

## BRIEF RESEARCH REPORT

## Emergency Medical Services

# Feasibility of extracorporeal membrane oxygenation cardiopulmonary resuscitation by low volume centers in Belgium

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**Abstract**

**Objective:** To assess the feasibility of delivering extracorporeal cardiopulmonary resuscitation (ECPR) in refractory out-of-hospital cardiac arrests (OHCA) by low volume extracorporeal membrane oxygenation (ECMO) centers and to explore pre-ECPR predictors of survival.

**Methods:** Between 2016 and 2020, we studied 21 ECPR patients admitted in 2 tertiary ECMO centers in Liège, Belgium. Our ECPR protocol was based on 6 prehospital criteria (no flow < 3 minutes, low flow < 60 minutes, initial shockable rhythm, end-tidal CO<sub>2</sub> > 15 mmHg, age < 65 years, and absence of comorbidities). A dedicated training, prehospital checklist and call number for 24/7 ECMO team assistance were implemented. Hemodynamics and blood gases on admission also were assessed.

**Results:** Twenty-one (28%) out of 75 refractory OHCA patients referred were treated by ECPR, with a hospital survival rate of 43% (n = 9/21), comparable to ECPR results from the international extracorporeal life support organization registry. Transient return of spontaneous circulation before ECPR (89% in survivors vs 17% in non-survivors, P = 0.002) and higher initial serum bicarbonate (med [P25-P75] 14.0 [10.6–15.2] vs 7.5 [3.7–10.5] mmol/L, P = 0.019) or lower initial base deficit (14.9 [11.9–18.2] vs 21.6 [17.9–28.9] mmol/L, P = 0.039) were associated with a more favorable outcome.

**Conclusion:** In low volume ECMO centers, the implementation of a specific ECPR protocol for refractory OHCA patients is feasible and provides potential clinical benefit. Highly selective inclusion criteria seem essential to select candidates for ECPR. Initial serum bicarbonate and base deficit integrating cumulative cell failure may be relevant pre-ECMO prognostic factors and require larger-scale evaluation.

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**KEYWORDS**

extracorporeal cardiopulmonary resuscitation, extracorporeal membrane oxygenation, out-of-hospital cardiac arrest, prehospital emergency care

## 1 | INTRODUCTION

In-hospital and out-of-hospital cardiac arrests (OHCA) treated by conventional cardiopulmonary resuscitation (CPR) feature ominous prognosis, with hospital mortality rates higher than 80% and 90%<sup>1</sup>, respectively. To face this reality, typical extracorporeal CPR (ECPR) inclusion criteria<sup>2</sup> include no flow time < 5 minutes (or witnessed cardiac arrest), low flow time < 100 minutes, good CPR quality with end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) > 10 mmHg, age < 65-75 years, no major comorbidities, and a presumed reversible cause, such as an initial shockable cardiac rhythm (suggesting a primary ischemic event with retained myocardial viability).

However, such classic inclusion criteria for consideration of ECPR failed to improve hospital survival. On the one hand, the Paris OHCA registry between 2011 and 2018 reported no improvement of the hospital survival rate after ECPR compared with conventional CPR (8% vs 9%, respectively). Only the transient return of spontaneous circulation (ROSC) and the prehospital extracorporeal membrane oxygenation (ECMO) implantation, together with an initial shockable rhythm, predicted better survival in the ECPR group.<sup>1</sup> On the other hand, the international extracorporeal life support organization (ELSO) registry found a much better hospital survival rate of 27.6% among OHCA ECPR patients and 29% for all ECPR (July 2020 summary). This large discrepancy in outcome could be attributed to the ECPR patients' selection criteria, still under debate<sup>3</sup>. Another explanation could be the emergency system's organization and the ECMO centers' volume. Indeed, the hospital volume of annual ECMO cases was shown to affect hospital mortality with an odds ratio of 0.61 (95% CI, 0.46–0.80) when more than 30 cases versus less than 6 annual cases<sup>4</sup>. ECMO centers should be located in geographical areas that can support a minimum of 6 ECMO patients per center per year, according to the ELSO center's guidelines. In order to optimize outcomes, a minimum of 20 and 30 adult annual ECMO cases are recommended for respiratory failure<sup>5</sup> and cardiac failure<sup>6</sup>, respectively.

The goals of our pilot study were to evaluate the feasibility of an ECPR for refractory OHCA in 2 low volume ECMO centers, guided by a specific protocol with highly selective inclusion criteria, and to investigate potential additional predictive variables, particularly on admission before ECMO implantation.

## 2 | METHODS

### 2.1 | Study design and settings

This observational, prospective, 2 center cohort study analyzed ECPR candidates among OHCA from 2016 to 2020. Both hospitals are tertiary referral ECMO centers: the University Hospital of Liège has 50

mixed ICU beds and Liège Regional Hospital Center has 36 mixed ICU beds (mean 26 and 23 annual ECMO cases during the period, respectively). The 2 centers are organized as a hospital network with a collaborative ECPR program addressed to Liège (medium-sized city of 200,000 inhabitants) and its province (1,100,000 inhabitants).

The OHCA care system in Belgium consists of 3 successive and escalating levels of medical assistance.

First, a bystander phone CPR is initiated as soon as the 112 emergency services call operator identifies a cardiac arrest, activates a double ambulance system, and gives prearrival instructions to the bystanders, namely a phone CPR. Second, a basic cardiac life support by emergency medical technicians including CPR, oxygen, and an automated external defibrillation is applied when the local ambulance first arrives on the scene. Third, advanced cardiac life support is implemented when the second emergency paramedic and physician-staffed ambulance arrives. Advanced CPR, manual defibrillation, venous accesses, airway protection, and treatment of the mnemonic 4H&4T (hypoxia, hypovolaemia, hypo/hyperkalaemia, hypothermia, thrombosis, cardiac tamponade, toxins, and tension pneumothorax) reversible causes of cardiac arrest are then executed. Prehospital portable echocardiography is also performed and prearrival instructions for the inhospital ECMO team are given. The incidence of OHCA in Belgium from the Belgian Health Care Knowledge Center was 10,880 cases in 2017, and in Liège Province is around 1000 confirmed OHCA cases a year, with a global hospital mortality of 95.1%. The Liège ambulance service network counts 41 local ambulances and 10 physician-staffed ambulances, including 1 helicopter.

### 2.2 | Inclusion and exclusion criteria for ECPR

Six prehospital inclusion criteria were defined in our ECPR protocol: (1) age < 65 years; (2) absence of known major comorbidities; (3) no flow time < 3 minutes (or any cortical signs of life during CPR); (4) presumed low flow time < 60 minutes; (5) initial shockable rhythm, and (6) ETCO<sub>2</sub> > 15 mmHg for non-hypothermic patients (Table 1). In case of severe hypothermia (< 28°C) criteria were adjusted as follows: no flow < 1 hour, low flow < 6 hours, any initial rhythm.

Additional hospital resuscitation discontinuation criteria were considered: ETCO<sub>2</sub> < 10 mmHg for > 20 minutes, extreme lactic acidosis (pH < 7.0 with lactate > 1800 mg/L or pH < 6.90 if severe hypercapnia PaCO<sub>2</sub> > 75 mmHg), extreme hypoxemia (PaO<sub>2</sub> < 50 mmHg, SaO<sub>2</sub> < 80%) and refractory hypotension despite CPR and vasopressors (while targeting a mean arterial pressure > 50 mmHg for cerebral perfusion pressure > 30 mmHg<sup>7</sup>).

General ECMO contraindications also were considered, namely aortic dissection, major aortic aneurysm, moderate-to-severe or severe aortic insufficiency, hemorrhagic shock, traumatic and/or hypoxic

**TABLE 1** Prehospital and hospital ECPR inclusion and exclusion criteria

ECPR	Prehospital inclusion criteria:	Prehospital exclusion criteria:
1	Age <sup>a</sup> < 65 years	
2	No major comorbidity	Major comorbidities:
-		Medical: extensive stroke, advanced dementia, O <sub>2</sub> -dependant COPD, or fibrosis, Child C cirrhosis, frailty in dialysis, palliative cancer
-		Vascular: end-stage arteriopathy, severe aortic disease, morbid obesity
3	No flow < 3 minutes <sup>b</sup> • Or cortical signs of life <sup>c</sup> during CPR	Is considered as prolonged no flow: • Unwitnessed cardiac arrest • Poor-quality of CPR by bystander (eg, insufficient rate or depth of external chest compression, soft surface)
4	Low flow < 60 minutes <sup>b</sup>	
5	Initial shockable rhythm <sup>b</sup>	Initial non-shockable rhythm Absence of shock by automated external defibrillator is assimilated to a non-shockable rhythm.
6	ETCO <sub>2</sub> > 15 mmHg	
		<b>Hospital resuscitation discontinuation criteria:</b>
7		Extreme metabolic acidosis (pH < 7.0 <sup>d</sup> with lactate > 1800 mg/L) or hypoxia (PaO <sub>2</sub> < 50 mmHg, SaO <sub>2</sub> < 80%)
8		ETCO <sub>2</sub> < 10 mmHg <sup>d</sup> for > 20 minutes
9		Refractory vasoplegia
10		General ECMO contraindications (eg, aortic, traumatic, hemorrhagic, limitation...)

Abbreviations: COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; ETCO<sub>2</sub>, end-tidal CO<sub>2</sub>.

<sup>a</sup>Physiological age is most relevant.

<sup>b</sup>If severe hypothermia, consider no flow < 1 hour, low flow < 6 hours, and all rhythms.

<sup>c</sup>Cortical signs of life: attempts of head/member oriented moving, speaking, eyes opening and moving.

<sup>d</sup>If severe hypercapnia (PaCO<sub>2</sub> > 75 mmHg), consider pH < 6.9, and ETCO<sub>2</sub> < 15 mmHg.

### The Bottom Line

Although showing dramatic associations and improved outcomes, the availability of extracorporeal membrane oxygenation (ECMO) for the resuscitation of out-of-hospital cardiac arrest remains limited because of its perceived complexity. In this series of 21 patients treated over 5 years in Liège, Belgium, the authors demonstrated the feasibility of ECMO cardiopulmonary resuscitation (ECPR) at a low volume center. This demonstration underscores that effective ECPR may be possible even at centers with limited regular experience.

ischemic brain injury, advanced cancer (median survival < 1 year), and do-not-resuscitate orders or therapeutic limitations. Of note, thrombolysis for pulmonary embolism was not an exclusion criterion for subsequent ECPR.

## 2.3 | Local Liège ECPR protocol

Our local ECPR experience for refractory OHCA started in 2011 without formal inclusion criteria and unfortunately no survivors (n = 5).

Therefore, in May 2016, a local Liège protocol-guided ECPR program was implemented and accepted by both hospitals' institutional ethical committees (ref. 2017272 and 1699, respectively). The study qualified for exception from informed consent under emergency circumstances. A training course of emergency physicians and a prehospital checklist with the 6 selected inclusion criteria were implemented. A unique 24/7 call number with 4 intensivists from the ECMO team also was dedicated to help emergency physicians in their ECPR decision. A play-and-run strategy to the closest center was implemented and the immediate mobilization of the surgical ECMO team was triggered as soon as the ECPR candidate met the 6 prehospital criteria, to avoid any delay in cannulation.

## 2.4 | Definitions

A refractory cardiac arrest refers to an absence of ROSC within 30 minutes of CPR. Sustained ROSC (longer than 20 minutes) rules out patients from ECPR definition, even if such patients may subsequently need venoarterial ECMO for postarrest cardiogenic shock. A low flow time is defined from CPR start to ECMO flow, not to start of cannulation (ECMO implementation usually takes 20-30 minutes). Signs of life are of cortical origin, that is, attempts of head/member oriented moving, of speaking or eyes opening and moving, whereas member flexion/

extension, pupillary myosis, gasping, gagging, or biting of the tracheal tube are not signs of life but only—even favorable—brainstem reflexes.

## 2.5 | Measurements

Inclusion criteria, details of arrest, timings, hemodynamics, and blood gases on admission were assessed. Details on the collapse circumstances, the bystander CPR, and various timings were systematically confirmed afterwards by a call with the 112 operator and a debriefing by the on-scene physician.  $\text{ETCO}_2$  was recorded on intubation, 20 minutes after CPR initiation, and on hospital admission. First electroencephalogram (EEG) was recorded and scored according to early EEG postanoxic coma classification<sup>8</sup>. Neuron-specific enolase (NSE) was measured on the 3 first days using chemiluminescence. Survival to hospital discharge and 3-month neurological status (Glasgow outcome scale) were recorded.

## 2.6 | Outcomes

The primary outcome was the feasibility of ECPR implementation for refractory OHCA in low volume centers. Secondary outcomes were the survival to hospital discharge of the ECPR patients, their 3-month neurological status, and the potential identification of prehospital and early hospital (pre-ECMO) predictors of hospital survival.

## 2.7 | Statistical analysis

Univariate analysis of variables comparing survivors and non-survivors was performed using Mann-Whitney ranksum *U* test for continuous variables and Fisher exact test for qualitative variables. Correlations between continuous variables were obtained by Pearson correlation test. Cutoff values offering best sensitivity/specificity balance were determined by Youden's *J* statistics. Because of limited sample size, we could not perform logistic regression model with multivariate analysis. *P* value < 0.05 was considered significant. Statistics were performed using Stata 16.1 (StataCorp 2021, College Station, TX) and RStudio (RStudio Team 2020, Boston, MA) software.

## 3 | RESULTS

### 3.1 | Baseline characteristics of our ECPR patients

From May 2016 to April 2020 (protocol period – 48 months), 75 patients with refractory OHCA were referred to our ECPR team as potential ECPR candidates, out of a total of 3365 encoded emergency calls for cardiac arrest; among these 75 candidates, only 21 (28%) received ECPR, including 2 children (< 18 years). Indeed, 39 patients (52%) were excluded from ECPR based on unsatisfied prehospital inclusion criteria (low flow *n* = 24; rhythm *n* = 12; no flow *n* = 9;

$\text{ETCO}_2$  *n* = 7; age *n* = 6), often with multiple reasons (*n* = 17), 1 or more discontinuation criteria (*n* = 12) or ECMO contraindications (*n* = 6). The remaining 15 patients (20%) presented sustained ROSC on admission and were therefore no longer eligible for ECPR; among them, 4 required a venoarterial ECMO for in-hospital cardiac arrest (IHCA) or postarrest cardiogenic shock. The etiology of cardiac arrest was mainly acute coronary syndrome (52%), if not non-ischemic cardiac disorders (Takotsubo, arrhythmic, hypertrophic and pulmonary embolism, 24%) and non-cardiac origin (hypothermia and drowning, 24%). A flow diagram of our sample is presented in the supplement (Figure S1).

### 3.2 | Main results

Our local Liège ECPR protocol involving 2 low volume ECMO centers allowed the inclusion of 21 patients with refractory OHCA for ECPR, with a survival rate to hospital discharge of 43% (*n* = 9/21). After 3 months, 7 presented a favorable neurological outcome, 1 a persistent vegetative state, and 1 a moderate disability. The 6 inclusion criteria allowed prehospital selection of ECPR patients but when comparing the values for each criterion between survivors and non-survivors, none was found to significantly predict better outcome (Table 2).

### 3.3 | Secondary results

Prehospital (Table 2) and hospital (Table 3) potential predictive variables of survival were analyzed. The occurrence of a bystander CPR (*n* = 16, of good quality in 71% of cases) did not correlate with survival, even if its duration tended to correlate negatively with survival. No one benefited from automated external defibrillation. Timings of arrival and of transport were not significantly different between survivors and non-survivors.

Among hospital variables available on admission before ECMO, 2 were associated with a better outcome: any transient ROSC pre-ECPR (89% in survivors vs 17% in non-survivors, *P* = 0.002) and higher initial serum bicarbonate (14.0 [10.6-15.2] vs 7.5 [3.7-10.5] mmol/L, *P* = 0.019), or equivalently lower initial base deficit and lower initial lactate levels (see Figure S2). Three post-ECPR variables were also associated with survival, namely higher serum fibrinogen (obtainable at 1 hour, Figure S2), lactate at the sixth hour, and peak of NSE in the first 72 hours (44 [31-55] vs 192 [65-283]  $\mu\text{g/L}$ , *P* = 0.010). The best cutoffs on admission for survival prediction were serum bicarbonate > 10 mmol/L (positive predictive value 85%), and base deficit < 18 mmol/L (positive predictive value 81%). We found a significant correlation between the time from call to ECPR and the base deficit (*r* = 0.44, *P* = 0.023), the lactate (*r* = 0.43, *P* = 0.030), and the fibrinogen (*r* = -0.52, *P* = 0.014) on admission.

Initial EEG was also informative, because all patients with isoelectric or burst suppression EEG patterns (*n* = 5) on day 1 or 2 presented high NSE levels (> 65  $\mu\text{g/L}$ ) and died, whereas those with a continuous pattern had a more favorable neurological outcome.

**TABLE 2** Prehospital characteristics of ECPR patients

	Survivors n = 9	Nonsurvivors, n = 12	P
Age (years)	47 (32–53; 1–61)	55 (51–60; 42–68)	0.065
Male (%)	7 (78)	8 (67)	0.63
Comorbidity (%)	0 (0)	2 (17)	0.49
No flow (minutes)	2 (0–5; 0–6)	0 (0–2; 0–3)	0.13
Low flow (minutes)	75 (18–95; 5–270)	83 (52–94; 46–104)	0.52
Shockable rhythm (%)	5 (55)	9 (75)	0.40
PEA	2	0	
Asystole	2	3	
VF	5	9	
ETCO <sub>2</sub> (mmHg)	28 (20–34; 13–47)	17 (15–30; 6–66)	0.26
Arrest etiology:			0.25
Acute coronary syndrome	3	8	
Non-ischemic cardiomyopathy (Takotsuko, arrhythmic, hypertrophic, pulmonary embolism)	2	3	
Non-cardiac (hypothermia, drowning)	4	1	
Bystander CPR (%)	5 (55)	11 (92)	0.34
Bystander CPR (minutes)	2 (2–2; 2–2)	9 (5–10; 2–25)	0.09
Hypothermia < 32°C (%)	4 (44)	1 (8)	0.28
Time from call to rescue (minutes)	12 (10–14; 6–24)	13 (11–14; 6–27)	0.78
Time from rescue to hospital (minutes)	43 (35–49; 31–61)	38 (32–56; 16–93)	0.46
Time from call to hospital (minutes)	54 (44–60; 32–75)	48 (44–76; 28–93)	0.80

Abbreviations: CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; ETCO<sub>2</sub>, end-tidal CO<sub>2</sub>; PEA, pulseless electrical activity; VF, ventricular fibrillation.

Results are presented as n (%) and median (interquartile range; range).

The ECMO cannulation rate was 100%. However, there were ECMO-related complications, mainly hemorrhagic: peripheral cannulation site bleeding (n = 8), resuscitation-derived hemoperitoneum (n = 1), and diffuse coagulopathy (n = 4), but no tamponade nor mechanical complications. One patient presented leg ischemia requiring amputation and another a left ventricular overload requiring Impella. ECMO-non-related complications in survivors were neurological impairments (n = 3), ventilator-associated pneumonia (n = 3), acute renal insufficiency (n = 2), and ribs and sternal fracture (n = 1). ECPR non-survivors died from hypoxic cerebral edema (n = 6), hemorrhagic shock (n = 4), refractory postcardiac arrest syndrome (n = 1), and septic shock (n = 1). Finally, 4 (15%) patients were brain dead and allowed organ donation.

### 3.4 | Limitations

Limitations of our observational pilot study was its small sample size and its bicentric design, related to our low hospital-level volume and geographical area. Our study was not designed to compare in a randomized manner ECPR to conventional cardiopulmonary resuscitation, nor to proceed to any multivariate analysis, neither to draw conclusions on relevance—or not—of more selective ECPR inclusion criteria. The age limit of 65 years we chose referred to Eurotransplant's rela-

tive contraindication of heart transplantation and left ventricular heart device until 2019<sup>9</sup>. We excluded 6 patients according to their age, yet physiological age (rather than chronological age) was always considered and integrated with comorbidities. Also, serum bicarbonate and base deficit on admission that were pointed out as potential pre-ECPR predictors of survival certainly require large-scale validation.

## 4 | DISCUSSION

Our local pilot study raises several points concerning ECPR implementation for refractory OHCA patients.

First, this observational study supports the feasibility of ECPR program for refractory OHCA in low volume ECMO centers. Twenty to 30 annual ECMO cases are usually recommended as the minimum number to offer optimal extracorporeal life support in respiratory<sup>5</sup> and cardiac<sup>6</sup> failure, respectively. Barbaro et al.<sup>4</sup> demonstrated lower odds of hospital mortality for adult patients receiving ECMO in hospitals with more than 30 adults annual ECMO cases. Our study suggests that hospital network organization with modest hospital volumes with 20 to 30 annual adult ECMO cases could succeed in delivering ECPR for refractory OHCA patients. It therefore encourages local ECMO teams to implement collaborative multicenter ECPR programs and to offer ECPR for refractory OHCA to wider geographical areas.

**TABLE 3** Hospital characteristics of ECPR patients

	Survivors n = 9	Non-survivors n = 9	P
Time from hospital to ECPR (minutes)	30 (22–41; 15–62)	27 (23–96; 20–149)	0.27
Time from call to ECPR (minutes)	85 (81–95; 68–111)	100 (70–130; 53–196)	0.36
ROSC pre (%)	8 (89)	2 (17)	<b>0.002</b>
MAP (mmHg) <sup>a</sup>	73 (63–79; 50–92)	69 (68–87; 67–104)	0.81
Noradrenaline	0.11 (0–0.14; 0–0.3)	0.27 (0.14–0.39; 0–0.67)	0.12
APACHE II	24 (22–27; 21–29)	27 (24–34; 19–36)	0.29
SAPS II	63 (49–71; 41–83)	67 (51–85; 47–93)	0.28
Risk of death SAPS II (%)	74 (45–85; 27–94)	80 (48–95; 39–97)	0.28
SOFA pre	10 (7–12; 5–14)	9 (7–11; 4–12)	0.59
Reactive pupils (%)	5 (55)	3 (25)	0.27
PaCO <sub>2</sub> pre (mmHg)	71 (57–92; 41–125)	62 (40–75; 21–101)	0.18
PaO <sub>2</sub> pre (mmHg)	61 (40–98; 18–130)	55 (34–72; 14–100)	0.56
SaO <sub>2</sub> pre (%)	87 (66–95; 28–97)	72 (60–89; 31–99)	0.37
pH pre	6.94 (6.8–7.07; 6.8–7.33)	6.94 (6.8–7.04; 6.79–7.14)	0.45
HCO <sub>3</sub> <sup>-</sup> pre (mmol/L)	14.0 (10.6–15.2; 4.3–21.7)	7.5 (3.7–10.5; 2.0–13.6)	<b>0.019</b>
Base deficit pre (mmol/L)	14.9 (11.9–18.2; 4.0–26.0)	21.6 (17.9–28.9; 12.9–32.5)	<b>0.039</b>
Lactate pre (mg/L)	780 (681–1480; 170–1530)	1295 (1050–1450; 680–1800)	0.20
Lactate > 900 (mg/L)	4 (44)	11 (92)	<b>0.046</b>
Fibrinogen pre (g/L)	2.7 (2.2–2.9; 2.2–3.0)	1.2 (0.6–1.9; 0.4–3.2)	<b>0.008</b>
Fibrinogen < 1.8 (g/L)	0 (0)	5 (42)	<b>0.045</b>
After ECPR:			
Coronarography	4	10	0.16
Stenting	3	6	0.38
Lactate hour 6 (mg/L)	260 (140–270; 100–710)	849 (410–891; 240–1530)	<b>0.020</b>
ECMO duration (h)	63 (43–72; 26–181)	7 (4–64; 4–266)	0.063
NSE max <sup>b</sup> (μg/L)	44 (31–55; 30–56)	192 (65–283; 62–337)	<b>0.010</b>

Abbreviations: APACHE, acute physiology and chronic health; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; MAP, mean arterial pressure; NSE, neuron-specific enolase; ROSC, return of spontaneous circulation; pre, before ECPR; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment.

Results are presented as n (%) and median (interquartile range; range).

<sup>a</sup>n = 8.

<sup>b</sup>n = 16.

Second, our study stresses the need to use highly restrictive prehospital inclusion criteria, namely by limiting no flow duration < 3 minutes, total low flow < 60 minutes, ETCO<sub>2</sub> > 15 mmHg until ECPR decision, instead of classical criteria of 5 minutes, 100 minutes, and 10 mmHg, respectively, and age < 65 years according to Eurotransplant's age limit. Thanks to this restrictive strategy we obtained a hospital mortality rate for ECPR patients similar to the one reported by the international ELSO registry. Furthermore, ECPR protocol requires a play-and-run prehospital strategy in ECPR candidates rather than a stay-and-play one, as usually recommended in trauma and OHCA patients. However, the lack of statistical power in our study precludes any generalization of our local selection criteria. In addition the potential key role of restrictive selection criteria in low volume centers in achieving similar ECPR efficacy to larger centers remains unclear.

Better definition of ECPR criteria for refractory OHCA remains a key challenge in the future.

Third, next to the 6 classic prehospital selection criteria for ECPR in refractory OHCA patients, our study demonstrated that a transient ROSC and a better-preserved serum bicarbonate and initial base deficit on admission before ECPR could serve as 3 additional predictive tools to better discriminate between survivors and non-survivors and to guide the ECPR decision. Indeed, we interpret transient ROSC occurrence, preserved serum bicarbonate and lower base deficit as direct consequences of a higher CPR quality, and of a more reversible condition, with notably better lactate clearance and neuronal survival. Similarly, serum bicarbonate before ECMO has already been selected as a prognostic factor in the survival after venoarterial-ECMO score for refractory cardiogenic shock,<sup>10</sup> and ischemic cardiogenic shock,<sup>11</sup> and

base deficit for hemorrhagic shock in trauma patients.<sup>12</sup> CPR quality in fact is the priority rather than a low flow time only.

Fourth, a few studies reported local ECPR experiences in low volume centers. The Australian studies CHEER from Melbourne<sup>13</sup> and 2CHEER from Sidney<sup>14</sup> are from comparable ECMO referral centers providing ECMO support in their large districts. They included a mixed population of 11 OHCA and 15 IHCA/14 IHCA to reach promising survival rates of 54%/44% with full neurological recovery by combining protocolized care and predefined selection criteria, with additional hypothermia in the CHEER trial. Their criteria allowed larger age range (up to 70 years), a 10 minute window to start chest compressions, and longer low flow time counting 60 minutes from collapse to arrival at the emergency department. By contrast, the small randomized feasibility Extracorporeal Cardiopulmonary Resuscitation for Refractory Out of Hospital Cardiac Arrest (EROCA) trial from Ann Arbor<sup>15</sup> enrolled 5 among 12 eligible patients for expedited transport to an ECPR-capable hospital within 30 minutes, and for ECPR initiation within another 30 minutes of ED arrival, but failed to save any patients. However, the phase 2 Arrest trial from Minneapolis<sup>16</sup> is the first randomized trial succeeding in treating fifteen 18-75 year-old patients with refractory ventricular fibrillation by early ECPR, with a survival to hospital discharge of 43% compared with 7% in 15 controls receiving standard advanced cardiac life support treatment. Restructuring of their emergency medical service response was necessary to facilitate early transport and prompt activation and deployment of their ECMO team within 20 minutes. A Minnesota mobile ECMO cannulation team<sup>17</sup> is now activated as soon as emergency medical services identify an ECMO candidate to meet at the closest ECMO initiation hospital, for cannulation and cardiac catheterization, before secondary transfer to the reference ECMO center. Wider implementation will require multicenter phase 3 randomized ECPR trials (such as the Dutch INCEPTION trial<sup>18</sup>).

Finally, ECPR implementation also allowed organ donation in 4 of our ECPR non-survivors in the event of brain death condition. It was also previously reported that more than 40% of brain-dead patients after cardiac arrest allowed organ transplantation.

In summary, our pilot study supported the feasibility and the clinical benefit of ECPR implementation for refractory OHCA patients in low volume ECMO centers. It underlined the likely importance of a highly restrictive selection among ECPR candidates. Our results confirmed the favourable predictive value of transient ROSC and highlighted the serum bicarbonate and base deficit on admission as 2 new potential relevant pre-ECPR prognostic factors requiring large-scale evaluation.

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## AUTHOR CONTRIBUTIONS

PBM, SJ, PM, and GLD were responsible for the study conception and design and for the extracorporeal cardiopulmonary resuscitation phone assistance. PBM, SJ, AB, and DL were responsible for the extraction, analysis, and interpretation of data. DL was responsible for statistical analysis. PBM drafted the original manuscript. All authors were responsible for patient care and acquisition of the data, meet ICMJE authorship criteria, reviewed and approved the final manuscript. PBM takes responsibility for the integrity of the data, the accuracy of the data analysis, and for the paper as a whole.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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