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REVIEW

National and reporting differences of pre-hospital factors in extracorporeal cardiopulmonary resuscitation studies

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Abstract

Extracorporeal cardiopulmonary resuscitation is the rapid deployment of extracorporeal life support during cardiac arrest and has emerged as a rescue therapy for refractory cardiac arrest. Systemic circulation and oxygenation are temporarily restored, such that medical efforts can be focussed on the diagnosis and treatment of the underlying cause of the arrest. Observational research has shown this may improve survival with good neurological outcome. Crucial in resuscitation is the interval between arrest and return of circulation. Four factors are of influence during this phase: 1) witnessed arrest, 2) no-flow duration, 3) bystander basic life support, and 4) low-flow duration. The purpose of this review is to describe the current level of evidence for these factors in conventional and extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest. Underreporting and national variability of the pre-hospital links in the chain-of-survival is prevalent. Consistent reporting is essential for new trials to enable comparison and generalisation to other regions.

Introduction

Extracorporeal cardiopulmonary resuscitation (ECPR) is defined as the rapid deployment of extracorporeal life support (ECLS) during cardiac arrest. In recent years this treatment has emerged as a rescue therapy for refractory cardiac arrest. Systemic circulation and oxygenation are temporarily restored by a heart-lung machine, such that medical efforts can be focussed on the diagnosis and treatment of the underlying cause of the arrest without return of spontaneous circulation (ROSC). Observational research has shown this may improve survival with good neurological outcome. ECPR programs are fascinating as they require intensive coordination, collaboration and dedication in pre- and in-hospital performance to mobilise a highly trained multidisciplinary team and to bring this team and the patient together at a moment's notice. This challenging effort is performed differently around the world and we can learn from each other's experience.

ECPR can be divided into three phases:
1. Pre-hospital care
2. In-hospital ECPR logistics
3. Post-resuscitation ECLS care

Several excellent reviews have been written on the complexity of the in-hospital ECPR logistics.[1-5] Although the quality of the ECPR procedure itself and of the post-resuscitation ECLS care is of major importance, outcome is still very much dependent on the first phase, which will be the focus of this review. Before ECPR is started, a patient has to pass through the well-known chain-of-survival: early recognition, start of basic life support and rapid defibrillation. While these steps are well-defined, their execution is different in different countries or regions. These differences may partly attribute to the varying results on the effectiveness of ECPR in out-of-hospital cardiac arrest (OHCA) in over 30 publications, which has hampered meaningful meta-analyses.[6,7] We describe here the current pre-hospital resuscitation care, defined by four factors: 1) witnessed arrest, 2) no-flow duration, 3) bystander basic life support, and 4) low flow duration. While other factors, such as automated electronic defibrillator (AED) use, time to arrival of the emergency medical service (EMS), and quality of chest compressions, are of importance too, these are either uncommon in the early years of ECPR, or difficult to measure and report. We evaluate whether these four factors have been used in the trial design and reporting of relevant publications on ECPR for OHCA and if there are national differences. In addition, we present an overview of their use in the currently recruiting ECPR trials.

Table 1. Pre-hospital factors in ECPR studies in Asia

Author	City, country	N	Witnessed		No-flow		BLS		Low-flow			Other time frames	
			In-/ exclusion criteria	Results	In-/ exclusion criteria	Results	In-/ exclusion criteria	Results	In-/ exclusion criteria (min)	(max)	Results	Total arrest	Other (start – stop)
Tanno '08 (42)	Sapporo, Japan	66	Yes	68.2% bystander 10.6% EMS 21.2% not witnessed	-	6 min (to EMS)	-	39.4% (AED was not permitted)	20 min ACLS	-	-	-	21.5 min (hospital)
Nagao '10 (25)	Tokyo, Japan	171	Yes	-	<15 min (EMS)	-	-	55%	10 min ACLS	-	Reported according to time-to-34°C	63-68 min	-
Kagawa '10 (47)	Hiroshima, Japan	39	-	82%	<15 min	1 min (1-8) (BLS)	-	72%	20 min ACLS	-	-	59 min (45-65)	-
Maekawa '13 (26)	Sapporo, Japan	53	Yes	All patients	-	2 min (0-8) (BLS) 6 min (2-9) (EMS)	-	54.7%	>20 min CPR	-	49 min (41-59)	-	-
Mochizuki '14 (27)	Asahi, Japan	50	Yes (except for hypothermia or young patients)	72% 14 unwitnessed	-	7,4 min (±10.4) (BLS)	Yes (except for hypothermia or young patients)	64% 18 did not receive bystander CPR	-	-	84 min (±48)	-	-
Sakamoto '14 (66)	Yokohama, Japan	260	-	71.5%	-	-	-	48.8%	>15 min CPR with doctor present	<45 min arrest - hospital	-	-	29.8 min (CA - hospital)
Otani '18 (28)	Osaka, Japan	135	Yes	All patients	-	-	-	55%	If ROSC was not achieved in > 5 min despite CPR > 20 min	-	47 min (41-57)	-	10 min (7-13) (scene - hospital)
Kim '14 (29)	Seoul, South Korea	55	Yes (unless expected to be short)	78.2%	Expected to be short	7 min (0-13)	No (when delay is expected to be short)	41.8%	-	-	62 min (47-89)	-	13 min (7-17) (CA - hospital)
Choi '15 (48)	Seoul, South Korea	320	-	71%	-	6 min (5-8) (EMS)	-	30%	-	-	-	-	7 min (4–10) (on-scene time) 6 min (4–8) (transport time)
Ha '17 (60)	Seoul, South Korea	35	-	29/35 witnessed	-	-	Exclusion: 'Unrelated CPR'	43%	-	-	-	72 min (57-91) (NS) 82 min (65-104.8) (S)	20.0 min (15.0–24.5) (NS) (CA - hospital) 23.5 min (18.8–27.3) (S) (CA - hospital)
Han '19 (43)	Seoul, South Korea	75	Yes (unless delay expected to be short)	86%*	Expected to be short (also in unwitnessed)	-	Not necessary	85.7%* (S) 70.9%* (NS)	>30 min ACLS	-		64 min* (±24.5) (S) 76 min* (±30) (NS)	57 min (±20.1)* (S) 72 min (±27.6)* (NS) (ACLS - ECPR)
Wang '14 (30)	Taipei, Taiwan	31	Yes	All patients	-	1-5 min (BLS)	Exclusion: arrest without active CPR	'CPR was started rapidly'	>10 min CPR	-	-	56 min (35-182)	-

*including data from in-hospital ECPR; N = patients who received ECPR for OHCA AED = automated electronic defibrillation; ACLS = advanced cardiac life support; BLS = basic life support; CA = cardiac arrest; CPR = cardiopulmonary resuscitation; ECPR = extracorporeal cardiopulmonary resuscitation; ED = emergency department; EMS = emergency medical services; ICU = intensive care unit; IHCA = in-of-hospital cardiac arrest; NS = non-survivors; S = survivor; OHCA = out-of-hospital cardiac arrest; ROSC = return of spontaneous circulation

Table 2. Pre-hospital factors in ECPR studies in Europe

Author	City, country	N	Witnessed		No-flow		BLS		Low-flow			Other time frames	
			In-/ exclusion criteria	Results	In-/ exclusion criteria	Results	In-/ exclusion criteria	Results	In-/ exclusion criteria (min)	(max)	Results	Total arrest	Other (start – stop)
Le Guen '11 (31)	Paris, France	51	Yes	All patients	<5 min	3 min (1-6) (BLS) 71% conformity	-	-	>30 min CPR	<100 min	< 100 min in 27%	120 min (102-149)	90 min (65-115) (CA - ICU)
Megarbane '11 (32)	Paris, France	66	Yes	All patients	-	2 min (0-6)*	-	43%	-	-	155 min (120-180) *	-	110 min (80-138)* (CA - ICU)
Belle '12 (33)	Annecy, France	17	Yes	-	<5 min	1 min (0-8) ≤5 n=13 >5 n=4	-	-	-	<100 min	104 min (85-123)	119 min (90-130)	81 min (53-94) (CA - CCL)
Lamhaut '13 (35)	Paris, France	7	Yes	-	<5 min	4 min (±4)	Yes	-	>30 min ACLS	On-site ECPR	72 min (±12)	79 min (±15)	57 min (±21) (ACLS - ECPR)
Pozzi '16 (36)	Lyon, France	68	Yes	-	<5 min	2.1 min (±2.2) (BLS)	-	'OHCA was firstly managed by bystanders performing CPR'	-	≤75 min (≤100 min from January 2010 to July 2012)	83.6 min (±20.7)	-	-
Lamhaut '17 (34)	Paris, France	114	Yes	-	<5 min	3.7 min (±4.1)	-	-	>30 min ACLS	Transport time >20 min on-site ECPR; <20 min in-hospital	93 min (±26.7) <60 min 9.6% 60-100 min 57.7% >100 min 32.7%	-	On-site ECPR 41.4%
		42	Yes	-	<5 min	2.5 min (±3.7) >5 min 22%	Yes	-	>20 min CPR with AED	<100 min (goal <60 min)	70.9 min (±20.2) <60 min 34.2% 60-100 min 52.6% >100 min 13.2%	-	On-site ECPR 64.3%
Voicu '18 (21)	Paris, France	27	-	93%	<5 min	1 min (0-4)* (BLS)	-	80%	'Refractory CA'	-	120 min (115–140)	-	100 min (80 - 118) (CA- hospital)
Avalli '11 (37)	Monza, Italy	18	Yes	-	-	1 min (1-7.25)	-	55%	30 min CPR	-	77 min (69-101)	-	-
Cesana '18 (38)	Monza, Italy	46	Yes	-	<6 min	3 min (±4)*	-	-	> 15 min CPR	<45 min before start cannulation	56 min (±24) *	58 min (±25)*	-
Haneya '12 (44)	Regensburg, Germany	26	-	-	<10 min (BLS/EMS)	-	Yes	-	>10 min CPR	>30 min transport time	70 min (55-110)) >90 min arrest	-	-
Leick '13 (39)	Bad Neuheim, Germany	28	Yes	All patients	-	-	-	-	>10 min CPR	-	44 min (31-45) (S) 53 min (40-61.3) (NS)	-	-
Spangenberg '16 (65)	Hamburg, Germany	22	-	85%*	-	-	-	77%*	>25 min ACLS	-	90.6 min (±30.9)	-	-
Wengenmayer '17 (40)	Freiburg, Germany	59	Yes	'Short average no-flow time of 2.6 minutes (*) might be explained by our centre policy to rarely cannulate patients with nonwitnessed cardiac arrest'	-	5.4 min (±1.5) (BLS)	-	-	-	-	72.2 min (±7.4)	-	-
Fagnoul '13 (41)	Brussels, Belgium	14	Yes	22/24 witnessed*	<5 min	10 min (5-15) (ACLS)*	-	92%	>10 min ACLS	<60 min ECPR initiation	-	66.5 min (56-80)	-
Wallmuller '13 (49)	Vienna, Austria	33	-	All patients	-	0 min (0-1)*	-	-	'Prolonged resuscita-tion'	-	85 min (71-121)*	102 min (65-115)*	43 min (5–71) (CA - ED)
Schober '17 (50)	Vienna, Austria	7	-	86%	-	0 min (0-1,5) (BLS)	-	28%	>30 min CPR	-	97 min (79-147)		38 min (27-66) (CA - hospital)
Fjolner '16 (20)	Aarhus, Denmark	21	Yes (no single factor excluded patients from ECPR)	-	Immediate CPR	5 min (0-21) (BLS) 7 min (0-28) (ACLS)	Yes	Instruction by dispatcher	-	<100 min	121 min (55-192)	-	54 min (5-100) (CA - hospital)

Methods

To identify all relevant articles on ECPR in OHCA for this narrative review, a search in PubMed was conducted. MeSH terms "extracorporeal cardiopulmonary resuscitation", "out of hospital cardiac arrest" and "extracorporeal membrane oxygenation" were used and references were checked for more relevant publications. Thirty-four studies on ECPR for OHCA were included, 13 were excluded. In seven papers the percentage of OHCA patients was below 25% and the data could not be distinguished from in-hospital cardiac arrest (IHCA). Two papers did not concern ECPR, two papers were unavailable, one paper used data from several countries and the last paper was a survey on ECPR. The included studies have been summarised in *tables 1 to 4*, categorised according to continent and country. All patients with ECPR for OHCA were extracted. Each study was evaluated on whether witnessed arrest, no-flow duration, bystander basic life support (BLS), and minimum and maximum duration of low-flow were used in the inclusion and exclusion criteria and reported in the results. When the no-flow and low-flow duration were not reported in the paper, other timeframes are used for reference in the tables (e.g. total arrest duration (no-flow + low-flow) or time from cardiac arrest to hospital/intensive care/cardiac catheterisation laboratory admission).

Results

Witnessed arrest and no-flow

Whether an arrest is witnessed is of utmost importance. Research repeatedly demonstrates that prompt initiation of cardiopulmonary resuscitation (CPR) significantly improves the odds of surviving an OHCA.[8-11] This was underlined by a recent review of 27,301 non-traumatic, witnessed OHCAs in France that showed that survivors with a good outcome on the cerebral performance category score had a significantly lower no-flow time than patients with a poor outcome (severe neurological disability, persistent vegetative state or death).[12] The no-flow period lasts from the moment of collapse to the start of chest compressions either by bystanders or the EMS. Unless the arrest is witnessed, the no-flow duration is uncertain. Monitored arrest by the EMS is the most reliable; when witnessed by bystanders there is a higher risk of recall bias. Several systems can be employed to support bystanders and to shorten time to CPR. Volunteer notification systems are increasing in prevalence, with 'HartslagNu' in the Netherlands, 'Goodsam' in England,[13] 'SMSlivräddare' in Stockholm, Sweden,[14] 'Pulsepoint' in the USA[15] and 'MyResponder' in Singapore. The dispatch centre notifies the volunteers, simultaneously with the EMS, based on GPS-location or predefined zip-code. Furthermore, instead of relying on a high level of training in the general population, this system makes use of the BLS trained volunteers in the area and warrants a better chance at higher quality chest compressions. This has proven to decrease time to start of BLS[14,16] and has increased survival from 16% up to 27% in the Netherlands.[17] The system is good but not perfect – turnout depends on the population density, and time of day and location. A study in France demonstrates that within a country there are major regional differences in levels of BLS training and AED availability.[18] Other possibilities to limit no-flow time are 1) the two-tiered system, in which police and/or fire-fighters are deployed as first responders when they are in the close vicinity, such as is common in Australia, France, the Netherlands and Denmark,[17,19-21] and 2) dispatch-assisted CPR, as is used in Singapore and rural areas in Japan.[22,23] Ong et al. described the EMS dispatcher as the 'true first responder on scene'.[24] They can prompt and instruct the witness to start CPR, which increases initiation of CPR by bystanders and chances of ROSC. Of the 34 ECPR studies summarised in *tables 1 to 4*, twenty studies used 'witnessed arrest' as an inclusion criterion.[20,25-43] In these cases, the witnessed status is often not referenced in the results, but the assumption is that all patients adhere to the criterion. When it is not used in the inclusion and exclusion criteria, it is often reported in the results. Four studies did not mention 'witnessed arrest' in the inclusion criteria or the results.[19,44-46] In sixteen publications an upper limit of duration of no-flow is reported in the inclusion and exclusion criteria with a maximum no-flow period of 15 minutes.[19-21,25,29,31,33-36,38,41,43,44,46,47] A couple of studies allowed for patients to be included if the delay was unknown but assumed to be short. Twenty-three studies reported on no-flow times in their results, ranging from 0 to 10 minutes.[20,21,26,27,29-38,40-42,45,47-51] Fjølner et al. in Denmark reported a no-flow range extending up to 21 minutes.[20]

Bystander BLS

The importance of bystander BLS is evident.[52,53] A recent study in the New England Journal of Medicine showed that the risk of all-cause death at one year, anoxic brain damage or nursing home admission was considerably lower among those who received bystander CPR or bystander defibrillation.[11] However, even when fully compliant with the guidelines, chest compressions only provide 10-30% of normal cardiac output.[54-56] The period between the start of chest compressions and the achievement of either ROSC or adequate perfusion by ECLS (in the case of ECPR) is referred to as the low-flow period. The blood flow to the heart may sustain ventricular fibrillation, prolonging the time window for defibrillation[57,58] and thus increasing the odds of ROSC by successful defibrillation. Timely return to ROSC is evidently the best option for the patient's outcome. Bystander

*including data from in-hospital ECPR; N = patients who received ECPR for OHCA
AED = automated electronic defibrillation; ACLS = advanced cardiac life support; BLS = basic life support; CA = cardiac arrest; CCL = cardiac catheterisation laboratory; CPR = cardiopulmonary resuscitation; ECPR = extracorporeal cardiopulmonary resuscitation; ED = emergency department; EMS = emergency medical services; ICU = intensive care unit; IHCA = in-of-hospital cardiac arrest; NS = non-survivors; S = survivor; OHCA = out-of-hospital cardiac arrest

Table 3. Pre-hospital factors in ECPR studies in North-America

Author	City, country	N	Witnessed		No-flow		BLS		Low-flow			Other time frames	
			In-/ exclusion criteria	Results	In-/ exclusion criteria	Results	In-/ exclusion criteria	Results	In-/ exclusion criteria (min)	(max)	Results	Total arrest	Other (start – stop)
Bellezzo '12 (46)	San Diego, USA	8	-	-	<10 min (BLS/EMS)	-	-	Rapid institution of CPR	-	>60 min arrest	-	-	-
Yannopoulos '16 (51)	Minneapolis, USA	18	-	11/18 witnessed	-	5.8 min (±3.1) (EMS)	-	66%	After 3 shocks	<30 min scene-CCL	-	66 min	-
Bartos '18 (45)	Minneapolis, USA	100	-	-	-	7.6 min (±1.2) (EMS)	-	72%	After 3 direct shocks	<30 min transport time + EMS activation - CCL > 90 min	-	-	56.7 min (±1.8) (CA - CLL)

**including data from in-hospital ECPR; N = patients who received ECPR for OHCA
BLS = basic life support; CA = cardiac arrest; CCL = cardiac catheterisation laboratory; CPR = cardiopulmonary resuscitation; ECPR = extracorporeal cardiopulmonary resuscitation; EMS = emergency medical services; OHCA = out-of-hospital cardiac arrest

Table 4. Pre-hospital factors in ECPR studies in Australia

Author	City, country	N	Witnessed		No-flow		BLS		Low-flow			Other time frames	
			In-/ exclusion criteria	Results	In-/ exclusion criteria	Results	In-/ exclusion criteria	Results	In-/ exclusion criteria (min)	(max)	Results	Total arrest	Other (start – stop)
Stub '15 (19)	Melbourne, Australia	11	-	-	<10 min	-	Started by bystander or EMS	-	-	-	-	56 min (40-85)*	-
Dennis '16 (73)	Sydney, Australia	12	-	73%* witnessed 16%* unclear if witnessed	-	-	-	81%* <5 min 76% 5-10 min 3% Unknown 22%*	-	-	-	63 min (45-77)	-

*including data from in-hospital ECPR; N = patients who received ECPR for OHCA
BLS = basic life support; ECPR = extracorporeal cardiopulmonary resuscitation; EMS = emergency medical services; OHCA = out-of-hospital cardiac arrest

BLS was used as an inclusion criterion in only nine out of 34 ECPR studies *(tables 1 to 4)*.[19,20,27,30,34,35,44,59,60] Some studies included exceptions to this criterion, when the delay was expected to be short or when patients were young. Whether or not bystander BLS was performed was reported in 24 studies, the incidence ranging from 28%[50] to 92%.[41] Debaty et al. reported that ECPR patients with bystander BLS had a favourable outcome with an OR of 2.81 (95% CI 0.95-8.32; p=0.06). Patients with BLS had a 25% favourable outcome rate compared with 10% in patients without. However, substantial between-study heterogeneity was observed (I2, 63.8%; p=0.007).[61]

Minimum low-flow duration

ECPR is a rescue therapy, and rapid return of spontaneous circulation without invasive measures is the preferred option. Some patients, however, fail to achieve ROSC within a reasonable period of time and are considered to have a refractory arrest. A cardiac arrest is suggested to be refractory after 15-30 minutes, although there is no clear consensus on this time frame.[24] Survival rates after cardiac arrest vary, Grunau et al. and Reynolds et al., respectively, report that 49% and 35.4% achieved ROSC, 14% and 10.8% survived to hospital discharge, and 10% and 8.0% with favourable neurological outcomes.[62,63] Overall survival to discharge in the Netherlands is 13-27%.[64] Grunau et al. showed that median time to ROSC is 13 minutes for shockable rhythms and 16.4 minutes for non-shockable rhythms, after 15 minutes the probability of survival fell below 1% in patients with non-shockable rhythms and after 48 minutes in those with shockable rhythms.[62] Reynolds et al. showed that 90% of patients with good neurological outcome achieved ROSC in 20 minutes, 99% within 37 minutes. No survivors were seen with good neurological outcome after 47 minutes of no/low-flow.[63] Kim et al. found in their propensity-matched population that after 21 minutes the outcome became better in ECPR than with continued CPR.[29] For patients with refractory arrest, ECPR may thus provide a viable rescue therapy. Twenty-two ECPR studies have defined a minimum duration of low-flow as a criterion with a duration varying from 3 shocks/10 minutes to 30 minutes – or more ambiguous descriptors as 'prolonged arrest'.[21,25,26,28,30,31,34,35,37-39,41-45,47,49-51,65,66] In some studies,

a minimum low-flow period during advanced cardiac life support (ACLS) was required before advancing to ECPR. Many Asian centres report very short times to hospital *(table 1 – other time frames)*, but often require CPR to be continued in-hospital before starting ECPR,[25,42] still resulting in a total arrest time of approximately 60 minutes.

Maximum low-flow duration

Once the decision for ECPR is made, the next important consideration is the upper time limit of low-flow duration, since the duration of arrest is inversely related to the chance of good neurological survival. D'Arrigo et al. studied the effect of low-flow duration in ECPR and found a significantly lower low-flow duration in 171 survivors compared with 399 non-survivors (28.7±4.1 vs. 46.1±5.1 min).[67] These data should be interpreted with care, quality was judged to be low and several studies report on in-hospital ECPR with shorter times to implementation. Debaty et al. studied the same effect in ECPR of OHCA and found a summary geometric mean of 54 minutes for 51 patients with favourable outcomes (95% CI 45-66) compared with 64 minutes for the 265 patients with unfavourable outcomes (95% CI 52-77).[61] In the individual studies, duration is associated with outcome, but results vary so much that a true upper limit is hard to establish. Maekawa et al. and Otani et al. reported a low-flow upper limit of 58 and 65 minutes, respectively, for good neurological survival.[26,28] Han et al. reported decreased probability of survival after more than 65 minutes.[43] Both Haneya et al. and Chen et al. found the highest survival within 30 minutes, yet after 60 minutes (and even after 90 minutes) they still had survivors.[44,68] Wengenmayer et al. calculated the probability for survival as 30% at 22 minutes, 20% at 39 minutes, 10 % at 64%, 5% at 87 minutes, and 1% at 139 minutes.[40] Yet some studies found no difference in median CPR duration in survivors vs. non-survivors,[34,39,60] one other study found a longer CPR duration in survivors (102 min (65-122) vs. 85 min (72-121)[49] and Fjølner et al. found a survival of 33% despite median low-flow duration of 125 minutes.[20] Lamhaut et al. looked at pre-hospital implementation of ECPR as a measure to decrease low-low duration but found no difference in survival with in-hospital ECPR.[34] Thirteen studies have defined a maximum duration of low-flow, these reflect either a limit to the total low-flow time or give logistical time limits (time to hospital/ cardiac catheterisation laboratory or transport time).[20,31,33-36,38,41,44-46,51,66] Reporting on low-flow duration is very diverse, not only does the duration vary from 44-155 minutes, but the time frames that are reported differ as well. In some cases, low-flow duration or total arrest time is not reported but only time-to-hospital, giving no indication of arrest duration. In other cases, the duration of

Table 5. Currently recruiting ECPR trials

NCT	Title	City, country	N	RCT	Start	Completion	Witnessed	No-flow	BLS	Low-flow	
										(min)	(max)
01511666	Hyperinvasive Approach in Cardiac Arrest	Prague, Czech Republic	200	Yes	March 2013	2019	Witnessed OHCA of presumed cardiac cause	-	-	>5 min ACLS	<60 min admission to CCL
01605409	Emergency Cardiopulmonary Bypass for Cardiac Arrest (ECPB4OHCA)	Vienna, Austria	40	Yes	November 2014	On Hold	Witnessed OHCA, with presumed cardiac cause	0 min	Immediate initiation of bystander CPR	>15 minutes ACLS	>30 min estimated transport time
02527031	A Comparative Study Between a Pre-hospital and an In-hospital Circulatory Support Strategy (ECLS) in Refractory Cardiac Arrest (APACAR2)	Paris, France	210	Yes	March 2016	March 2020	Not mentioned	<5 min	Yes	>20 min ACLS + ≥3 cycles AED or equivalent	-
02832752	BC ECPR Trial for Out-of-Hospital Cardiac Arrest	British Columbia, Canada	420	No	July 2016	May 2023	Yes	<10 min	Bystander CPR (performed by laypersons or EMS if the arrest was EMS-witnessed)	≥3 cycles of CPR (by any professional provider) and intubation	-
03065647	ECPR for Refractory Out-Of-Hospital Cardiac Arrest (EROCA)	Ann Arbor, Michigan, USA	15	Yes	Completed on May 28th, 2020	December 2019	Witnessed arrest or initial shockable rhythm (VT or VF)	-	-	Persistent cardiac arrest after initial cardiac rhythm analysis	Predicted arrival time at ECPR-capable hospital within timeframe specified
03101787	Early Initiation of Extracorporeal Life Support in Refractory OHCA (INCEPTION)	Multicentre, the Netherlands	134	Yes	May 2017	December 2020	Yes	≤5 min	Started by bystander	>15 min CPR	<60 min estimated start of cannulation
03658759	Rapid Response VA-ECLS in Refractory Out-of-hospital Cardiac Arrest (RESuSCITATe)	Amsterdam, the Netherlands	105	No	July 2018	July 2020	Yes	-	Yes	>10 min ACLS	<60 min expected time from transport decision to start ECLS
03700125	Pre-hospital ECLS in Advanced Resuscitation in Patients With Refractory Cardiac Arrest (SUB30)	London, UK	6	No	July 2018	December 2020	Yes	-	Yes	>10 min ACLS	<60 min expected time from transport decision to start ECLS

AED = automated electronic defibrillation; ACLS = advanced cardiac life support; BLS = basic life support; CCL = cardiac catheterisation laboratory; CPR = cardiopulmonary resuscitation; ECPR = extracorporeal cardiopulmonary resuscitation; ECLS = extracorporeal life support; EMS = emergency medical services; OHCA = out-of-hospital cardiac arrest; RCT = randomised controlled trial; VF or VT = ventricular fibrillation or tachycardia

the low-flow period for OHCA patients is indistinguishable from the IHCA patients, even though CPR duration in OHCA is expected to be longer.

Current trials on ECPR for OHCA

Eight trials on ECPR for OHCA have been identified on clinicaltrial.gov and the use of the pre-hospital determinants in their trial designs has been summarised in *table 5*. The Hyperinvasive trial in Prague, Czech Republic, compares their current standard – on site ACLS – to a hyperinvasive arm with immediate institution of mechanical chest compression and direct transfer to the cardiac catheterisation laboratory for ECPR and is expected to finish inclusion later this year.[69] The ECPB4OHCA trial in Vienna, Austria, and the EROCA trial in Michigan, USA, compare on site ACLS with ECPR in the emergency department. The APACAR2 trial in Paris, France, compares pre-hospital with in-hospital ECPR. In the BC ECPR in British Columbia, Canada, two ECPR regions are compared with a control region. In the INCEPTION trial in the Netherlands, both arms are transported to hospital, ECPR is performed in the cardiac catheterisation laboratory or emergency department.[70] The RESuSCITATe trial in Amsterdam is investigating the feasibility of a new local clinical pathway to provide ECPR for refractory OHCA patients. The SUB30 trial study in London, UK, is investigating the technical and logistical feasibility of instituting pre-hospital ECPR within 30 minutes of collapse for selected patients. All trials require a witnessed arrest with the no-flow duration ranging from 0 to 10 minutes. Six out of eight trials require BLS by bystanders, two trials did not define an upper limit of low-flow.

Discussion

We demonstrate variability in the pre-hospital resuscitation care and in the reporting of these factors and time frames in ECPR studies. Studies often focus on the cannulation process, yet the steps before the actual ECPR procedure are equally if not more important and form an integral part of the entire ECPR chain-of-survival. Current reporting is based on the Utstein guidelines for CPR and has become more uniform and comparable since their introduction in 1991.[71,72] However, we propose that time frames as no-flow and low-flow times should also be consistently assessed and reported as well. But these are only part of the full picture, we believe the next step in resuscitation research will be the early and real-time monitoring of the quality of the resuscitation. Based on the current evidence it seems appropriate for regions performing ECPR to switch to a scoop-and-run strategy to limit low-flow duration before ECPR. This means preparing for transport after 15 minutes of CPR, as chances of ROSC will decrease steadily afterwards. If ECPR were to become a standard treatment for OHCA, more rigorous changes would need to be made to our pre-hospital practice. It would then become imperative to make the treatment available to as many patients as possible.

Conclusion

This review discusses the variability in the pre-hospital phase in the design and reporting of 34 observational studies on ECPR for OHCA. As we move further towards a solid scientific foundation of this resource-intensive and highly invasive treatment, it is imperative that new trials report consistently on the pre-ECPR phase to enable generalisation to other regions and comparison of data.

Disclosure

The authors are members of the Trial Steering Committee of the INCEPTION trial.

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