Doi: 10.5152/TJAR.2019.73558

Original Article

Intensive Care

Turkish Journal of Anaesthesiology & Reanimation

Effect of Mean Blood Pressure During Extracorporeal Life Support on Outcome After Out-of-Hospital Cardiac Arrest

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Cite this article as: Jouffroy R, Guyard A, Philippe P, Carli P, Vivien B. Effect of Mean Blood Pressure During Extracorporeal Life Support on Outcome After Out-of-Hospital Cardiac Arrest. Turk J Anaesthesiol Reanim 2019; 47(2): 134-41.

Abstract

Objective: Extracorporeal Life Support (ECLS) can help to improve the outcome of refractory cardiac arrest (CA). ECLS allows to maintain blood pressure and tissue perfusion until the cause of CA is treated. The aim of the present study was to describe the mean blood pressure (MBP) during the first 24 h of ECLS for out-of-hospital CA (OHCA).

Methods: We performed a retrospective analysis of consecutive refractory OHCA requiring ECLS admitted to the intensive care unit. MBP was examined after starting ECLS (H0) and every 6 h during the first 24 h (H6, H12, H18 and H24).

Results: Forty patients were analysed. MBP significantly differs between survivors and non-survivors since 6 h: 77 vs 44 mm Hg (p=0.002), 51 vs 87 mm Hg at H12 (p=0.008), 57 vs 75 mm Hg at H18 (p=0.015) and 79 vs 53 mm Hg at H24 (p=0.004), whereas no difference was observed at H0: 69 vs 55 mm Hg (p=0.06). An MBP lower than 65 mm Hg since 6 h is associated with a poor outcome (sensitivity and specificity of death of 87% and 66% at H6, 80% and 75% at H12, 100% and 75% at H18 and 70% and 80% at H24, respectively).

Conclusion: Despite high levels of catecholamine, the inability to maintain MBP higher than 60 mm Hg after starting ECLS for OHCA is associated with a poor outcome.

Keywords: Extracorporeal life support, mean blood pressure, outcome, out-of-hospital cardiac arrest

Introduction

Cardiopulmonary resuscitation (CPR) was initially described in 1960 (1) and has been under continuous development ever since up to the guidelines for Advanced Life Support (ALS) published by the national and international societies, American Heart Association (AHA) and European Resuscitation Council (2). Nevertheless, survival rates are still low varying from 8.2% to 22% for in-hospital patients and from 6% to 11% among critically ill patients (3-6). For patients benefiting from ALS longer than 10-15 min without return of systemic circulation, a rapid decline in the chances of survival over time has been described (7-9).

Extracorporeal Life Support (ECLS), for extracorporeal cardiopulmonary resuscitation (eCPR), aims to replace the mechanical effects of cardiac pump, i.e. allowing blood circulation under pressure (10). Recent technological developments (miniaturised extracorporeal devices, heparin-coated circuits and percutaneous cannulation techniques (11-13)) allowed the use of ECLS in the pre-hospital setting (14) and an improvement of the prognosis of in-hospital cardiac arrest (IHCA) (15) and out-of-hospital CA (OHCA) (16-18). Thus, in the 2015 guidelines for CA management, the AHA suggests to consider eCPR for IHCA and OHCA with a brief no-flow and a reversible underlying condition (e.g. hypothermia or drug intoxication) (19).

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Received: 30.06.2018 Accepted: 06.09.2018
Available Online Date: 14.02.2019

The aim of the present study was to describe the effect of mean blood pressure (MBP) during the first 24 h of ECLS for OHCA.

Methods

Consecutive patients admitted for refractory OHCA to the intensive care unit (ICU) from January 2011 to April 2013 were included in the study and retrospectively analysed.

The indication criteria for ECLS were: non-traumatic CA, no-flow duration <5 min, 18<age<75 years, CA with witness, end-tidal carbon dioxide of at least 10 mm Hg and ALS started in the pre-hospital setting.

According to the French legislation, the ethical committee (Comité pour la Protection des Personnes Est 3, Nancy, France) considered that consent of patients was waived for participation in this retrospective observational study (no. 17.12.05).

Therapeutic management of patients

All patients received medical care by the same team of critical care physicians. Protocols for management did not change over the study period, ensuring no major discrepancies between patients with regard to organ supports and therapies.

Haemodynamic support was achieved by ECLS (Cardiohelp System®; Maquet, Germany), set up via venous-arterial femoral cannulation by two experienced physicians at ICU admission (H0).

Fluid replacement (fluid administration 30 mL kg^{-1} day^{-1} chloride saline) and catecholamine (dobutamine 5 µg kg^{-1} min^{-1} and norepinephrine) were adjusted to obtain an MBP between 50 and 60 mm Hg and to prevent pulmonary oedema. Invasive MBP was continuously after radial artery catheterisation.

Sedation was started as soon as possible. All patients were sedated using midazolam 0.1 mg kg^{-1} h^{-1} and sufentanil 0.2 μg^{-1} kg^{-1} h^{-1} and paralysed with atracurium 0.1 mg kg^{-1} h^{-1} (dose adjusted to obtain a neuromuscular response ≤2 at the 'trend of four' monitoring). Sedation status was monitored using bispectral index (BIS monitor®; Covidien, Republic of Ireland). Ventilation was adjusted to obtain a $PaCO_2$ of 40 mm Hg and a PaO_2 between 100 and 200 mm Hg. Minimum lung ventilation was maintained to avoid pulmonary collapse with a tidal volume of 5 mL kg^{-1}, a respiratory rate of 8 min^{-1} and positive end-expiratory pressure (PEEP) of 5 cm H_2O.

During the first 24 h following ICU admission, mild therapeutic hypothermia was performed. Core body temperature was maintained between 32°C and 34°C using external cooling (ice packs placed on femoral and humeral vessels) and the heat exchanger device of ECLS.

Blood transfusion was performed to obtain a target of haemoglobin 10 g dL^{-1}, platelets 100,000 mm^{-3}, fibrinogen >1.5 g L^{-1} and prothrombin time >50%.

To prevent coagulation of the ECLS membrane oxygenator, unfractionated heparin was intravenously administered at a low dose during ECLS, with repeated controls to maintain the activated clotting time ratio >2.0. Continuous veno-venous haemodiafiltration was initiated during the first 6 h upon ICU admission.

Data collection and analysis

The primary endpoint was in-hospital mortality, defined as death occurring within 28 days after ICU admission. No-flow duration corresponds to the time-lapse from collapse to the initiation of CPR, and low-flow duration corresponds to the time duration from the initiation of CPR to the start of ECLS/eCPR.

Data are expressed as mean±standard deviation or median (interquartile range, 25 to 75) for non-Gaussian variables.

Comparison of two means was performed using the unpaired Student's t-test, comparison of two medians was performed using the Mann-Whitney U test and comparison of proportions was performed using the Fisher's exact test.

The evaluation of the predictive accuracy of MBP on mortality at day 28 was performed by a receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was determined. The optimal cut-off value of MBP was assessed using Youden approach at each of the following time: 6 h=H6, 12 h=H12, 18 h=H18 and 24 h=H24. The optimal cut-off value was then used to stratify patients into the high- and low-risk groups of death occurrence to determine sensitivity and specificity at each time period. Data analysis was performed using STATEL software© (Ad Science, Paris, France).

Results

A total of 40 patients were enrolled in the study, with 29 males (73%). The mean age of the patients was 52±7 years. The mean index gravity score II score was 88±12 (62-110). No-flow duration was 0 (0-2) min in survivors and 4 (0-6) min in non-survivors (p>0.05). Low-flow duration was 100 (95-103) min in survivors and 120 (108-131) min in non-survivors (p>0.05).

Patients' demographic and clinical characteristics are summarised in Table 1.

The main cause of CA was acute coronary syndrome (ACS) in 23 (58%) patients. All CA related to ACS were documented by a coronary angiogram performed and positive in 15 (65%) patients or by ST-segment changes (ST-segment

Table 1. Patients' demographic and clinical characteristics in the overall population

Age (years)	52±7
Sex ratio (M:F)	29:11
Median length of stay in ICU (days)	6 (1-49)
Mortality at day 1, n (%)	24 (60)
IGS II	88±12
Mortality at day 28, n (%)	29 (73)

Data are expressed as mean±standard deviation for quantitative variable and as absolute numbers with percentage for qualitative data. ICU: intensive care unit; IGS: index gravity score; M: male; F: female

Table 2. Cardiac arrest aetiologies

	Mortality	
	n	**%**
Acute coronary syndrome	23	58
Drowning	1	3
Drug intoxication	3	7
Sepsis	1	3
Not determined	12	29

Data are expressed as absolute numbers with percentage

Table 3. Biological data at H0, H6, H12, H18 and H24 in survivors and non-survivors

	H0			H6		
	Survivors	**Non-survivors**	**p**	**Survivors**	**Non-survivors**	**p**
pH	7.17 (7.10-7.26)	7.11 (6.97-7.18)	0.051	7.31 (7.21-7.40)	7.25 (7.18-7.34)	0.16
$PaCO_2$ (mm Hg)	34 (32-44)	43 (34-59)	0.054	37 (31-46)	36 (29-41)	0.55
PaO_2 (mm Hg)	99 (96-174)	121 (65-261)	0.27	112 (77-186)	172 (98-226)	0.37
HCO_{3-} (mmol L^{-1})	13.3 (11.6-18.4)	14.4 (10.2-15.6)	0.96	17.4 (16.1-19.4)	13.9 (9.7-20.0)	0.051
BE (mmol L^{-1})	-13.8 (-15.4 --7.7)	-15.3 (-18.3 --11.9)	0.61	-7.9 (-9.3 --6.1)	-12.6 (-17.1 --5.9)	0.012*
SaO_2 (%)	93.8 (91.5-96.1)	94.3 (86.4-96.3)	0.17	95.6 (92.8-96.8)	95.6 (94.2-96.9)	0.76
Na (mmol L^{-1})	142 (135-147)	144 (141-147)	0.36	144 (142-145)	148 (142-152)	0.19
K (mmol L^{-1})	3.5 (3.1-3.7)	4.7 (4.2-6.7)	0.002*	3.1 (2.9-4.0)	3.8 (3.6-4.6)	0.13
Cl (mmol L^{-1})	107 (96-110)	104 (99-108)	0.24*	113 (107-115)	109 (106-111)	0.11
Glucose (mmol L^{-1})	18.9 (8.3-28.2)	14.8 (9.8-19.5)	0.92	8.7 (5.5-10.7)	7.9 (4.1-10.1)	0.5
Lactates (mmol L^{-1})	14 (10-19)	15 (11-20)	0.16	9 (6-11)	14 (7-20)	0.007*
Troponin (ng L^{-1})	0.4 (0.1-3.2)	1.5 (0.4-12.3)	0.15	2.1 (0.6-52.1)	21.4 (3.8-108.9)	0.12
Haemoglobin (g dL^{-1})	12.9 (11.1-13.4)	12.3 (10.6-13.3)	0.44	10.1 (9.7-12.0)	9.9 (8.3-11.5)	0.42
TP (%)	64 (63-74)	54 (41-68)	0.06	62 (55-65)	48 (24-52)	0.0005*
TCA ratio	1.4 (1.3-2.0)	1.7 (1.3-3.1)	0.47	1.7 (1.5-1.8)	2.1 (1.9-3.2)	0.47
Fibrinogen (g L^{-1})	1.8 (1.6-2.3)	0.9 (0.3-1.5)	0.02*	1.7 (1.5-2.3)	1.2 (0.3-1.6)	0.009*
	H12			**H18**		
	Survivors	**Non-survivors**	**p**	**Survivors**	**Non-survivors**	**p**
pH	7.36 (7.33-7.42)	7.33 (7.27-7.37)	0.2	7.44 (7.39-7.46)	7.35 (7.33-7.41)	0.3
$PaCO_2$ (mm Hg)	35 (28-40)	36 (29-39)	0.9	32 (28-38)	38 (35-41)	0.09
PaO_2 (mm Hg)	124 (108-192)	134 (122-214)	0.6	133 (100-174)	153 (69-176)	0.84
HCO_{3-} (mmol L^{-1})	18.2 (16.8-21.4)	20.6 (19.9-22.0)	0.3	20.8 (19.9-22.2)	19 (16.6-22.1)	0.34
BE (mmol L^{-1})	-5.9 (-7.5 to -3.6)	-9.5 (-11.5 to -2.8)	0.2	-3.5 (-4.1 to -2.3)	-6.6 (-9.2 to -1.9)	0.21
SaO_2 (%)	96.6 (95.8-97.1)	96.2 (95.7-96.9)	0.7	96.5 (95.6-96.9)	95.7 (92.5-96.5)	0.17
Na (mmol L^{-1})	145 (140-147)	145 (144-148)	0.7	141 (139-144)	144 (142-147)	0.09
K (mmol L^{-1})	3.4 (3.2-4.6)	3.3 (2.8-3.4)	0.4	4.2 (3.7-4.7)	4.1 (3.1-4.5)	0.47
Cl (mmol L^{-1})	111 (110-112)	109 (108-110)	0.2	109 (108-111)	111 (110-113)	0.12
Glucose (mmol L^{-1})	6.9 (5.1-5.7)	6.8 (6.8-8.0)	0.6	5.9 (5.5-7.4)	4.7 (3.2-6.0)	0.052
Lactates (mmol L^{-1})	8 (5-9)	8 (4-11)	0.5	5 (3-5)	6 (4-10)	0.38
Troponin (ng L^{-1})	25.1 (1.9-131.7)	272.5 (259.6-340.4)	0.1	148.7 (31.2-179.9)	380.1 (227.2-451.5)	0.01*
Haemoglobin (g dL^{-1})	9.9 (9.0-10.5)	10.3 (9.4-10.9)	0.8	10.1 (9.2-10.7)	9.3 (7.5-10.1)	0.09
TP (%)	68 (55-72)	62 (49-70)	0.06	70 (65-79)	56 (39-70)	0.07
TCA ratio	1.5 (1.4-1.6)	1.4 (1.3-1.5)	0.2	1.4 (1.3-1.6)	1.9 (1.5-2.6)	0.5
Fibrinogen (g L^{-1})	1.9 (1.5-2.2)	1.4 (1.3-1.9)	0.2	2.1 (1.9-2.5)	1.7 (1.4-2.1)	0.2

Table 3. Biological data at H0, H6, H12, H18 and H24 in survivors and non-survivors (continued)

	H24			
	Survivors	**Non-survivors**	**p**	
pH	7.41 (7.37-7.47)	7.37 (7.25-7.41)	0.3	
$PaCO_2$ (mm Hg)	36 (31-38)	36 (34-39)	0.3	
PaO_2 (mm Hg)	118 (94-140)	152 (83-207)	0.9	
HCO_{3-} (mmol L^{-1})	21.6 (21.2-23.1)	19.0 (15.3-22.2)	0.3	
BE (mmol L^{-1})	-2.7 (-4.2 to -0.5)	-5.3 (-10.2 to -1.8)	0.3	
SaO_2 (%)	96.1 (95.0-96.3)	95.6 (94.4-96.4)	0.7	
Na (mmol L^{-1})	140 (139-142)	144 (141-145)	0.1	
K (mmol L^{-1})	4.0 (3.4-4.9)	4.8 (4.0-5.4)	0.1	
Cl (mmol L^{-1})	109 (108-110)	111 (111-115)	0.02*	
Glucose (mmol L^{-1})	6.4 (4.8-7.6)	5.3 (3.7-5.5)	0.3	
Lactates (mmol L^{-1})	3 (2-5)	5 (2-11)	0.3	
Troponin (ng L^{-1})	41.6 (1.8-89.4)	344.1 (123.8-581.3)	0.1	
Haemoglobin (g dL^{-1})	9.9 (9.3-11.5)	9.6 (8.8-11.3)	0.6	
TP (%)	70 (61-79)	52 (45-65)	0.1	
TCA ratio	1.6 (1.4-2.3)	1.50 (1.49-1.99)	0.9	
Fibrinogen (g L^{-1})	2.3 (1.7-2.9)	1.9 (1.6-2.2)	0.1	

*corresponds to a difference between survivors and non-survivors. Data are expressed as median (min-max). BE: base excess; SaO2: arterial oxygen saturation; TP: prothrombin time; TCA: acclotine cephalin time

Table 4. Evolution of mean blood pressure (MBP) (mm Hg), ECLS pump flow (L min^{-1}) and doses of catecholamine in survivors and non-survivors at H0, H6, H12, H18 and H24

	H0			H6			H12		
	Survivors	**Non-survivors**	**p**	**Survivors**	**Non-survivors**	**p**	**Survivors**	**Non-survivors**	**p**
MBP (mm Hg)	69	55	0.06	77	44	0.002*	87	51	
	58-74	48-66		65-94	31-58		74-95	66-83	0.008*
NE (mg h^{-1})	3.00	5.00	0.2	1.50	8.00	0.0002*	0.50	3.09	
	1.60-5.50	3.00-7.00		1.00-3.50	5.75-10.00		0.98-2.60	2.46-3.87	0.0014*
Dobu (µg kg^{-1} min^{-1})	5	5	0.5	5	10	0.55	5	8	
	5-10	5-10		5-10	10-10		5-9	5-11	0.09
Pump flow (L min^{-1})	2.87	3.14	0.15	2.87	2.61	0.79	2.51	3.09	
	2.77-3.00	2.82-3.44		2.18-3.32	2.14-3.62		2.14-3.62	2.46-3.87	0.62
	H18			**H24**					
	Survivors	**Non-survivors**	**p**	**Survivors**	**Non-survivors**	**p**			
MBP (mm Hg)	75	57	0.015*	79	53				
	71-89	47-74		63-91	44-61	0.004*			
NE (mg h^{-1})	0.60	6.06	0.007*	0.55	7.50				
	0.00-2.13	4.00-8.00		0.00-1.88	4.00-15.00	0.007*			
Dobu (µg kg^{-1} min^{-1})	5	10	0.03	5	10				
	5-8	8-10		5-9	8-10	0.02			
Pump flow (L min^{-1})	3.10	3.36	0.43	2.76	3.22				
	2.73-3.54	2.35-4.18		2.17-3.51	2.56-3.83	0.75			

Data are expressed as median with a range (interquartile). NE: norepinephrine; Dobu: dobutamine

elevation AMI) on the electrocardiogram after return of sinus rhythm in 8 (35%) patients. Aetiologies of CA are listed in Table 2.

Table 5. Predictive values of mean blood pressure threshold at H0, H6, H12, H18 and H24 after starting Extracorporeal Life Support (ECLS)

H6				
	Sensitivity	**Specificity**	**PPV**	**NPV**
MBP <65 mm Hg	87%	66%	83%	73%
H12				
	Sensitivity	**Specificity**	**PPV**	**NPV**
MBP <72 mm Hg	80%	75%	73%	82%
H18				
	Sensitivity	**Specificity**	**PPV**	**NPV**
MBP <71 mm Hg	100%	75%	67%	100%
H24				
	Sensitivity	**Specificity**	**PPV**	**NPV**
MBP <66 mm Hg	70%	88%	88%	60%

PPV: positive predictive value; NPV: negative predictive value

Within the first 24 h, 24 (60%) patients died. The median length of stay in ICU was 6 (1-49) days, and the overall 28-day mortality rate was 73%.

Among the 11 survivors, 9 evolved to a cerebral performance score (CPC) score of 1, and 2 a CPC score of 4 at day 28.

Biological data for overall population are presented in Table 3.

Table 6. Calculated SVR (dyn s^{-1} cm^{-5}) in survivors and non-survivors at H0, H6, H12, H18 and H24

	Calculated SVR (dyn s^{-1} cm^{-5})		
	Survivors	**Non-survivors**	**p**
H0	2384 (1756-2438)	1624 (1349-2011)	0.07
H6	2547 (2202-3644)	1734 (1076-2256)	0.06*
H12	3214 (2006-3661)	1820 (1417-2220)	0.03*
H18	2311 (2057-28,310)	1581 (1371-2269)	0.03*
H24	2420 (1818-4099)	1642 (1294-1764)	0.02*

Data are expressed as median with a range and interquartile. SVR: systemic vascular resistance

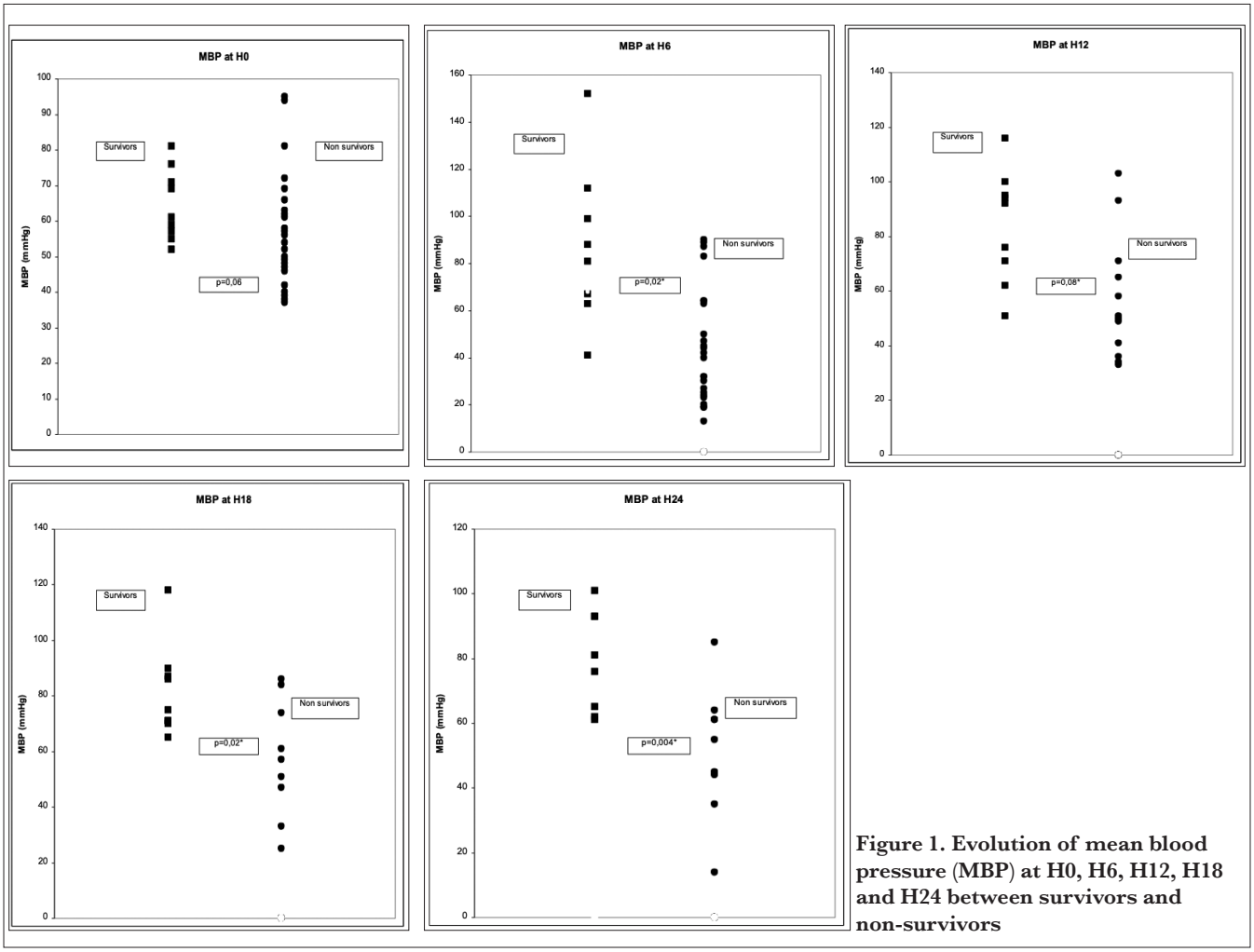

Figure 1. Evolution of mean blood pressure (MBP) at H0, H6, H12, H18 and H24 between survivors and non-survivors

At admission, the overall median MBP was 58 (50-71) mm Hg, overall median ECLS pump output was 3.00 (2.49-3.48) l min^{-1}, overall median dose of norepinephrine was 4.4 (2.6-7.0) mg h^{-1} and overall median dose of dobutamine was 5 (5-10) µg kg^{-1} min^{-1}.

At H0, survivors had a median MBP of 69 (59-74) mm Hg, whereas non-survivors had a median MBP of 55 (48-66) mm Hg (p=0.06).

At H6, survivors had a median MBP of 77 (65-94) mm Hg, whereas non-survivors had a median MBP of 42 (31-58) mm Hg (p=0.002).

At H12, survivors had a median MBP of 87 (74-95) mm Hg, whereas non-survivors had a median MBP of 51 (66-83) mm Hg (p=0.008).
At H18, survivors had a median MBP of 75 (71-89) mm Hg, whereas non-survivors had a median MBP of 57 (47-74) mm Hg (p=0.015).

At H24, survivors had a median MBP of 79 (63-91) mm Hg, whereas non-survivors had a median MBP of 53 (44-61) mm Hg (p=0.004) (Table 4).

Figure 1 describes MBP between survivors and non-survivors from H0 to H24.

Using ROC curve analysis, the 'optimal' threshold of MBP associated with survival was 64 mm Hg (AUC=0.85) at H6, 71 mm Hg (AUC=0.79) at H12, 70 mm Hg (AUC=0.75) at H18 and 65 mm Hg (AUC=0.84) at H24.

The related sensitivity and specificity at each time period are summarised in Table 5.

Under ECLS, blood flow is non-pulsatile with only a blood pressure represented by the MBP. In this situation, blood circulation can be considered as an electrical circuitry. Thus, in comparison with an electrical circuitry in which flow is governed by the Ohm's law (20), we can consider that the cardiac output (CO expressed in l min^{-1}), systemic vascular resistance

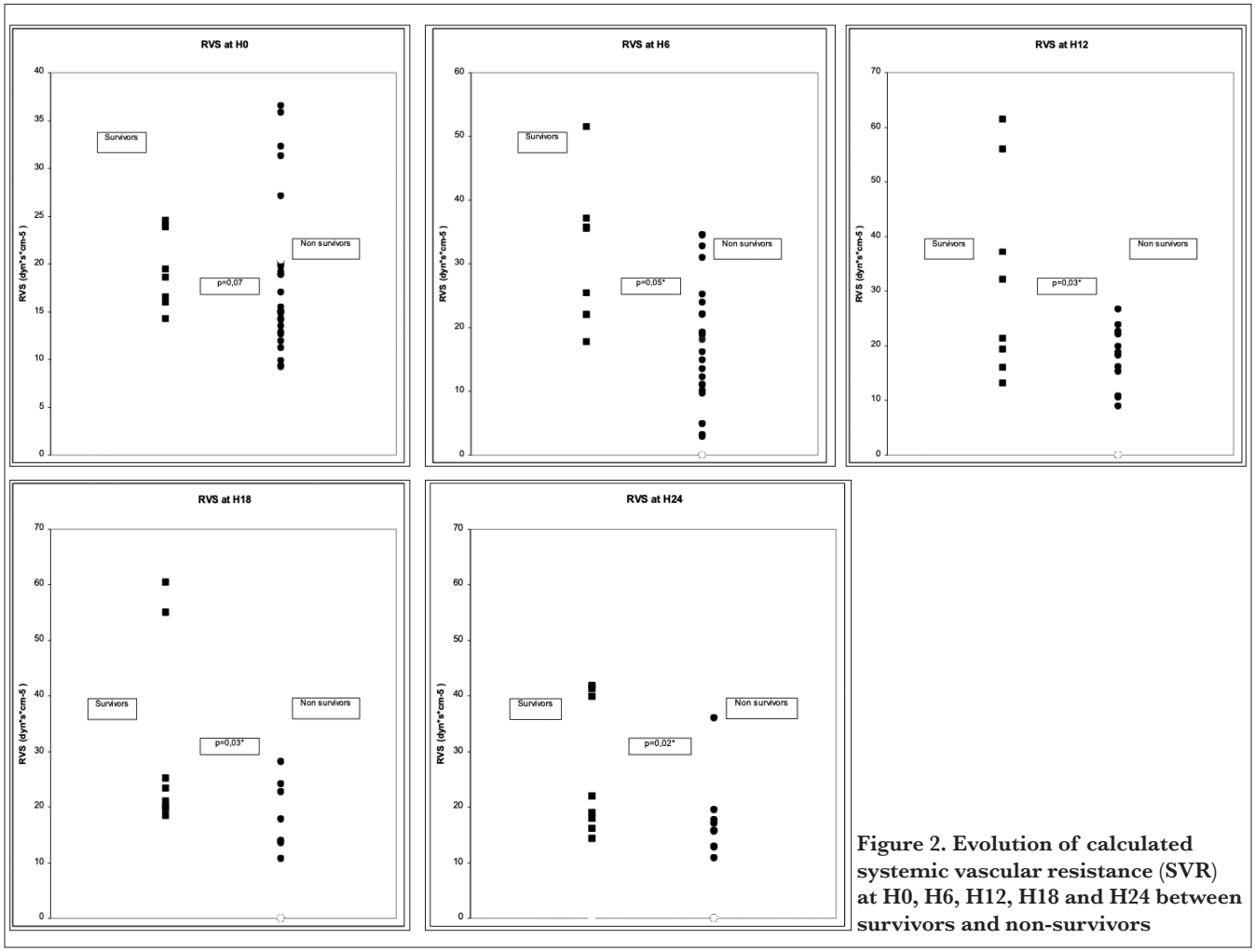

Figure 2. Evolution of calculated systemic vascular resistance (SVR) at H0, H6, H12, H18 and H24 between survivors and non-survivors

(SVR expressed in dyn s^{-1} cm^{-5}) and mean pressure at the end of the circuit (P0 expressed in mm Hg) are related by the following relationship: MBP−P0=CO*SVR. With ECLS, CO is equivalent to the ECLS pump flow, and P0 to the PEEP. Using this relationship, we calculated the related SVR in survivors and in non-survivors at each time period (Table 6 and Figure 2).

Discussion

In the present study, we observed that the ability to maintain MBP differs between survivors and non-survivors since 6 h after starting ECLS for refractory OHCA.

During resuscitation of CA, two successive phases occur: ischaemia and reperfusion. Ischaemia is most of the time considered to be the most detrimental factor on outcome, whereas it is not the only one, some authors suggest that reperfusion inflicts the 'coup de grace' (21).

With ECLS, blood pressure is not pulsatile but linear and continuous with one value represented by the MBP. The optimal value of MBP to reach during ECLS is not clearly established and remains under debate. As post-CA has been described as a 'sepsis-like' syndrome, it may be logical to target an MBP of 65-70 mm Hg (22, 23). Nevertheless, despite similarities between inflammation during sepsis and inflammation during reperfusion after CA (24, 25), a transposition is not strictly possible. Ischaemia creates a progressive chaos in the physiological components responsible for retaining cellular architecture that may produce structural and metabolic cell destruction (26).

We observed that in non-survivors despite high levels of norepinephrine infusion and maximal ECLS pump flow, we did not succeed to reach our MBP objective. This suggests that the vessels lost their mechanical function and their reactivity to catecholamines akin to the ultimate and irreversible 'sepsis-like' stage observed during prolonged resuscitation (24, 27). This state is apparent to a 'vascular cellular death' as we observed an arterial intravascular pressure approximately 30 mm Hg corresponding approximately to the mean systemic filling pressure (28, 29). From a pathophysiological point of view, we can hypothesise that the vascular cellular death state implies the loss of fundamental mechanisms affecting arteriolar resistance of different vascular territories: flow-mediated dilation (30), myogenic response (31) and metabolic response (32). Adenosine, lactate, H+ and K+ accumulation leads to smooth muscle cell relaxation (32) as acidosis induces a decrease in catecholamine sensitivity (33). Nevertheless, in the herein observed results, it is impossible to define which mechanism is involved in vascular tone failure because we do not have the possibility to evaluate intracellular adenosine, lactate, H+ and K+ levels.

Our study presents several limitations deserving generalisation. First, it is a single-centre study with a restricted number of patients. Second, ECLS was inserted 30 min at least after CA to respect the legal definition of refractory CA in France (34). Third, 'no-flow' and 'low-flow' durations were not standardised; both are known to be major prognostic factors after CA (34). Fourth, we cannot rule out the possible intervention of key determinants of outcome, especially 'reoxygenation' which has, recently, been observed (35). Fifth, recent studies identified criteria associated with better outcomes for eCPR recipients after OHCA (36-39), thus inclusion of such selected patients would affect our results.

Conclusion

Mean blood pressure significantly differs between survivors and non-survivors 6 h after starting ECLS for OHCA with a threshold of approximately 65 mm Hg.

Further studies are required to define the mechanisms involved to the observed differences to enhance treatments and outcome.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Comité pour la Protection des Personnes Est 3, Nancy, France (no. 17.12.05).

Informed Consent: Consent of patients was waived for participation in this retrospective observational study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – R.J., B.V.; Design – R.J.; Supervision – B.V., P.C.; Data Collection and/or Processing – R.J., A.G., P.P.; Analysis and/or Interpretation – R.J., A.G., P.P., B.V.; Literature Search – R.J., B.V.; Writing Manuscript – R.J.; Critical Review – A.G., P.P., B.V., P.C.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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