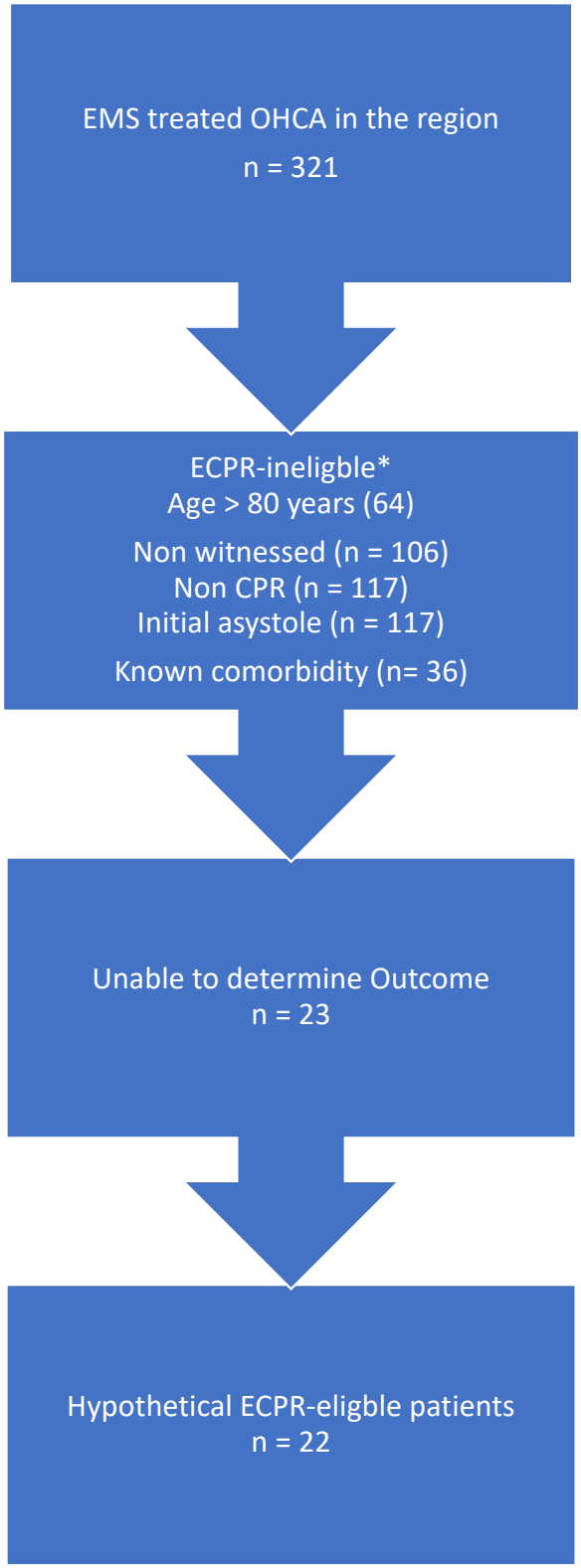
CA = Cardiac arrest, *To and From location* = estimates over time and distance to/from location, *Ground time* = A given ground time for both EMS and HEMS that is necessary before e.g. Transportation of patients under ongoing CPR.

Table 5: Patient characteristics

No.	Distance to UNN (kilometers)	Transport duration (minutes)	Initial rhythm	Number of pre-hospital DC	LUCAS2/ CPR	Time on ECMO (hours)	Survival (days)
23.	135	115	VF	2	yes	-	n
24.	24	20	VF	5	-	-	n
25.	159	136	VF	5	yes	-	n
26.	87	100	VF	6	no	-	n
27.	7,6	6	VF	3	yes	-	4 days
28.	238	203	VF	5	yes	-	n
29.	163	139	VF	5	-	-	n
30.	6	5	VF	7	yes	48	2 days
31.	4	3	VF	3	-	168	
32.	6,7	5	PEA	0	-	-	n
33.	7	6	VF	8	yes	-	n
34.	12,4	10	PEA	1	yes	-	n
35.	301	265	PEA	0	-	48	2 days
36.	277	237	PEA	0	N	-	n
37.	253	216	VF	5	-	-	n
38.	53	45	PEA	0	-	-	n
39.	5	4	VF	8	yes	96	30 days
40.	12	10	VF	10	yes	12	n
41.	255	218	PEA	0	-	-	n
42.	292	250	PEA	0	yes	-	n
43.	185	158	VF	3	-	-	n
44.	236	202	VF	1	-	-	n

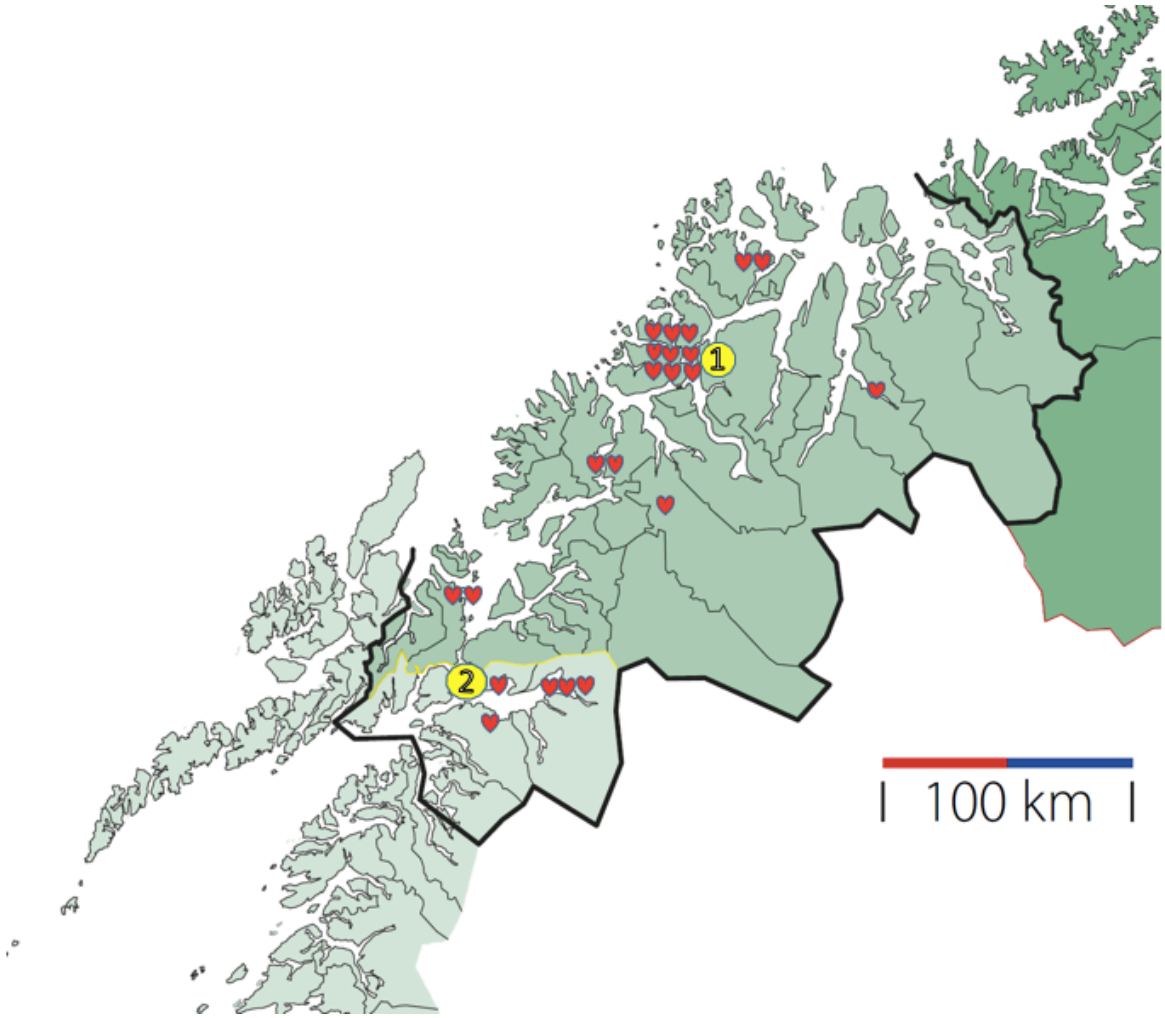
VF = Ventricular fibrillation, *VT* = Ventricular tachycardia, *PEA* = Pulseless Electrical Activity, *DC* = Direct-Current, *LUCAS2/CPR* = Mechanical compression devices

Figure 1: Study Flow



*Patients were excluded by

Figure 2: Distribution of the *OHCA´s in our region*



8. GRADE assessment of main articles

Reference: Chen YS, Chao A, Yu HY, Ko WJ, Chen RJ, Huang SC, et al. Analysis and results of prolonged resuscitation in cardiac arrest patients rescued by extracorporeal membrane oxygenation. J Am Coll Cardiol. 2003;41:197-203.	**Design:** Observational study (case series)
	Documentation level: III
	GRADE: 1

Objective	Material and Method	Results	Discussion/Comments
Determine the result of prolonged CPR with ECMO and the predictive factors for hospital discharge and ECMO weaning. **Conclusion** Prolonged CPR rescue by ECMO provides an acceptable survival rate and outcome in survivors. Further investigations of the wider application of ECMO in CPR is recommended. **Country** Taiwan (not specified) **Year of data collection** Six year period (not specified when)	**Data source:** Not specified, but collected from 57 ECPR patients from one single institution. **Study population** (n = 57): *Inclusion criteria for ECPR:* - Refractory CA - No ROSC within 10 to 20 minutes - Received ECMO in the hospital *Exclusion criteria:* - Previous irreversible brain damage - Terminal malignancy - Age >75 years. **Primary outcome**: The effect of ECPR on weaning (successful weaning from ECMO and survival beyond 48 h) and survival (weaning followed by discharge from the hospital). **Statistical analysis:** • Fischer exact test • Mann-Whitney U test or Kruskal-Wallis test continuous variables • Spearman correlation • Logistic regression	Mean duration of CPR was 47,6 ± 13,4 min and that of ECMO was 96,1 ± 87,9 hours. The rate of weaning was 66,7%, and the survival rate was 31,6%. Multiple-organ failure was the major reason for mortality, despite successful weaning. Among survivors, long-term follow-up revealed 88.9% survival, and only 5.6% had a severe neurologic deficit. The results indicate that a shorter CPR duration, postcardiotomy arrest, myocardial indicators, a hepatic indicator, and lactic acid are significantly correlated with both weaning and survival, whereas late damage (level on the third or seventh day of reperfusion) rather than initial damage (level on the first day) was more predictive of the results. **Table 2.** Relationship Between Weaning or Survival and CPR Duration CPR Duration / n / % / Weaning n (%) / Survival n (%) <15 min: 0 / 0 / / <30 min: 2 / 3.5 / 2 (100%) / 2 (100%) <45 min: 14 / 24.56 / 11 (78.57%) / 8 (57.14%)† <60 min: 31 / 54.39 / 25 (80.65%)* / 15 (48.39%)* >60 min: 26 / 46.61 / 13 (50%) / 3 (11.5%) Total: 57 / 100 / 38 (66.7%) / 18 (31.6%) *p < 0.05 compared with CPR >60 min. †p < 0.05 compared with CPR >45 min. CPR = cardiopulmonary resuscitation.	**Checklist:** **1)** Were the study based on a random selection from a suitable patient group? **Not sufficiently described.** **2)** Was it made sure that the study population wasn´t selected? **Not sufficiently described.** **3)** Were the inclusion criteria's clearly defined? **Yes.** **4)** Is the response rate high enough? **Not relevant.** **5)** Were the exposed individuals in the same stage of the disease? **Uncertain. All had cardiac arrest, but the most admitted to hospital with different diseases.** **6)** Was the follow up time lengthy enough to prove positive and/or negative outcomes? **A retrospective study, but short follow-up time of patients.** **7)** Were objective criteria´s used to assess/validate the endpoints? **Yes**. **8)** When comparing case series, are the series sufficient described and prognostic factors distribution described? **No.** **9)** Was the study prospective? **No**. **Limitations** • The data source is not described. • Minimal epidemiological background information about included patients. • Not specified where and when the study is performed. • Most of the patients were admitted to hospital when the arrest occurred, and most were witnessed, and the results can not be transferred to the general population. • Confounding factors because of different diseases and surgery among the included patients. • Short follow-up time of patients. • Small number of cases and only a few significant associations to weaning and survival may be identified.

Reference: Lamhaut L, Hutin A, Puymirat E, Jouan J, Raphalen JH, Jouffroy R, et al. A Pre-Hospital Extracorporeal Cardio Pulmonary Resuscitation (ECPR) strategy for treatment of refractory out hospital cardiac arrest: An observational study and propensity analysis. Resuscitation. 2017;117:109-17.	**Design:** Observational study (Case series)
	Level of scientific evidence: III
	Grade: 2

Objective	Material and Method	Results	Discussion/Comments
The SAMU of Paris has developed strategies to implement ECPR in the pre-hospital setting to reduce the time to implementation of ECPR. The aim of this study were to compare the two main strategies for the use of ECPR in the management of OHCA patients in Paris. **Conclusion** In one of the largest series of patients treated with ECPR for OHCA, an aggressive ECPR strategy based on an aggressive management of OHCA by a dedicated emergency team with prehospital implementation of ECPR in selected patients is feasible, with a favorable survival rate. Larges registries and randomized trials are warranted to confirm these results. **Country** France **Years Data Collection** 2011-2015.	**Data source:** This study used data from the MOICU (part of the EMS of Paris), but there is not specified which kind of register they have used. **Study population:** All OHCA patients receiving ECPR between 2011 and 2015. **Period 1 vs. period 2:** A first protocol applied in November 2011 to December 2014, and in January 2015 a new protocol was initiated. • *Period 1 (n=114):* ECPR indicated in selected patients after 30 min of advanced life support (in- or pre-hospital). • *Period 2 (n=42):* A dedicated pre-hospital ECPR-team was on call at all times to reduce delays to ECPR implementation, initiation after 20 min of resuscitation, stringent patient selection, epinephrine dose limitation. **Primary outcome:** Survival with good neurological function, Cerebral Performance Category score (CPC-score) 1 and 2 at ICU discharge or day 28. **Statistical analysis:** • Qualitative variables: X^2 and Fisher exact test • Quantitative variables: T-test, Mann-Whitney or Wilcoxon test.	**Survival was significantly higher with period 2: 29 % vs. 8 %** ($p < 0,001$). OR 7.92, 95% CI 1.07-58.92. Presence of signs of life before ECPR was the most potent correlate of survival (OR 59.6, 95 % CI 4.9-723.6). The implantation site of ECPR (pre versus in-hospital) did not appear to influence survival.	**Checklist:** **1)** Were the study based on a random selection from a suitable patient group? **Yes.** **2)** Was it made sure that the study population wasn´t selected? **Yes.** Are the groups recruited from the same section of the population? **Yes, included all patients with OHCA and ECPR in the period.** **3)** Were the inclusion criteria's clearly defined? **Yes.** **4)** Is the response rate high enough? **Not relevant.** **5)** Were the exposed individuals in the same stage of the disease? **Yes, all had OHCA.** **6)** Was the follow up time lengthy enough to prove positive and/or negative outcomes? **Not relevant.** **7)** Were objective criteria´s used to assess/validate the endpoints? **Yes.** **8)** When comparing case series, are the series sufficient described and prognostic factors distribution described? **Yes.** **9)** Was the study prospective? **No.** **Strengths** • Included all patients with OHCA and ECPR in the study period • Minimal differences in baseline characteristics as age, gender, and BMI between patients in the two periods. **Limitations** • More stringent patient selection in period 2, which will contribute to a higher survival rate (the presence of signs of life before ECPR was observed more often in period 2). • ECPR-team probably had more experience. In period 2. • Selection bias in favor of in-hospital ECPR (had to keep the indication criteria during transportation time) may explain the mismatch between survival rate and pre-hospital ECPR and reduced low-flow time • Total number of patients is low. • Broad confidence intervals • Not specified what register which was used to collect data.

Reference:
Poppe M, Weiser C, Holzer M, Sulzgruber P, Datler P, Keferböck M, et al. The incidence of «load&go» out-of-hospital cardiac arrest candidates for emergency department utilization of emergency extracorporeal life support: A one year-review. Resuscitation. 2015;91:131-6.

Design: Observational study (case series)	
Level of scientific grade	III
GRADE	2

Objective

Identify the incidence of patients which fulfill "load&go"-criteria for E-ECLS at the ED.

Conclusion

Further promotion of «load&go"-criteria for EMS personel is needed to reduce futile transportation efforts. Clear criterias and a clear course of action for EMS personel should be made to reduce duration of resuscitation befor E-ECLS installation. More studies needed to decide which patient should be transported with on-going CPR.

Country

Austria

Year of data collection

August 1, 2013 – July 31, 2014.

Material and Method

Data source:
The Vienna Cardiac Arrest Registry (VICAR).

Included (n = 864/948):
Age >18
EMS treated OHCA´s

"Load&go"-criteria:
- Initial shockable rhythm
- Age < 75
- Bystander witnessed
- Bystander CPR and no sustained ROSC within 15 min of ALS by EMS personnel

Data acquisition:
- Data collected from VICAR by trained chart reviewers.
- 84 cases was not taken into account because of criteria being impossible to determine or missing.
- Initial rhythm not clear: included but not counted as "load&go" candidates.

Endpoints:
- Number of "load&go"-criteria patient transported or treated
- 30-day survival and favorable neurological outcome.

Statistical analysis:
- Chi square test
- T-test

Results

Of 948 patients the **"load&go"-criteria where fulfilled by 55 (6%)**. 96 (11%) were transported with ongoing CPR to the ED. Of the transported patients only 16 (17%) met the "load&go"-criteria. Of those 96 patients, 12 were treated with E-ECLS at the ED despite only 5 of the met the criteria.

Distribution of "load&go"-criteria within the study population.

	Total	ROSC at the scene	Ongoing CPR on transport	Died on the scene	p value
Count (%)	864 (100)	257 (29.7)	96 (11.1)	511 (59.1)	
load&go criteria, n (%)					
VF/VT	215 (24.9)	118 (45.9)	37 (38.5)	60 (11.7)	<0.001
Basic life support	514 (59.5)	169 (65.8)	69 (71.9)	276 (54.0)	<0.001
Witnessed collapse	482 (55.8)	172 (66.9)	68 (70.8)	242 (47.4)	<0.001
Age <75 year	574 (66.4)	198 (77.0)	72 (75.0)	304 (59.5)	<0.001
CPR >15 min of ALS	400 (46.3)	94 (36.6)	–	306 (59.9)	<0.001
All "load&go" criteria fulfilled, n (%)	55 (6.4)	17 (6.6)	16 (16.7)	22 (4.3)	<0.001

ROSC: return of spontaneous circulation; VF/VT: ventricular fibrillation/ventricular tachycardia.

Discussion/Comments

Checklist:

1) Were the study based on a random selection from a suitable patient group? **Yes.**
2) Was it made sure that the study population wasn´t selected? **Yes.**
3) Were the inclusion criteria´s clearly defined? **Yes.**
4) Is the response rate high enough? ***Response rate not relevant, but 84 patients were not included due to missing data.***
5) Were the exposed individuals in the same stage of the disease? **Yes.**
6) Was the follow up time lengthy enough to prove positive and/or negative outcomes? ***Not relevant, retrospective study.***
7) Were objective criteria´s used to assess/validate the endpoints? **Yes.**
8) When comparing case series, are the series sufficient described and prognostic factors distribution described? **Yes.**
9) Was the study prospective? **No.**

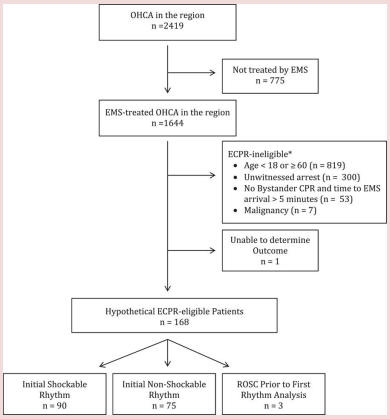
Strengths
- Use of a reliable registry with all OHCA´s in Vienna.
- Good validation of the diagnosis (CA).
- Trained chart reviewers.

Limitations
- Excluding 84 patients due to missing or non-determinable data and age<18.
- Inclusion of not clear initial rhythms.
- The "Wrong" patients was transported
- There were no "load&go"-criteria or obligatory E-ECLS criteria during the observational period.

Reference: Fjølner J, Greisen J, Jørgensen MR, Terkelsen CJ, Ilkjaer LB, Hansen TM, et al. Extracorporeal cardiopulmonary resuscitation after out-of-hospital cardiac arrest in a Danish health region. Acta Anaesthesiol Scand 2017;34:107-11.	**Design:** Observational study (case series)
	Documentation level: III
	GRADE: 2

Aim	Material and Method	Results	Discussion/Comments
Describe the first experiences, treatment details, complications and outcome with ECPR for OHCA in a Danish health region. ECMO is feasible as a rescue therapy in normothermic refractory OHCA in highly selected patients. Low-flow time was longer than previously reported. Survival with favorable neurological outcome is possible despite prolonged low-flow duration. **Country** Denmark **Year of data collection** 2011-2015	**Data source:** Electronical medical records from the Aarhus University Hospital and a local ECMO database. **Study population: (n = 21)** All normothermic, refractory OHCA > 18 years treated with ECPR. **Patients selection:** -Pre-defined algorithm (it incorporated evaluation of comorbidities, no-flow time, low-flow time, initial rhythm, ETCO2, heart movement judged by ECCO, signs of life during CCPR and heart movement during internal pacing if indicated by ECG. **Data acquisition and outcomes:** - Data were taken from the electronical medical records and patients were identified by the local ECMO database. - Low-flow time, pre-ECPR lactate level and pH, first recorded CA rhythm, ECPR duration, ICU length of stay, time om mechanical ventilation and survival to and CPC at hospital discharge were recorded. **Statistical analysis**: • Non-parametric data: Wilcoxon´s rank-sum test. • Categorical values: Fischer´s exact test	**A total of 21 patient were included.** - The median age was 56 years. - Median pre-hospital low-flow time was 54 min [range 55-100] and median total low-flow time was 121 min [range 55-192]. - **7 patients survived (33%).** - Survivors had a CPC score of 1 or 2 at hospital discharge. **- 5 survivors had a shockable initial rhythm**. - In all survivors coronary occlusion was the presumed cause of cardiac arrest. - Pre-hospital, in-hospital and total low-flow time and response times were similar in both groups but survivors had higher pre-ECPR pH and lower pre-ECPR lactate level. **Complications:** - Causes of death were related to circulatory failure, lower extremity ischemia and brain damage (all of which led to withdrawal of ECPR therapy).	**Checklist:** **1)** Were the study based on a random selection from a suitable patient group? **Yes.** **2)** Was it made sure that the study population wasn´t selected? **Yes.** **3)** Were the inclusion criteria´s clearly defined? ***Yes, but there were no* strict age limit, and the decision were ultimately subjectively taken by the ECMO team.** **4)** Is the response rate high enough? **Not relevant.** **5)** Were the exposed individuals in the same stage of the disease? **Yes.** **6)** Was the follow up time lengthy enough to prove positive and/or negative outcomes? **No, there is a low number of total ECPR patients, and further experience is necessary to conclude.** **7)** Were objective criteria´s used to assess/validate the endpoints? **Yes.** **8**) When comparing case series, are the series sufficient described and prognostic factors distribution described? **Yes.** **9)** Was the study prospective? **No.** **Limitations** • No single factor included or excluded the patients • Low number of ECPR patients • Ultimately the decision of ECPR therapy was determined subjectively by a ECMO team.

Reference: Granau B, Scheuermeyer F, Stub D, Boone R, Finkler J, Pennington S, et al. Potential Candidates for a Structured Canadian ECPR Program for Out-of-Hospital Cardiac Arrest. Canadian Journal of Emergency Medicine. 2016;18(6):453-60.	**Design:** Observational study (Post-hoc hypothetical cohort)
	Level of scientific grade: III
	GRADE: 2

Objective	Material and Method	Results	Discussion/Comments
Identify patients with refractory cardiac arrest who fulfilled a set of ECPR-criteria in order to estimate: (1) the proportion of patients with refractory cardiac arrest who may have benefited from ECPR; and (2) the outcomes achieved with conventional resuscitation. **Conclusion** 10% of the EMS-treated patients fulfilled the ECPR criteria, 1/3 of whom had resuscitation been terminated prior to hospital admission and may have benefited from ECPR. An ECPR program may have a small but clinically important effect on patient outcomes. **Country** Canada **Years data collection** 2007-2011.	**Data source:** Resuscitation Outcomes Consortium registry, all pre-hospital data were collected from standardized EMS template charting. **Study population:** All non-traumatic OHCA patients within the Vancouver region. **Included** (n = 1644/2419): *ECPR eligible patients criteria:* - Age between 17 and 60 years - Witnessed arrest - Bystander CPR **Outcome:** - The primary outcome was the proportion of patients who were ECPR-eligible and had refractory CA, defined as having resuscitative efforts terminated in the pre-hospital setting or at the ED. These represent the group that may have benefited from ECPR therapy. - The secondary outcomes were the proportion of ECPR-eligible patients who survived to hospital admission, hospital discharge, and the proportion of those with favorable neurological outcomes (defined as CPC 1-2). **Statistical analysis:** • Dichotomous variables are reported as percentages and 95% confidence intervals • Continuous variables are presented as means with SD or medians with IQRs.	A total of 1644 EMS treated OHCA was included in the study. **168 (10,2%) fulfilled the ECPR criteria.** 54 (32%) of the ECPR-eligible patients had refractory cardiac arrest. Of ECPR-eligible patients 114 (68%) survived to hospital admission, and 70 (42%) survived to hospital discharge.  	**Checklist:** **1)**Are the groups comparable in relation to important background factors? **Yes, those included in the study fulfilled the ECPR criteria.** **2)**Are the groups recruited from the same section of the population? **Yes**, **3)**Were the exposed individuals representative for a defined section of the population? **Yes, all OHCA´s within the region were included.** **4)**Was the study prospective? **Yes.** **5)**Were exposure and outcome measured equal and reliable in the two groups? **Yes.** **6)**Were sufficient number of persons in the cohort followed up? **Yes, yes all OHCA´s in the region in the period between 2007-2011.** **7)**Is it performed drop out analyses? **Not relevant.** **8)**Was the follow up time lengthy enough to prove positive and/or negative outcomes? **Yes.** **9)**Are important confounding factors in design/implementation considered? **No?** **10)**Was the person who evaluated the results (endpoints) blinded group identification? **Not specified.** **Strengths** • Good validation of the diagnosis (CA). • Inclusion of all non-traumatic OHCA´S in the region **Limitations** • There may be systematic differences in patient characteristics between the initial shockable and non-shockable groups, such as etiology, which may affect outcomes. • Total number of patients is low. • Excluding age >60 and <18 years, may include only those with the already best prognosis.