CLINICAL RESEARCH

ExtraCorporeal life support for Cardiac ARrest in patients with post cardiac arrest syndrome: The ECCAR study

Prise en charge du syndrome post arrêt cardiaque par ECMO veino-artérielle : l'étude ECCAR

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Summary
Background. — Post cardiac arrest shock (PCAS) occurring after resuscitated cardiac arrest (CA) is a main cause of early death. Extracorporeal life support (ECLS) could be useful pending recovery from myocardial failure.
Aim. — To describe our PCAS population, and the factors associated with initiation of ECLS.
Methods. — This analysis included 921 patients admitted to two intensive care units between 2005 and 2014 for CA and PCAS; 43 of these patients had ECLS initiated. Neurological and ECLS-related outcomes were gathered retrospectively.

Results. — The 43 patients treated with ECLS were predominantly (70%) young males with evidence of myocardial infarction on coronary angiography. ECLS was initiated in patients with severe cardiovascular dysfunction (median left ventricular ejection fraction 15% [interquartile range 10—25%]), a median of 9 hours [interquartile range 6—16 hours] after the CA. At 1 year, eight patients (19%) had survived without neurological disability. Blood lactate and coronary aetiology were associated with neurological outcomes. Logistic regression conducted using 878 controls with PCAS identified age > 62 years, location of CA, use of a high dose of adrenaline (> 3 mg) and blood lactate and serum creatinine concentrations (> 5 mmol/L and > 109 μmol/L, respectively) as risk factors for initiation of ECLS.
Conclusions. — ECLS, as a salvage therapy for PCAS, could be an acceptable alternative for highly-selected patients.

MOTS CLÉS
ECMO ;
syndrome post arrêt
cardiaque

Résumé
Objet. — Le choc post-arrêt cardiaque est l'une des principales causes de décès précoce après arrêt cardiaque (AC) ressuscité. Une assistance extra corporelle par ECMO veino-artérielle (ECMO VA) pourrait être utile en attendant la récupération de la fonction myocardique. L'objectif de cette étude est de décrire au sein d'une cohorte de patients survivants à un arrêt cardiaque les facteurs associés à la mise en place d'une ECMO veino-artérielle et le pronostic des patients ayant bénéficié d'une telle assistance.
Matériels et méthodes. — Cette étude a porté sur 924 patients admis dans deux unités de réanimation entre 2005 et 2014 après arrêt cardiaque récupéré, et sur 43 patients chez qui une assistance par ECMO VA a été initiée. Les données ont été recueillies de façon rétrospective.
Résultats. — Les 43 patients assistés par ECMO VA étaient principalement de patients de sexe masculin et dont la cause de l'arrêt cardiaque était une ischémie myocardique. L'ECMO VA était mise en place 9 [6-16] heures après l'AC, chez des patients avec une fraction d'éjection ventriculaire gauche de 15 [10-25] %. A un an, huit patients avaient survécu (19%) sans incapacité neurologique. Le lactate artériel et l'étiologie coronarienne étaient associés au pronostic neurologique. Une régression logistique effectuée chez 878 patients ayant présenté un choc post-arrêt cardiaque a permis d'identifier l'âge, les concentrations plasmatiques de lactate artériel et de créatinine et la localisation de l'arrêt cardiaque comme des facteurs associés avec la mise en place de l'ECMO VA.
Conclusions. — L'ECMO VA pourrait représenter une technique de sauvetage chez des patients très sélectionnés souffrant de choc post-arrêt cardiaque.

Background

Despite many improvements in the management of cardiac arrest (CA), survival rates range from 11% to 17% [1,2]. Among patients with CA who survive initial resuscitation, < 30% survive to hospital discharge [3—5]. Post cardiac arrest shock (PCAS), defined as the combination of myocardial dysfunction and vasoplegia occurring after return of spontaneous circulation (ROSC) [6], is globally responsible for one-third of deaths [4]. While persistence of myocardial dysfunction at 24 hours may be associated with early death [7], no differences in neurological outcomes have been shown between patients with and without PCAS [4,7].

Recently, two studies have described the use of extracorporeal life support (ECLS) in successfully resuscitated patients with CA experiencing severe PCAS [8,9]. Although

a survival benefit was not demonstrated, ECLS-assisted patients had an acceptable neurological prognosis. A solid understanding of the key factors that lead to the death of these patients is thus required to better select those who are most likely to benefit from this strategy.

Our objectives were to describe a cohort of patients with PCAS treated with ECLS, and to identify the factors that lead physicians to initiate ECLS after a CA.

Methods

Population and data collection

This retrospective observational study was conducted in two tertiary university centres in Paris. We included consecutive patients admitted to an intensive care unit (ICU)

for CA and PCAS (defined as the need for continuous norepinephrine or epinephrine infusion to maintain mean arterial pressure above 60 mmHg for more than 6 hours after ROSC despite adequate fluid loading [4]), and for whom an ECLS was initiated. Patients with a refractory CA or an in-hospital CA (except those that occurred in the catheterization laboratory or the emergency ward) were not included.

Data from patients treated with ECLS were collected retrospectively. A prospective database implemented in Cochin University Hospital was used to identify a control group of patients experiencing PCAS without ECLS [2].

Our local ethics committees approved the data collection and study protocol (CE SRLF N° 12-384).

Treatment protocol

Patients admitted for CA were treated according to international guidelines; similar procedures have been described elsewhere [2,10]. ECLS implantation and patient management during ECLS support, including anticoagulant treatment or weaning procedure, followed ELSO guidelines [11], and have been described previously [12].

Neurological outcome was assessed daily by ICU physicians, until death or ICU discharge. According to guidelines [13—16], neuroprognostication was performed daily using a multimodal approach, and the decision to withdraw life-sustaining therapies was taken during a collegial consultation.

Outcomes

The primary outcome was neurological evolution at 1 year, assessed by cerebral performance category (CPC) [17] (favourable outcome: CPC score I—II; poor outcome: CPC score III—V) [18].

Statistical analysis

We described factors associated with unfavourable neurological outcomes at 1 year in the population of patients with PCAS treated with ECLS. A logistic regression was performed to assess the association between the selected variables and the neurological outcome. The ECLS group was compared with the control group using the two-sided t test or the χ^2 test, as appropriate. Finally, we performed univariate and multivariable analyses, using stepwise logistic regression, to identify factors associated with ECLS implantation.

Results are expressed as medians [interquartile ranges] or numbers (percentages). R project software (The R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis.

Results

From January 2005 to December 2014, 46 patients with PCAS were treated with ECLS; three of these patients were excluded from the study because of in-hospital CA. The first of the excluded patients was admitted for septic shock consecutive to a pulmonary infection; the CA occurred 8 days after admission, and the patient died.

The second excluded patient was severely burned, with acute respiratory distress syndrome; he died 17 days after admission while on ECLS for a CA consecutive to pulmonary embolism occurring 14 days after his admission. The third excluded patient was admitted for intoxication with beta-blockers, and ECLS was initiated 5 days after admission, for extreme haemodynamic instability; he died while on ECLS.

Forty-three patients fulfilled the inclusion criteria. We also included a control population of 878 patients with PCAS. The ECLS population predominantly constituted young men, with a history of coronary events (Table 1); 60% presented a shockable initial rhythm, with no-flow of 2 (IQR 0—10) minutes and low-flow of 28 (IQR 14—42) minutes. Haemodynamic variables are described in Table 2.

Nine patients (21%) survived to ICU discharge: myocardial recovery was observed in seven patients (78%); one patient benefited from a heart transplantation; and one patient died at 1 year from end-stage cancer. A favourable neurological outcome at 1 year was observed for eight (19%) of the ECLS cohort (89% of survivors).

The death rate (79%) during the stay in the ICU was mainly related to multiple organ failure (63%); 45% of deaths by multiple organ failure occurred in the first 3 days after ICU admission (Fig. 1). ECLS inefficacy, defined as the inability to maintain cardiac output and arterial pressure despite maximal therapeutic investment, was observed in 11 (31%) of the patients who died. Life-sustaining therapy was withdrawn for nine of these patients (26%) and cerebral brain death was pronounced for two (6%).

No statistical differences were found between centres, except for percentage of bystander cardiopulmonary resuscitation (CPR) (56% vs. 85%, $P = 0.039$, respectively, in Cochin and Lariboisière hospitals) and low-flow duration (14 [IQR 10 − 32] vs. 30 [IQR 22 − 44] min, $P = 0.032$, respectively, in Cochin and Lariboisière hospitals).

ECLS-treated patients who survived without severe neurological disability were younger than those with severe neurological impairment (Table 1). CPR characteristics and severity scores did not differ between favourable and poor neurological outcome groups, despite the out-of-hospital CA score showing a trend towards higher values in the poor neurological outcome group. By contrast, blood lactate concentration at ECLS implantation discriminated the two groups (Table 2 and Fig. A.1). Coronary aetiology of CA was associated with unfavourable outcome at 1 year, whereas arrhythmia was associated with a better prognosis (Table 1).

ECLS-treated patients were younger, with a longer time to ROSC and higher proportions of non-public location of CA and bystander CPR compared with the control group (Table 3). ECLS-treated patients had higher blood lactate and serum creatinine concentrations than the control group.

In the multivariable analysis (Fig. 2), factors independently associated with ECLS implantation were as follows: age < 62 years; serum creatinine > 109 μmol/L; administration of adrenaline < 2 mg; and public location of CA.

When considering the whole PCAS population, patients who had died at ICU discharge were older and had

Table 1 General characteristics of patients treated with extracorporeal life support, according to neurological outcome.

	All (n = 43)	Favourable neurological outcome (n = 8)	Poor neurological outcome (n = 35)	P
Age (years)	54 [46–59]	43 [35–54]	55 [49–61]	0.029
Men	32 (74)	5 (62)	27 (77)	0.41
Body mass index (kg/m^2)	26 [25–28]	27 [25–31]	26 [25–28]	0.74
Previous medical diseases				
Coronary artery disease	9 (21)	1 (12)	8 (23)	0.54
Diabetes mellitus	7 (16)	0 (0)	7 (20)	0.18
Hypertension	15 (35)	1 (12)	14 (40)	0.15
Dyslipidaemia	6 (14)	1 (12)	5 (14)	0.92
Active smoker	4 (9)	0 (0)	4 (11)	0.34
Severity scores on admission				
IGS II score	73 [67–81]	70 [66–79]	73 [68–82]	0.47
SOFA score	12 [11–15]	12 [10–12]	13 [12–15]	0.23
SOFA cardiovascular	4 [4]	4 [4]	4 [4]	-
Out-of-hospital CA score	39 [31–51]	32 [26–36]	42 [33–52]	0.078
Biological data on admission				
pH	7.19 [7.05–7.26]	7.15 [7.11–7.23]	7.19 [6.97–7.26]	0.52
Troponin (μmol/L)	5.5 [1.32–63.2]	7.2 [1.86–20.98]	4 [1.35–63.7]	0.98
Blood lactate (mmol/L)	10 [6–13]	6 [4–8]	11 [7–14]	0.029
Serum creatinine (μmol/L)	148 [138–188]	150 [134–164]	148 [138–198]	0.71
Serum potassium (mmol/L)	3.7 [3.2–4.2]	3.3 [2.9–4]	3.8 [3.4–4.4]	0.15
CA characteristics				
No-flow (minutes)	2 [0–10]	1 [0–9]	3 [0–10]	0.73
Low-flow (minutes)	28 [14–42]	25 [11–30]	28 [18–48]	0.28
Adrenaline bolus (mg)	3 [1–9]	1 [0–3]	4 [1–9]	0.17
Non-public location	16 (37)	2 (25)	14 (40)	0.45
Bystander CPR	32 (74)	5 (62)	27 (77)	0.41
Shockable initial rhythm	26 (60)	4 (50)	22 (63)	0.52
Coronary angiogram	38 (88)	7 (88)	31 (89)	0.37
Coronary angioplasty	15 (35)	2 (25)	13 (37)	0.41
Hypothermia	33 (77)	6 (75)	27 (77)	0.21
CA diagnoses				
Atrioventricular block	3 (7)	1 (12)	2 (6)	0.50
Coma	1 (2)	0 (0)	1 (3)	0.69
Hyperkalaemia	2 (5)	0 (0)	2 (6)	0.53
Asphyxia	3 (7)	1 (12)	2 (6)	0.50
ACS	26 (60)	2 (25)	24 (69)	0.009
Tamponade	1 (2)	0 (0)	1 (3)	0.69
Arrhythmia	6 (14)	3 (38)	3 (9)	0.03
Drowning	1 (2)	0 (0)	1 (3)	0.69
Assistance				
Impella® device[a]	7 (16)	1 (12)	6 (17)	0.77
IACPB	8 (19)	3 (38)	5 (14)	0.14

Data are expressed as median [interquartile range] or number (%). ACS: acute coronary syndrome; CA: cardiac arrest; CPR: cardiopulmonary resuscitation; IACPB: intra-aortic counter-pulsation balloon; IGS: simplified Index of Gravity; SOFA: sequential organ failure assessment.

[a] Abiomed Inc., Danvers, MA, USA.

higher blood lactate and serum creatinine concentrations (Table 4). Time to ROSC was longer when comparing non-survivors with survivors. The aetiology for CA in survivors was predominantly cardiac, with higher rates of coronary angioplasty. The proportions of ECLS-treated patients were not different in survivors versus non-survivors.

Discussion

The present retrospective study aimed to report the 10-year experience of two Parisian ICUs in the use of ECLS for patients with PCAS. Although the death rate was high, the survivors from the ECLS-treated PCAS population had no or minor neurological disabilities. Furthermore, the death rate

Table 2 Haemodynamic variables and complications in patients treated with extracorporeal life support, according to neurological outcome.

	All (n = 43)	Favourable neurological outcome (n = 8)	Poor neurological outcome (n = 35)	P
ECLS implantation data				
CA to ECLS delay (hours)	9 [6—16]	8 [7—18]	10 [6—15]	0.97
Haemodynamic				
MAP (mmHg)	58 [44—72]	60 [55—74]	57 [42—68]	0.55
Cardiac index (L/min/m^2)	1.37 [0.9—1.81]	1.73 [1.08—2.05]	1.36 [0.94—1.39]	0.79
Cardiac power (W)	0.27 [0.14—0.44]	0.38 [0.25—0.49]	0.18 [0.14—0.35]	1
LVEF (%)	15 [10—25]	15 [12—21]	20 [10—25]	0.60
Inotropic equivalent	220 [137—410]	160 [118—193]	230 [140—410]	0.25
ECLS efficacy				
ECLS withdrawal	8 (19)	7 (88)	1 (3)	< 0.001
Inefficacy	11 (26)	0 (0)	11 (31)	0.09
CPC score ≤ 2 at day 90	8 (19)	7 (88)	1 (3)	< 0.001
Death at 1 year	35 (81)	0 (0)	35 (100)	< 0.001
Potentially ECLS-related complications				
All complications	36 (84)	6 (75)	30 (86)	0.55
Total per patient (n = 71)	2 [1—3]	1 [1,2]	2 [1,2]	0.74
Haemorrhage	10 (23)	0 (0)	10 (29)	-
Lower limb ischaemia	12 (28)	3 (38)	9 (26)	-
Coagulopathy	12 (28)	0 (0)	12 (34)	-
Haemolysis	1 (0)	0 (0)	1 (3)	-
ARDS	1 (0)	0 (0)	1 (3)	-
Femoral site infection	2 (0)	2 (25)	0 (0)	-
Renal replacement therapy	21 (50)	5 (63)	16 (46)	-
VAP	4 (1)	0 (0)	4 (11)	-
Gastrointestinal bleeding	1 (0)	0 (0)	1 (3)	-
Mesenteric ischaemia	7 (16)	1 (13)	6 (17)	-

Data are expressed as median [interquartile range] or number (%). ARDS: acute respiratory distress syndrome; CA: cardiac arrest; CPC: cerebral performance category; ECLS: extracorporeal life support; LVEF: left ventricular ejection fraction; MAP: mean arterial pressure; VAP: ventilator-associated pneumonia.

in the ECLS-treated population was similar to the death rate in the PCAS population, although severity was higher in the ECLS-treated population. This last observation might raise a question about the potential benefit of ECLS in such a severe population; it also highlights the need for better identification of patients who could benefit from such investment. Therefore, we have identified blood lactate concentration at ECLS implantation and reversible cause of out-of-hospital CA as potential factors associated with better outcomes.

In the survivors in the ECLS-treated PCAS population, the potential for recovery of neurological function was high (89% of surviving patients were without severe neurological impairment). These data are consistent with previously published data [4,7], although ECLS was not used in those studies. Faster time to implantation could be a particular endpoint to achieve, as suggested by data available in the setting of refractory cardiogenic shock [19]. Well-designed studies are lacking to support this hypothesis in the setting of PCAS.

Selecting patients who are most likely to benefit from ECLS could improve functional outcomes. Whereas we observed that mortality was not significantly different in the ECLS-treated population compared with the control group, blood lactate concentration and aetiology of CA
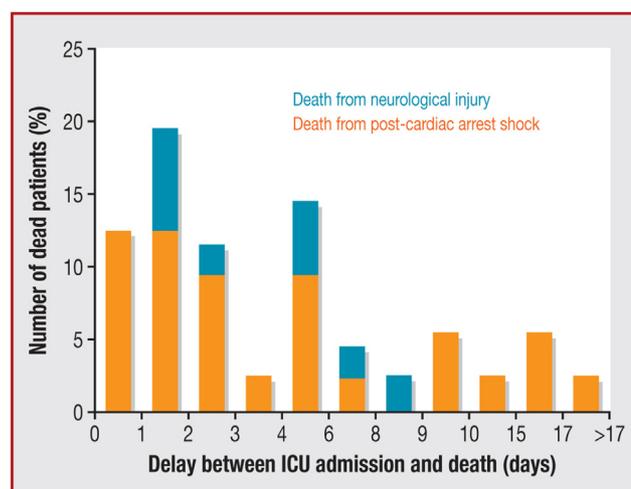
Figure 1. Mode and timing of death during intensive care unit (ICU) stay in patients treated with extracorporeal life support.

were associated with neurological outcome. Initiating ECLS in patients with a low blood lactate concentration and PCAS consecutive to reversible cause could improve survival rates. Although Bougouin et al. [8] showed no association between

Table 3   Comparison between patients treated and not treated with extracorporeal life support.

	Overall (n = 921)	ECLS group (n = 43)	Control group[a] (n = 878)	P
Age (years)	62 [52—74]	54 [46—59]	63 [52—74]	< 0.001
Male sex	633 (69)	32 (74)	601 (68)	0.50
Body mass index (kg/m^2)	25 [23—28]	26 [25—28]	25 [23—28]	0.19
Previous medical history				
Coronary artery disease	205 (24)	9 (21)	196 (25)	0.72
Diabetes mellitus	184 (22)	7 (16)	177 (23)	0.45
Arterial hypertension	374 (45)	15 (35)	359 (46)	0.21
Dyslipidaemia	210 (26)	6 (14)	204 (26)	0.08
Active smoker	295 (40)	4 (9)	291 (42)	< 0.001
Biological data on admission				
Blood lactate (mmol/L)	5 [3—10]	10 [6—13]	5 [3—10]	0.002
Serum creatinine (μmol/L)	109 [84—146]	148 [138—188]	108 [83—144]	< 0.001
Potassium (mmol/L)	3.9 [3.3—4.5]	3.7 [3.2—4.2]	3.9 [3.3—4.5]	0.66
CA characteristics				
No-flow (minutes)	3 [0—8]	2 [0—10]	3 [0—8]	0.33
Low-flow (minutes)	16 [10—25]	28 [14—42]	16 [10—25]	0.001
Adrenaline bolus (mg)	2 [0—5]	3 [1—9]	2 [0—5]	0.41
Non-public location	617 (67)	16 (37)	601 (69)	< 0.001
Bystander CPR	482 (52)	32 (74)	450 (51)	0.007
Shockable initial rhythm	439 (48)	26 (60)	413 (47)	0.09
Coronary angiogram	622 (68)	38 (90)	584 (67)	0.001
Coronary angioplasty	238 (27)	15 (35)	223 (25)	0.14
Hypothermia	755 (80)	33 (77)	722 (82)	0.83

Data are expressed as median [interquartile range] or number (%). CA: cardiac arrest; CPR: cardiopulmonary resuscitation; ECLS: extracorporeal life support.
[a] Patients not treated with ECLS.
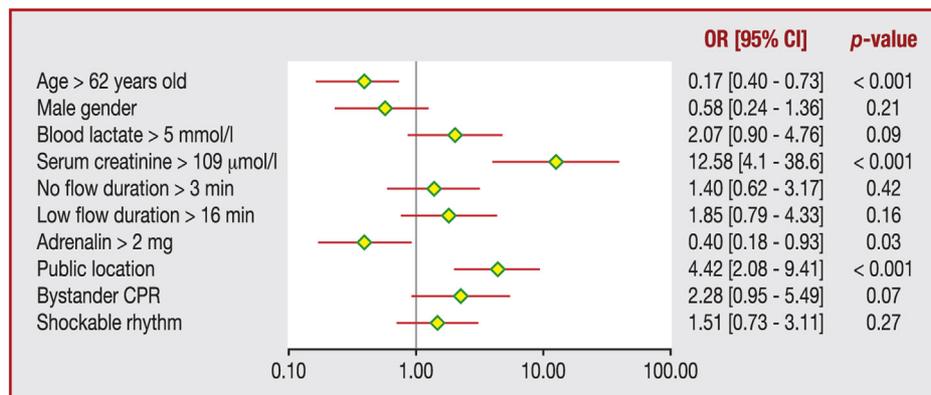
Figure 2.   Multivariable analysis of factors associated with initiation of extracorporeal life support in patients with post cardiac arrest shock. Conf.: confidence; CRP: cardiopulmonary resuscitation; OR: odds ratio.

ECLS implantation and survival, our study suggests that the coronary aetiology could be a potential confounding factor. Reversible causes of myocardial dysfunction could therefore have a better prognosis in terms of myocardial recovery [20]. By contrast, in the case of constituted myocardial infarct, the potential for recovery could be altered [21—23]. In fact, the mortality rate in patients treated with ECLS for PCAS secondary to acute coronary syndrome was higher than the mortality rate in patients treated with ECLS for reversible causes. Although the mortality rates in our study were high, they were similar to those reported in the two studies published previously (72% [9] and 73% [8]).

Complications occurred frequently, but were close to those reported in a meta-analysis of 20 studies evaluating ECLS usage [24]. The most frequent complication in our study was acute kidney injury requiring renal replacement therapy (50%), which is probably more a marker of the severity of the shock rather than a specific complication of ECLS. By comparison, the high rates of specific ECLS-related complications observed in our cohort, such as the rate of lower limb ischaemia (28% versus 17% in the study by Cheng et al. [24]), could have worsened the prognosis of some patients. However, ECLS implantation was performed by physicians trained

Table 4 Factors associated with survival at discharge from the intensive care unit in all patients with post cardiac arrest shock ($n = 921$).

	Survivors ($n = 237$)	Those who died ($n = 684$)	P
Age (years)	61 [49—71]	63 [53—75]	0.01
Male sex	165 (70)	468 (68)	0.73
Body mass index (kg/m^2)	26 [22—28]	25 [23—30]	0.22
Previous medical diseases			
Coronary artery disease	13 (6)	27 (4)	0.35
Diabetes mellitus	28 (13)	156 (26)	< 0.001
Hypertension	91 (41)	283 (47)	0.18
Dyslipidaemia	66 (30)	144 (24)	0.11
Active smoker	84 (40)	211 (40)	0.91
Biological data on admission			
Blood lactate (mmol/L)	3 [2—5]	9 [5—13]	< 0.001
Serum creatinine (μmol/L)	98 [76—124]	129 [97—169]	< 0.001
Serum potassium (mmol/L)	3.6 [3.1—4.2]	4 [3.4—4.8]	< 0.001
CA characteristics			
No-flow (minutes)	2 [0—5]	5 [0—10]	< 0.001
Low-flow (minutes)	13 [7—20]	20 [13—30]	< 0.001
Adrenaline (mg)	0 [0—3]	3 [2—6]	< 0.001
Non-public location	110 (47)	188 (28)	< 0.001
Bystander CPR	140 (61)	342 (51)	0.008
Shockable initial rhythm	163 (69)	276 (40)	< 0.001
Coronary angiogram	187 (79)	435 (64)	< 0.001
Coronary angioplasty	85 (39)	153 (24)	< 0.001
Hypothermia	216 (92)	539 (79)	< 0.001
Assistance			
ECLS	9 (4)	34 (5)	0.59

Data are expressed as median [interquartile range] or number (%). CA: cardiac arrest; CPR: cardiopulmonary resuscitation; ECLS: extracorporeal life support.

in percutaneous cannulation, with good results published previously [12].

Study limitations

The retrospective study design limited the strength of the findings. We focused on a specific subpopulation of patients with PCAS, and we retrieved data on 10 years' experience in two tertiary care centres. No randomized study could have been achievable in a reasonable time frame. A matched analysis designed to identify the variables associated with survival would have been useful, but the low sample size of the ECLS cohort and the particular severity of these patients prevented us from conducting such an analysis. Moreover, we were unable to collect information about severity at admission in the control population.

We limited inclusion to patients admitted for out-of-hospital CA on purpose, although the outcomes of the three excluded patients could have influenced the overall results of this study. Out-of-hospital CA is a sudden and life-threatening pathology, and delay in initiation of treatment is a key aspect of the prognosis. In-hospital CA is a more heterogeneous entity, where pre-existing life-threatening pathology leads to CA. The prognosis of the CA should be the combination of the pre-existing condition and the CA itself. It would have been difficult to draw conclusions about the ECLS intervention because of this heterogeneity.

Conclusions

Despite a high rate of death in the ECLS-treated population, the neurological outcomes of the survivors suggest a potential beneficial effect of ECLS on neurological recovery, and justify its implantation in an extremely severe population, as a salvage therapy. Reversible aetiologies of CA were associated with better outcomes, emphasizing the need for selection of patients who could benefit from such a therapy. Considering this assistance only for patients in whom myocardial depression has the potential to recover could be an interesting option to improve outcomes. Then, considering ECLS for a carefully selected population of patients with PCAS could be a promising strategy.

Authors' contributions

Adrien Bouglé and Arthur Le Gall contributed equally to this work.

Funding statement

Acknowledgments

Disclosure of interest

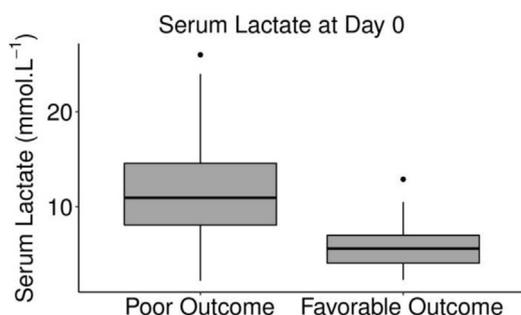The authors declare that they have no competing interest.

Appendix A. Appendix A

We would like to thank the ICUs in Lariboisière and Cochin University Hospitals for helping us to gather data.

Figure 2. Figure A.1. Serum lactate concentrations according to neurological outcomes.

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