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Clinical paper

A Pre-Hospital Extracorporeal Cardio Pulmonary Resuscitation (ECPR) strategy for treatment of refractory out hospital cardiac arrest: An observational study and propensity analysis

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ABSTRACT

Background: Out of hospital cardiac arrest (OHCA) mortality rates remain very high with poor neurological outcome in survivors. Extracorporeal cardiopulmonary resuscitation (ECPR) is one of the treatments of refractory OHCA. This study used data from the mobile intensive care unit (MOICU) as part of the emergency medical system of Paris, and included all consecutive patients treated with ECPR (including pre-hospital ECPR) from 2011 to 2015 for the treatment of refractory OHCA, comparing two historical ECPR management strategies.

Methods: We consecutively included refractory OHCA patients. In Period 1, ECPR was indicated in selected patients after 30 min of advanced life support; in- or pre-hospital implementation depended on estimated transportation time and ECPR team availability. In Period 2, patient care relied on early ECPR initiation after 20 min of resuscitation, stringent patient selection, epinephrine dose limitation and deployment of ECPR team with initial response team. Primary outcome was survival with good neurological function Cerebral Performance Category score (CPC score) 1 and 2 at ICU discharge or day 28.

Findings: A total of 156 patients were included. (114 in Period 1 and 42 in Period 2). Baseline characteristics were similar. Mean low-flow duration was shorter by 20 min ($p < 0.001$) in Period 2. Survival was significantly higher in Period 2: 29% vs 8% ($P < 0.001$), as confirmed by the multivariate analysis and propensity score. When combining stringent patient selection with an aggressive strategy, the survival rate increased to 38%. Pre-hospital ECPR implementation in itself was not an independent predictor of improved survival, but it was part of the strategy in Period 2.

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Interpretation: Our data suggest that ECPR in specific settings in the management of refractory OHCA is feasible and can lead to a significant increase in neurological intact survivors. These data, however, need to be confirmed by a large RCT.

1 Introduction

Out-of-hospital cardiac arrest (OHCA) is a leading cause of mortality worldwide [1].

The use of Extracorporeal Cardio-Pulmonary Resuscitation (ECPR) has been described for the treatment of refractory in-hospital cardiac arrest with survival rates ranging from 20% to 30% [2–6]. However, this technique remains controversial [7–14]. Limitations include access to ECPR with reasonable timing, cost-effectiveness and optimal patient selection.

A relationship between short delay to the implementation of ECPR and positive outcomes of refractory in-hospital cardiac arrests has been suggested [15–20].

To our knowledge, there is no published randomized control study assessing the use of pre-hospital ECPR. The Service d'Aide Médicale Urgente (SAMU) of Paris, is based upon a broad use of mobile intensive care units (MoICU) dispatched on site. Since 2011 the SAMU of Paris, has developed a strategy to implement ECPR in the pre-hospital setting, to reduce time to implementation. This strategy was initiated after some negative results with a load and go strategy [7]. The first step of this strategy was to do a feasibility and safety study, after a specific training [21,22]. Since this date, the SAMU de Paris has applied two different strategies for the use of ECPR in the management of refractory OHCA patients. During period 1, the allocation between pre- or in hospital insertion of ECPR was liberal. During period 2, the pre-hospital ECPR was the standard care associated with new inclusion criteria, a limitation of epinephrine and systematic etiologic research. We compared these two strategies, both of which included possible pre-hospital ECPR.

2 Methods

The study was performed in Paris area, a city of 105 square kilometers with 2,2 million residents and an influence area of more than 12 million residents.

In 2011, the SAMU of Paris initiated a feasibility study on the use of pre-hospital ECPR for refractory OHCA [21]. The management of OHCA involves basic life support (BLS) and mobile intensive care units (MoICU), simultaneously dispatched to provide BLS and advanced life support (ALS) according to international guidelines.

The current observational study includes all consecutive OHCA patients having received ECPR since 2011. A first protocol, including the use of pre-hospital ECPR was applied from November 2011 to December 2014 (Period 1). In January 2015, a new protocol was initiated (period 2).

During Period 1, inclusion criteria for ECPR were based on the French national guidelines, and are summarized in Appendix 1 (Supplementary material). ECPR was either initiated pre-hospital or in-hospital (ICU) based upon the estimated time needed to reach the hospital (less than 20 min), after 30 min of ALS. This decision was made by the MoICU physician on site.

During period 2, a dedicated pre-hospital ECPR team with one trained emergency physician or intensivist, a nurse anesthetist and a paramedic was on call at all times. The aim of the strategy was to reduce delays to ECPR implementation with an objective of pump flow initiation within 60 min of the onset of cardiac arrest in selected patients. If a patient of less than 70 years of age presented with a witnessed OHCA, the ECPR team was immediately sent on site. The patients were selected after 20 min of resuscitation with inclusion and exclusion criteria summarized in Appendix B (Supplementary material).

Pre-hospital ECPR was the default strategy. Patients were transported for in-hospital ECPR only if OHCA occurred during transportation and if arrival to hospital was estimated to be less than 10 min.

The physicians who performed ECPR (pre-hospital and in-hospital) implementation were the same during both periods. They used a cutdown technique in the lower Scarpa area, to locate and visualize the vessels. The insertion was done secondarily by Seldinger technique. Arterial cannulae were 15–19 Fr and venous cannulae were 21 or 23 Fr. (Maquet©, Rastatt) The ECPR used was the Cardiohelp © (Maquet©, Rastatt) for all patients. Limb perfusion was systematically performed. In pre-hospital, the Cardiohelp© was primed by an anesthesiologic nurse, and in-hospital by the ICU team (doctor or nurse). The priming was done with saline serum without heparin which was started secondarily. In case of massive bleeding or to avoid disseminated intravascular coagulopathy, transfusion was administered. Resuscitation during ECPR implementation included mechanical CPR using LUCAS© (Physiocontrol©, Redmond) or Autopulse © (Zoll©,Chelmsford), systematic sedation and mild therapeutic hypothermia.

In Period 1, there was no upper limit to epinephrine administration. The cumulative epinephrine administration was limited to 5 mg in period 2.

Indications for coronary angiography in the two periods followed the European Guidelines [23].

The post ECPR-resuscitation was identical in both periods (Supplemental file 1).

Data were gathered according to the Utstein criteria [24] (Table 1).

Neurological evaluation was performed using the Cerebral Performance Category score (CPC) at ICU discharge or at 28 days. CPC 1 and 2 were considered favorable outcomes whereas CPC 3–5 were considered unfavorable. In patients presenting with brain death, organ donation was considered.

The study was reviewed and approved by the IRB. All patients or families were informed of the participation in the study in accordance to the French regulatory.

2.1 Statistical analysis

Qualitative variables were compared using the $\chi 2$ and Fisher exact tests, whereas quantitative variables were compared by Student T tests, Mann-Whitney or Wilcoxon tests.

The following parameters were analysed in the multivariate analysis: age, sex, cause of arrest, shockable rhythms, no and low-flow duration, epinephrine dose, pre-hospital vs in-hospital ECPR, period, cardiovascular risk factors, signs of life, temperature at admission, angiography, PCI.

In order to assess the impact of Period 2, a propensity score for belonging to period 2 was calculated using non-parsimonious binary logistic regression analysis (Table 2).

In addition to the main analysis, and in order to assess the intrinsic role of pre-hospital ECPR, we performed several analyses:

Table 1
Baseline and procedural characteristics of the whole population, the period 1 and 2 population.

Variables	N Available	Whole Population 156	Population Period 1 114	Population Period 2 42	P-Value
Pre-hospital ECPR	154	73	46	27	0.01
n (%)		(47.4)	(41.4)	(64.3)	
Sex (Male)		128	91	37	0.23
n (%)		(82.0)	(79.8)	(88.1)	
Age		51.5	50.6	53.8	0.15
mean (SD)		(12.2)	(12.9)	(10.1)	
Age >60 YO		37	27	10	0.99
n (%)		(23.7)	(23.7)	(23.8)	
BMI	98	27.5	27.5	27.4	0.94
mean (SD)		(4.3)	(4.1)	(4.6)	
Past medical history					
CV Past medical history	138	29	17	12	0.12
n (%)		(21.0)	(17.5)	(29.3)	
CV Risk Factors	138	80	53	27	0.22
n (%)		(58)	(54.6)	(65.9)	
Initial presentation					
Cardiac death	151	112	80	32	0.33
n (%)		(74.2)	(72.1)	(80.0)	
Shockable rhythms	139	81	56	25	0.52
n (%)		(58.3)	(56.6)	(62.5)	
Signs of life before ECPR	141	72	43	29	0.0001
n (%)		(51.1)	(41.4)	(78.4)	
Epinephrine total dose (in mg)	132	8.6	10	5.1	<0.0001
(moy. ± SD)		(4.9)	(4.8)	(3.3)	
Epinephrine total dose >5 mg	132	90	78	12	<0.0001
n (%)		(68.2)	(82.1)	(32.4)	
No flow (min)	151	3.4	3.7	2.5	0.11
(mean ± SD)		(4)	(4.1)	(3.7)	
No flow ≥ 5 min	151	45	36	9	0.20
n (%)		(29.8)	(32.7)	(22)	
Low flow (min)	142	87.1	93	70.9	<0.0001
(mean ± SD)		(26.9)	(26.7)	(20.2)	
Low flow n (%)					
• <60 min	142	23 (16.2)	10 (9.6)	13 (34.2)	0.0008
• 60–100 min		80 (56.3)	60 (57.7)	20 (52.6)	
• >100 min		39 (27.5)	34 (32.7)	5 (13.2)	
ECPR implementation times (min)	129	21.8	22.6	19.30	0.03
(mean ± SD)		(10.3)	(11.4)	(5.4)	

Variables		Population globale	Population Période 1	Population Période 2	P-Value
Therapeutics					
Admission temperature (°C)	118	33.1	33.2	33.1	0.87
(mean ± SD)		(2.8)	(2.9)	(2.8)	
coronary angiography	144	72	43	29	0.0008
n(%)		(50)	(41.6)	(72.5)	
coronary angioplasty	139	42	24	18	0.007
n(%)		(30.2)	(23.8)	(47.4)	
Hospital evolution					
CPC 1-2			9	12	0.0008
n (%)			(7.9)	(28.6)	
CPC 3-4-5			105	30	
n (%)			(92.1)	(71.4)	
ROSC under ECPR	135	105	69	36	0.01
n(%)		(77.8)	(71.9)	(92.3)	
DIC	128	60	47	13	0.41
n (%)		(46.9)	(49)	(40.6)	
Transfusion	124	46	33	13	0.32
n (%)		(37.1)	(34.7)	(44.8)	
Sepsis	122	16	4	12	<0.0001*
n (%)		(13.1)	(4.4)	(40)	
Mean times on ECPR (Days)	131	2	2	3	0.006
(mean ± SD)		(2;3)	(1;3)	(2;6)	
Length of stay in ICU (Days)	152	2	2	3	0.001
(moy. ± SD)		(1;4)	(1;3)	(2;12)	

ECPR: Extracorporeal Cardio-Pulmonary Resuscitation.
BMI: Body Mass Index.
CV: Cardio-Vascular.
CPC: Cerebral Performance Category.
ROSC: Return Of Spontaneous Circulation.
DIC: Disseminated Intravascular coagulopathy.

Table 2
Comparison between Period 1 and 2 using a propensity analysis.

Variables	Period 1 N = 26	Period 2 N = 26	P-value
Pre-hospital ECPR	18	18	1.00
n (%)	(69.2)	(69.2)	
Sex (Male)	24	24	1.00*
n (%)	(92.3)	(92.3)	
Age >60 YO	4	4	1.00*
n (%)	(15.4)	(15.4)	
BMI	28.0	27.2	0.47
mean (SD)	(3.4)	(3.2)	
Past medical history			
CV Past medical history	4	6	0.73*
n (%)	(17.4)	(24.0)	
CV Risk Factors	10	17	0.09
n (%)	(43.5)	(68.0)	
Initial presentation			
Cardiac death	21	21	1.00
n (%)	(80.8)	(80.8)	
Shockable rhythms	17	17	1.00
n (%)	(65.4)	(65.4)	
Signs of life before	9	17	0.02
ECPR	(39.1)	(73.9)	
n (%)			
Epinephrine total dose	17	7	0.002
(in mg)	(77.3)	(30.4)	
(moy. ± SD)			
No flow (min)	2.9	2.8	0.91
(mean ± SD)	(3.1)	(4.1)	
No flow ≥ 5 min	6	6	1.00
n (%)	(23.1)	(23.1)	
Low flow (min)	84.2	69.8	0.04
(mean ± SD)	(26.5)	(22.5)	
Low flow n(%)			
• <60 min	5 (20)	11 (44)	1.00
• 60–100 min	15 (60)	11 (44)	
• ≥ 100 min	5 (20)	3 (12)	
ECPR implementation	20.00	19.67	0.88
times (min)	(8.9)	(5.8)	
(mean ± SD)			
In hospital therapeutics and evolution			
Admission	34.1	33.4	0.36
temperature (°C)	(2.1)	(2.5)	
(mean ± SD)			
coronary angiography	20	20	1
n(%)	(76.9)	(76.9)	
coronary angioplasty	10	14	0.21
n(%)	(38.5)	(56.0)	
Evolution and complications			
Mortality	24	18	0.03
n(%)	(92.3)	(69.2)	
ROSC under ECPR	21	24	0.35*
n(%)	(84)	(96)	
DIC	11	9	0.84
n(%)	(45.8)	(42.7)	
Transfusion	6	10	0.09
n(%)	(25)	(50)	
Sepsis	2	9	0.007
n(%)	(8.3)	(42.9)	

A propensity score to compare period 1 and 2 was calculated using the following variables representing initial patient presentation: age, sex, cause of arrest, past history of cardiovascular disease, shock delivered on site, epinephrine dose, use of prehospital ECPR, duration of no flow and low flow, angiography.

- First of all, a propensity score for using pre-versus in-hospital ECPR was calculated, excluding duration of low-flow as a shorter duration of low-flow was part of the rationale for using pre-hospital ECPR. (Table 3)
- A second propensity score for pre-vs in-hospital ECPR, using the duration of the low-flow and no-flow, was also calculated.

A 1/1 matching based on the propensity score or the adjustment variables was used to build cohorts with similar profiles.

The IBM SPSS v23.0 and NCSS 10 statistical packages were used for all statistical analyses, and P values <0.05 (two-sided) were considered significant.

3 Results

3.1 Baseline characteristics and management

During the period of the study 15 680 OHCA occurred in Paris.

Table 3
Comparison between in or pre-hospital ECPR insertion by a propensity analyze excluding duration of low flows.

Variables	In-hospital ECPR Insertion N = 27	Pre-hospital ECPR Insertion N = 27	P-value
Sex (Male) n (%)	25 (92.6)	25 (92.6)	1.00*
Age >60 YO n (%)	5 (18.5)	5 (18.5)	1.00
BMI mean (SD)	27.15 (4.4)	26.89 (3)	0.85
Past medical history			
CV Past medical history n (%)	10 (40.0)	2 (8.3)	0.01
CV Risk Factors n (%)	17 (68)	12 (50)	0.20
Initial presentation			
Cardiac death n (%)	22 (81.5)	22 (81.5)	1.00
Shockable rhythms n (%)	18 (66.7)	18 (66.7)	1.00
Signs of life before ECPR n (%)	14 (51.9)	14 (51.9)	1.00
Epinephrine total dose >5 mg n (%)	20 (74)	20 (74)	1.00
No flow (min) (mean ± SD)	3.44 (3.5)	3.26 (3.4)	0.85
No flow ≥ 5 min n (%)	8 (29.6)	8 (29.6)	1.00
Low flow (min) (mean ± SD)	104.00 (28.9)	76.04 (20.9)	0.0003
Low flow n(%)			
• <60 min	1 (3.9)	7 (29.1)	<0.0001*
• 60–100 min	11 (42.3)	16 (66.7)	
• ≥100 min	14 (53.9)	1 (4.2)	
ECPR implementation times (min) (mean ± SD)	22.20 (9.7)	20.71 (10.6)	0.62
In hospital therapeutics and evolution			
Admission temperature (°C) (mean ± SD)	32.88 (2.6)	33.69 (2.8)	0.35
Coronary angiography n(%)	11 (42.3)	17 (68.0)	0.07
Coronary angioplasty n(%)	8 (30.8)	11 (44.0)	0.33
Evolution and complications			
Survivor n(%)	3 (11.1)	4 (14.8)	1.00*
ROSC under ECPR n(%)	15 (57.7)	21 (84.0)	0.04
DIC n (%)	14 (58.3)	11 (50.0)	0.57
Transfusion n(%)	8 (33.3)	6 (30.0)	0.81
Sepsis n(%)	3 (12.5)	3 (13.6)	1.00*

ECPR: Extracorporeal Cardio-Pulmonary Resuscitation
BMI: Body Mass Index
CV: Cardio-Vascular
CPC: Cerebral Performance Category
ROSC: Return Of Spontaneous Circulation
DIC: Disseminated Intravascular coagulopathy
Propensity score for using pre-versus in-hospital ECPR was calculated using the following data: age, sex, shock delivered on site, epinephrine dose, cardiac cause of arrest, presence of vital signs before ECPR, and no-flow, but excluding duration of low flows

All 156 patients who received ECPR were included, 114 patients were included during Period 1 and 42 patients were included in Period 2.

Baseline and procedural characteristics are shown in Table 1.

Patients treated during the 2 periods had no significant differences in terms of demographic variables. Mean low-flow duration was shorter by more than 20 min in Period 2 ($p < 0.0001$). As expected from the selection criteria of Period 2, presence of signs

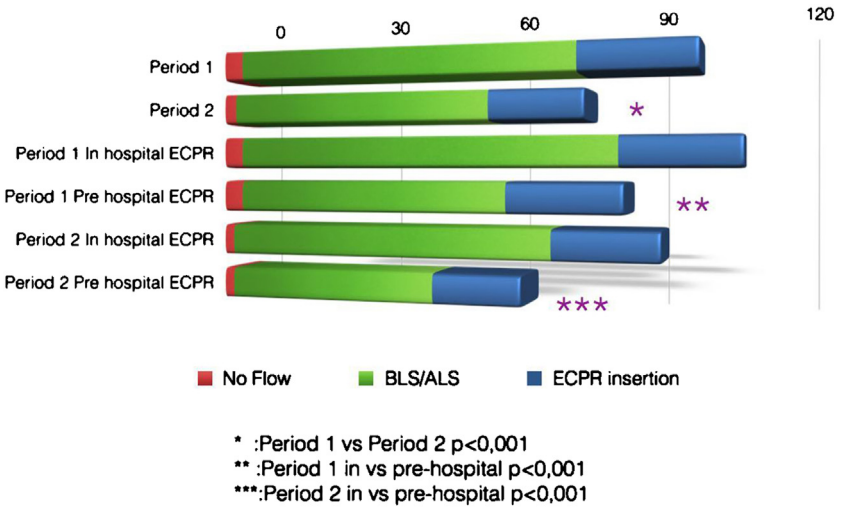

Fig. 1. Time report from different period. BLS: Basic Life support ALS: Advance Life Support ECPR: Extracorporeal Cardio-Pulmonary Resuscitation

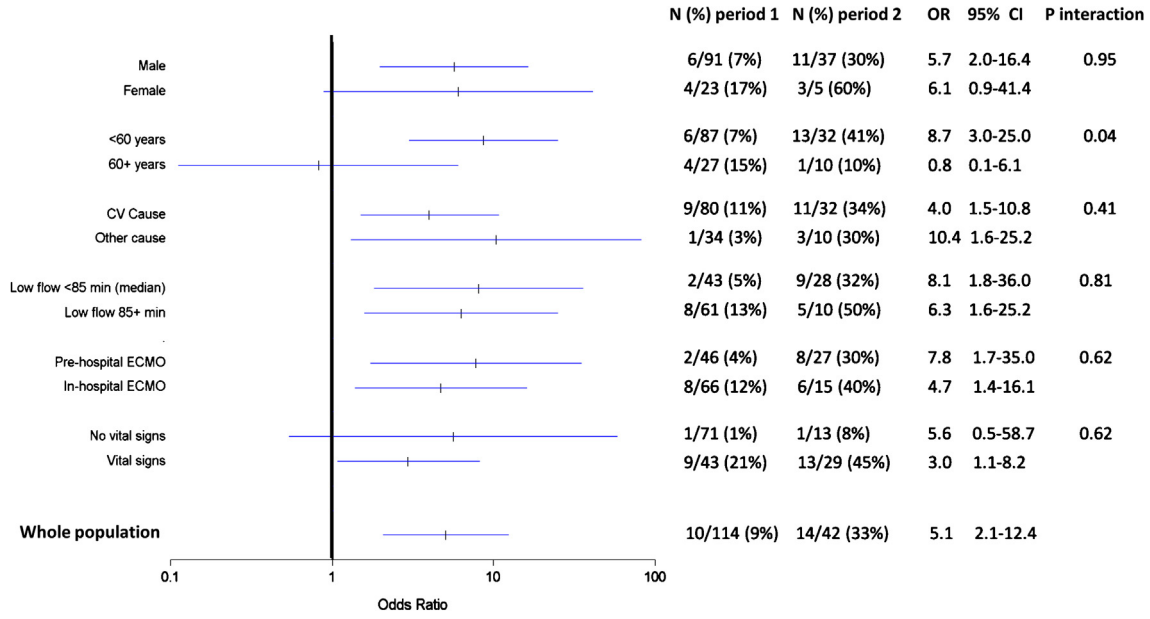

Fig. 2. Odds ratios of improved survival for period 2 compared with period 1.

of life (breathing efforts, gasp, movements, pupils different from mydriasis) during resuscitation before ECPR implementation was observed more often in period 2 (p = 0.0001) and epinephrine dose used in the field was lower (10 mg vs 5 mg p < 0.0001). Likewise, pre-hospital ECPR was more frequently used during Period 2. (p = 0.01) ECPR implementation times were shorter in Period 2 (p = 0.03), and tended to be shorter for pre-hospital ECPR during Period 2 (p = 0.08). (Fig. 1) Coronary angiograms and PCI were more frequently performed during Period 2. During both periods, no patients achieved ROSC during initiation of ECPR.

3.2 In-hospital outcomes according to strategy (period 2 compared with period 1)

Survival was significantly higher with Period 2: 29% vs 8%, P < 0.001; consequently mean duration of ICU stay was longer during period 2 (Table 1), and sepsis appeared more frequently during Period 2. Occurrence of intravascular disseminated coagulation and use of transfusion were similar in both periods.

Survival was strongly correlated with the presence of signs of life (breathing efforts, gasp, movements, pupils different from mydriasis) prior to ECPR (P < 0.001). Indeed, during Period 2, none of the patients with no sign of life survived.

Survival was higher in Period 2 in all subgroups tested (Fig. 2), except in patients over 60 years of age, in whom survival did not improve during Period 2 (p for interaction = 0.04).

Using multivariate analysis, Period 2 was significantly associated with survival (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). Predictors of mortality were pre-hospital ECPR (OR 27.85, 95% CI 3.03–255.81), male sex (OR 12.55, 95% CI 1.56–100.67), past history of cardiovascular disease (OR 52.52, 95% CI 4.43–623.02), administration of more than 5 mg of epinephrine (OR 23.96, 95% CI 3.26–176.03) and the absence of angiography (OR 71.39, 95% CI 5.95–856.15).

When using a propensity score in order to compare patients with similar characteristics in both periods, 26 pairs were found; survival was also higher during Period 2 (P = 0.03). Signs of life pre

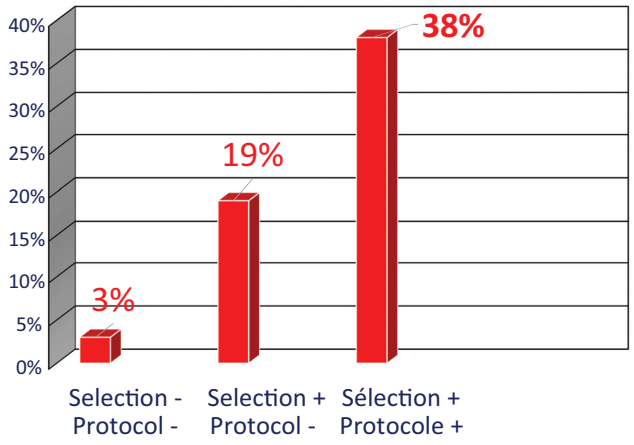

Fig. 3. Effect of an aggressive strategy for refractory cardiac arrest by the different part of this strategy. The selection is the patient selection of period 2 (Cf Annex 2). The protocol is: the prehospital ECPR, and epinephrine equal or less than 5 mg and systematic etiologic research.

ECPR and sepsis during the ICU stay were significantly higher during Period 2 respectively ($p = 0.02$ and $p = 0.007$). During the first period, the rate of patients receiving more than 5 mg of epinephrine was significantly higher ($p = 0.002$). (Table 2).

The survival rate in the total population (Period 1 + 2) increased to 38% for patients with aggressive selection criteria and care Prehospital ECPR, Epinephrine <5 mg and immediate etiologic research corresponding to Period 2 (Fig. 3).

3.3 Potential role of pre-hospital ECPR per se

Survival was similar in patients with pre-hospital versus in-hospital ECPR, both periods combined. Survival between pre-hospital and in-hospital ECPR was similar when implantation could be done within 60 min, as well as when time to implantation exceeded 60 min. In both patients with pre-hospital and in-hospital ECPR, survival improved from Period 1 to period 2, (respectively $p = 0.002$ and $p = 0.01$)

Comparing the 27 pairs matched by propensity score for receiving pre-hospital ECPR, (matched on: age, sex, shock delivered on site, epinephrine dose, cardiac cause of arrest, presence of vital signs before ECPR, and no-flow, but excluding duration of low flows) (Table 3), survival was not different with pre-hospital versus in-hospital ECPR ($P = 1$). However, the rate of ROSC was significantly higher in the pre-hospital group ($p = 0.04$). Low-flow duration was significantly lower in the pre-hospital group in continuous ($p = 0.0003$) or categorical analyses ($p < 0.0001$).

In the 42 pairs comparing pre-hospital ECPR implementation matched on age, sex, no-flow and low-flow durations, survival was 14% in patients with pre-hospital ECPR, compared with 21% of those with in-hospital ECPR ($P = 0.39$).

4 Discussion

Our results in this large series of ECPR suggest improved survival rates in refractory OHCA using an aggressive ECPR strategy. Compared with the initial period when a less stringent protocol was used, survival increased from 8% to 29% (Table 1).

As shown by the different analyses, a more stringent patient selection and the overall management strategy appeared to be the main drivers of improved survival, which did not appear related to any single specific procedure. Patients without the aggressive strategy had a survival rate of 3% compared to 38% for patients with the aggressive strategy (Fig. 3). However, the group of medical cardiac arrest without ECPR had only little hope of survival with such long low-flow times [26]. For selected patients, the use of ECPR may lead to survival rates similar to those of patients with ROSC after successful defibrillation. ECPR should be considered as a second line of treatment and not only as a rescue therapy.

As per protocol, low-flow duration was significantly reduced by Period 2 (93 min vs 71 min $p = < 0.0001$) compared to the previous period. Chen et al. demonstrated an inverse relationship between low-flow duration and survival [3]. The optimal threshold for survival seems to be 60 min, leading to the concept of a "cardiac arrest golden hour" [26]. In the current population, however, low-flow duration greater than 60 min was not significantly associated with lower survival rates (odds ratio, 95% CI: 0.93, 0.12–7.43), In our study, pre-hospital ECPR implementation was associated with reduced low-flow duration, compared to in-hospital ECPR implantation ($P < 0.001$), but not with lower mortality, as shown by multivariate and propensity score analyses. These results are in conflict with the reduction of low-flow in this group. In the different propensity score analyses, the implantation site of ECPR (pre-versus in-hospital) did not appear to influence survival. The mismatch between reduced low-flow with use of pre-hospital ECPR and survival can potentially be explained by a selection bias in favor of in-hospital ECPR. Patients with an in-hospital ECPR had to keep the indication criteria during transportation time. The patients deteriorating too much during transportation no longer fulfilled the criteria for ECPR implantation. This deterioration during transport may be multifactorial (quality of care, severity of the patient or time constraints); conversely, persistence of criteria for ECPR at admission might be explained in some patients by less severe arrhythmias (recurrent ventricular fibrillation, where low flow has less importance than for persistent ventricular fibrillation). In addition, comparison of pre- versus in-hospital ECPR is prone to "survival time bias". Our analysis shows the limits of observational data, particularly in the field of emergency medicine, and supports the need for a randomized study where death would have been counted in each group from the time of randomization, and not from the time of implantation of the device. To eliminate a bias of the delay in implementing time, we compared by propensity score pre-hospital ECPR patients with patients for whom it would have taken 50 min more to implement ECPR (due to transportation delay), if the implantation had been performed in hospital, we found more ROSC but no difference in survival (Data not shown).

The main limitations of in-hospital ECPR are patient extraction delays which are often underestimated in clinical practice. Median durations for in-hospital ECPR implementation (100 and 89 min during periods 1 and 2, respectively) are comparable with those reported in a comparable urban system using a "load and go" strategy [27]; however, this delay is longer than the time needed for pre-hospital ECPR implementation during Period 2 in our series (59 min). The presence of a physician on site does not seem to be a major determinant of ECPR implementation times, Wand et al. reported that 52 min were needed for ECPR implementation for half of their patients, in a system using paramedics only [27]. In large cities, the extraction time to the ambulance from the cardiac arrest scene is a determinant of low-flow duration for in-hospital ECPR compared to the actual distance to the hospital. In our study, despite the new procedure implemented in Period 2, the average durations for in-hospital ECPR insertion were higher than the initial goal of a maximal 60-min low-flow.

There were two major changes in the management of refractory OHCA between Periods 1 and 2: a new algorithm for patient selection and reduced timing to ECPR initiation.

During Period 1 we followed the French ECPR indication guidelines (Appendix A in Supplementary material). This guideline was based on the no-flow duration, as no-flow is known to be an independent prognostic factor for OHCA. However, in everyday practice, accurately determining the duration of no-flow is extremely difficult. Furthermore, maintaining a 24/7 pre-hospital ECPR program is time and resource-consuming, even though the team was on call and available for other tasks during the day. We therefore chose to carefully select patients with more favorable prognostic factors in order to continue the assessment of our strategy. This included signs of life which suggest adequate brain perfusion during resuscitation (Appendix B in Supplementary material). One of the major findings in our study is the major role of signs of life to predict survival: in Period 2, none of the patients without signs of life before ECPR survived.

In Period 1, refractory OHCA was defined by the absence of ROSC after 30 min of resuscitation according to international guidelines in use at the time. Furthermore, the MoICU physician was in charge of activating the ECPR team. In Period 2, the ECPR team was dispatched immediately after notification of an OHCA. ECPR was initiated after 20 min of resuscitation. In a large retrospective cohort, Reynolds and colleagues showed that beyond 16 min of CPR without ROSC, chances of survival with good functional recovery dropped below 1% [25]. Kim et al. found that the ideal timeframe for ECPR was at 21 min of CA [28]. Our rationale is now supported by the recent European Resuscitation Council (ERC) guidelines. This guidelines specified the ECPR need to be implemented early (1 h after the CA) for selected patient and can be done by emergency physician or intensivist [29]. In addition, during Period 2, total epinephrine administration before ECPR insertion was limited to 5 mg. Dumas et al. showed a direct independent relationship between total epinephrine administration and neurological prognosis [30]. This is likely to have led to an improvement in prognosis as well.

Pre-hospital management by MoICU and ECPR teams allows optimal treatment of OHCA similar to hospital treatment. Investigations to establish the cause of arrest were performed immediately before ICU admission. This etiologic research strategy allows identification of the cause of OHCA in 59% of cases [31]. Several registries or animal studies have shown that immediate or emergent coronary angiography may improve survival of OHCA [32,33]. The overall invasive strategy implemented may therefore have contributed to the higher survival rate, although improved survival with Period 2 was still observed after several types of adjustments for the use of myocardial revascularization procedures were made.

As for the first steps of the management of OHCA, it seems that an aggressive "bundle" improves survival of refractory OHCA rather than one aspect of the strategy [34].

4.1 Limitations and bias

Our study is observational non-randomized, and led within a single SAMU department. Management of OHCA and pre-hospital ECPR was performed by highly trained teams in an urban setting with short transportation delays.

During the second period, we assume that the ECPR team had more experience, despite the arrival of new physicians in the team. This experience probably explains the reduction of insertion times between the two periods.

Patients were selected on prognostic factors for survival in Period 2, which obviously introduced a bias in the comparison between both periods and precludes any final conclusion on the benefit of pre-hospital ECPR. However, we thought that this technique should be initially carefully assessed in selected patients by dedicated teams. To confirm the benefit of pre-hospital ECPR, a multi-centric randomized trial comparing pre- and in-hospital implementation of ECPR for refractory OHCA was recently started (NCT02527031).

As stated above, comparison of in-hospital with pre-hospital ECPR is fraught by a survival bias favoring the in-hospital group: as our series includes only patients with ECPR. Patients who presented exclusion criteria for ECPR during transportation to hospital in view of ECPR implantation were not included, thereby artificially increasing the survival rates of patients with inhospital ECPR.

Our study is one of the largest series of ECPR-treated patients, however the total number of patients included is low [24]. Because of the limited size of our population, the risk of type 2 error in our analyses is obvious, and differences not statistically significant in our analyses do not preclude authentic differences.

5 Conclusion

In 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 pre-hospital implementation of ECPR in selected patients is feasible, with a favorable survival rate. Larger registries and randomized trials are warranted to confirm these results.

Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2017.04.014.

References

[1]. Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. Circulation 2012;125(January (4)):620–37.
[2]. Chen Y-S, Chao A, Yu H-Y, Ko W-J, Wu I-H, Chen RJ-C, et al. Analysis and results of prolonged resuscitation in cardiac arrest patients rescued by extracorporeal membrane oxygenation. J Am Coll Cardiol 2003;41(2):197–203.
[3]. Chen YS, Lin JW, Yu HY, Ko WJ, Jerng JS, Chang WT, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. Lancet 2008;372(9638):554–61.
[4]. Lazzeri C, Sori A, Bernardo P, Picariello C, Gensini GF, Valente S. In-hospital refractory cardiac arrest treated with extracorporeal membrane oxygenation: a tertiary single center experience. Acute Card Care 2013;(August):1–5.
[5]. Shin TG, Choi J-H, Jo IJ, Sim MS, Song HG, Jeong YK, et al. Extracorporeal cardiopulmonary resuscitation in patients with inhospital cardiac arrest: a comparison with conventional cardiopulmonary resuscitation. Crit Care Med 2011;39(January (1)):1–7.
[6]. Kagawa E, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Kurisu S, et al. Assessment of outcomes and differences between in- and out-of-hospital cardiac arrest patients treated with cardiopulmonary resuscitation using extracorporeal life support. Resuscitation 2010;81(August (8)):968–73.
[7]. Le Guen M, Nicolas-Robin A, Carreira S, Raux M, Leprince P, Riou B, et al. Extracorporeal life support following out-of-hospital refractory cardiac arrest. Crit Care 2011;15(1):R29.

[8]. Maekawa K, Tanno K, Hase M, Mori K, Asai Y. Extracorporeal cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a propensity-matched study and predictor analysis. Crit Care Med 2013;41(May (5)):1186–96.
[9]. Martin GB, Rivers EP, Paradis NA, Goetting MG, Morris DC, Nowak RM. Emergency department cardiopulmonary bypass in the treatment of human cardiac arrest. Chest 1998;113(March (3)):743–51.
[10]. Massetti M, Tasle M, Le Page O, Deredec R, Babatasi G, Buklas D, et al. Back from irreversibility: extracorporeal life support for prolonged cardiac arrest. Ann Thorac Surg 2005;79(1):178–83.
[11]. Mégarbane B, Leprince P, Deye N, Résière D, Guerrier G, Rettab S, et al. Emergency feasibility in medical intensive care unit of extracorporeal life support for refractory cardiac arrest. Intensive Care Med 2007;33(March (5)):758–64.
[12]. Nagao K, Hayashi N, Kanmatsuse K, Arima K, Ohtsuki J, Kikushima K, et al. Cardiopulmonary cerebral resuscitation using emergency cardiopulmonary bypass, coronary reperfusion therapy and mild hypothermia in patients with cardiac arrest outside the hospital. J Am Coll Cardiol 2000;36(3):776–83.
[13]. Avalli L, Maggioni E, Formica F, Redaelli G, Migliari M, Scanziani M, et al. Favourable survival of in-hospital compared to out-of-hospital refractory cardiac arrest patients treated with extracorporeal membrane oxygenation: an Italian tertiary care centre experience. Resuscitation 2012;83(May (5)):579–83.
[14]. Bellezzo JM, Shinar Z, Davis DP, Jaski BE, Chillcott S, Stahovich M, et al. Emergency physician-initiated extracorporeal cardiopulmonary resuscitation. Resuscitation 2012;83(August (8)):966–70.
[15]. Patroniti N, Sangalli F, Avalli L. Post-cardiac arrest extracorporeal life support. Best Pract Res Clin Anaesthesiol 2015;29(December (4)):497–508.
[16]. Choi DS, Kim T, Ro YS, Ahn KO, Lee EJ, Hwang SS, et al. Extracorporeal life support and survival after out-of-hospital cardiac arrest in a nationwide registry: a propensity score-matched analysis. Resuscitation [Internet] 2015;(December) [cité 21 déc 2015]; Disponible sur: http://linkinghub.elsevier.com/retrieve/pii/S0300957215008862.
[17]. Siao F-Y, Chiu C-C, Chiu C-W, Chen Y-C, Chen Y-L, Hsieh Y-K, et al. Managing cardiac arrest with refractory ventricular fibrillation in the emergency department: conventional cardiopulmonary resuscitation versus extracorporeal cardiopulmonary resuscitation. Resuscitation 2015;92(July):70–6.
[18]. Pozzi M, Koffel C, Armoiry X, Pavlakovic I, Neidecker J, Prieur C, et al. Extracorporeal life support for refractory out-of-hospital cardiac arrest: should we still fight for? A single-centre, 5-year experience. Int J Cardiol 2016;204(February):70–6.
[19]. Anselmi A, Flécher E, Corbineau H, Langanay T, Le Bouquin V, Bedossa M, et al. Survival and quality of life after extracorporeal life support for refractory cardiac arrest: a case series. J Thorac Cardiovasc Surg 2015;150(October (4)):947–54.
[20]. Champigneulle B, Bellenfant-Zegdi F, Follin A, Lebard C, Guinvarch A, Thomas F, et al. Extracorporeal life support (ECLS) for refractory cardiac arrest after drowning: an 11-year experience. Resuscitation 2015;88(March):126–31.
[21]. Lamhaut L, Jouffroy R, Kalpodjian A, Deluze T, Phillipe P, Vivien B, et al. Successful treatment of refractory cardiac arrest by emergency physicians using pre-hospital ECLS. Resuscitation 2012;83(August (8)):e177–8.
[22]. Lamhaut L, Jouffroy R, Soldan M, Phillipe P, Deluze T, Jaffry M, et al. Safety and feasibility of prehospital extra corporeal life support implementation by non-surgeons for out-of-hospital refractory cardiac arrest. Resuscitation 2013;(July).
[23]. Noc M, Fajadet J, Lassen JF, Kala P, MacCarthy P, Olivecrona GK, et al. Invasive coronary treatment strategies for out-of-hospital cardiac arrest: a consensus statement from the European Association for Percutaneous Cardiovascular Interventions (EAPCI)/Stent for Life (SFL) groups. EuroIntervention 2014;10(May (1)):31–7.
[24]. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). Resuscitation 2004;63(3):233–49.
[25]. Reynolds JC, Frisch A, Rittenberger JC, Callaway CW. Duration of resuscitation efforts and functional outcome after out-of-hospital cardiac arrest: when should we change to novel therapies? Circulation [Internet] 2013;(November) [cité 24 nov 2013]; Disponible sur: http://circ.ahajournals.org/cgi/doi/10.1161/CIRCULATIONAHA.113.002408.
[26]. Wang C-H, Chou N-K, Becker LB, Lin J-W, Yu H-Y, Chi N-H, et al. Improved outcome of extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest – a comparison with that for extracorporeal rescue for in-hospital cardiac arrest. Resuscitation 2014;85(September (9)):1219–24.
[27]. 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(June):131–6.
[28]. Kim SJ, Jung JS, Park JH, Park JS, Hong YS, Lee SW. An optimal transition time to extracorporeal cardiopulmonary resuscitation for predicting good neurological outcome in patients with out-of-hospital cardiac arrest: a propensity-matched study. Crit Care 2014;18(5), 535.
[29]. Soar J, Nolan JP, Böttiger BW, Perkins GD, Lott C, Carli P, et al. European resuscitation council guidelines for resuscitation 2015: section 3: adult advanced life support. Resuscitation 2015;95(October):100–47.
[30]. Dumas F, Bougouin W, Geri G, Lamhaut L, Bougle A, Daviaud F, et al. Is epinephrine during cardiac arrest associated with worse outcomes in resuscitated patients? J Am Coll Cardiol 2014;64(December (22)):2360–7.
[31]. Chelly J, Mongardon N, Dumas F, Varenne O, Spaulding C, Vignaux O, et al. Benefit of an early and systematic imaging procedure after cardiac arrest: insights from the PROCAT (Parisian Region Out of Hospital Cardiac Arrest) registry. Resuscitation 2012;83(January (12)):1444–50.
[32]. Dumas F, Cariou A, Manzo-Silberman S, Grimaldi D, Vivien B, Rosencher J, et al. Immediate percutaneous Coronary intervention is associated with better survival after out-of-hospital cardiac ArrestClinical perspective insights from the PROCAT (Parisian region out of hospital cardiac arrest) registry. Circ Cardiovasc Interv 2010;3(January (3)):200–7.
[33]. Hutin A, Lamhaut L, Lidouren F, Kohlhauer M, Mongardon N, Carli P, et al. Early Coronary reperfusion facilitates return of spontaneous circulation and improves cardiovascular outcomes after ischemic cardiac arrest and extracorporeal resuscitation in pigs. J Am Heart Assoc 2016;5(December (12)).
[34]. Adabag S, Hodgson L, Garcia S, Anand V, Frascone R, Conterato M, et al. Outcomes of sudden cardiac arrest in a state-wide integrated resuscitation program: results from the Minnesota Resuscitation Consortium. Resuscitation 2017;110(January):95–100.