Venoarterial-Extracorporeal Membrane Oxygenation for Refractory Cardiogenic Shock Post-Cardiac Arrest

Marc Pineton de Chambrun[1], Nicolas Bréchot[1], Guillaume Lebreton[2], Matthieu Schmidt[1], Guillaume Hekimian[1], Pierre Demondion[2], Jean-Louis Trouillet[1], Pascal Leprince[2], Jean Chastre[1], Alain Combes[1], Charles-Edouard Luyt[1*]

[1] Service de Réanimation Médicale, Groupe Hospitalier La Pitié–Salpêtrière, Assistance Publique–Hôpitaux de Paris, Paris, France. Sorbonne Universités, UPMC Université Paris 06, INSERM, UMRS_1166-ICAN Institute of Cardiometabolism and Nutrition, Paris, France.

[2] Service de Chirurgie Thoracique et Cardiovasculaire, Groupe Hospitalier La Pitié–Salpêtrière, Assistance Publique Hôpitaux de Paris, Paris, France.

Short Title: VA-ECMO for Cardiogenic Shock Post-Cardiac Arrest

*Correspondence: Charles-Edouard Luyt, MD, PhD, Service de Réanimation Médicale, iCAN, Groupe Hospitalier La Pitié–Salpêtrière, 47–83, boulevard de l'Hôpital, 75651 Paris Cedex 13, France. tel: +33 (0)1 42 16 38 24; fax: +33 (0)1 42 16 38 17; email: charles-edouard.luyt@aphp.fr

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Conflicts of Interest

Dr Combes is the primary investigator of the EOLIA trial (NCT01470703), a randomized trial of VV-ECMO, supported in part by MAQUET. Drs Bréchot, Lebreton and Combes have received honoraria for lectures by MAQUET. The other authors declare that they have no conflicts of interest related to the purpose of this manuscript.

Abstract: Word count: 245

Purpose: To describe the characteristics, outcomes and risk factors associated with poor outcome of venoarterial-extracorporeal membrane oxygenation (VA-ECMO)-treated patients with refractory shock post-cardiac arrest.

Methods: We retrospectively analyzed data collected prospectively (March 2007– January 2015) in a 26-bed tertiary hospital intensive care unit. All patients implanted with VA-ECMO for refractory cardiogenic shock after successful resuscitation from cardiac arrest were included. Refractory cardiac arrest patients, given VA-ECMO under cardiopulmonary resuscitation, were excluded.

Results: Ninety-four patients received VA-ECMO for refractory shock post-cardiac arrest. Their hospital and 12-month survival rates were 28% and 27%, respectively. All 1-year survivors were cerebral performance category 1. Multivariable analysis retained INR >2.4 (OR 4.9; 95% CI 1.4–17.2), admission SOFA score >14 (OR 5.3; 95% CI 1.7–16.5) and shockable rhythm (OR 0.3; 95% CI 0.1–0.9) as independent predictors of hospital mortality, but not SAPS II, out-of-hospital cardiac arrest score or other cardiac arrest variables. Only 10% of patients with an admission SOFA score >14 survived, whereas 50% of those with scores ≤14 were alive at 1 year. Restricting the analysis to the 67 patients with out-of-hospital cardiac arrest of coronary cause yielded similar results.

Conclusion: Among 94 patients implanted with VA-ECMO for refractory cardiogenic shock post-cardiac arrest resuscitation, the 24 (27%) 1-year survivors had good neurological outcomes, but survival was significantly better for patients with admission SOFA scores <14, shockable rhythm and INR ≤2.4. VA-ECMO might be considered a rescue therapy for patients with refractory cardiogenic shock post-cardiac arrest resuscitation.

Keywords: Cardiac arrest · Cardiogenic shock · Extracorporeal membrane oxygenation · Post-cardiac arrest syndrome

Take-home message: Refractory cardiogenic shock is one of the leading causes of early death after successful cardiac arrest resuscitation. In this setting, venoarterial-extracorporeal membrane oxygenation is associated with 27% 1-year survival. Patients with SOFA scores >14 have poorer outcomes than the others (respective survival 10% vs. 50%), raising the question of futility in these patients.

Introduction

Hospital mortality of patients post-cardiac arrest resuscitation remains particularly high, ranging from 40% to 90% [1–9]. The main causes of death are multiorgan failure within the first hours following the return of spontaneous circulation and neurological damage (mainly anoxic cerebral lesions) several days later [10]. Early multiorgan failure may result from post-cardiac arrest syndrome or myocardial disease-related cardiogenic shock that led to cardiac arrest. Post-cardiac arrest syndrome exhibits a set of relatively stereotypical events, among which cardiocirculatory failure usually dominates the clinical picture and often leads to multiorgan failure. Post-cardiac arrest syndrome usually combines cardiogenic and vasodilatory components: left ventricular dysfunction begins early, within minutes after the return of spontaneous circulation and can be secondarily associated with severe vasodilatation, attributable to a generalized inflammatory syndrome, or myogenic and/or metabolic autoregulation [11–14]; it spontaneously reverses after several hours, but can sometimes be very severe, leading to multiorgan failure and death. However, cardiogenic shock may also occur without that syndrome, depending on cardiac disease origin (ischemic disease, drug overdose…).

Venoarterial-extracorporeal membrane oxygenation (VA-ECMO) is an effective technique to rescue patients with refractory cardiogenic shock [15–17]. In the setting of cardiac arrest, many studies focusing on VA-ECMO's role in extracorporeal cardiopulmonary resuscitation (e-CPR) for refractory cardiac arrest yielded conflicting results [18–20]. However, VA-ECMO usefulness in patients with refractory cardiogenic shock post-cardiac arrest has not yet been reported. Using such an invasive and expensive technique in this context is debatable because the neurological prognosis at the time of implantation is unknown. Therefore, we undertook this retrospective analysis of patients treated with VA-ECMO for refractory

cardiogenic shock post-cardiac arrest to describe their characteristics, outcomes and risk factors associated with poor outcome.

Methods

Patients

We retrospectively reviewed the prospectively constituted ECMO database of our 26-bed intensive care unit (ICU) to identify patients who received (March 2007–January 2015) VA-ECMO for refractory cardiogenic shock post-cardiac arrest resuscitation. Before VA-ECMO implantation, every patient underwent Doppler echocardiography to evaluate cardiac and hemodynamic status. In our unit and for this study, VA-ECMO for acute-refractory cardiogenic shock is usually indicated when the following criteria are met: persistence or aggravation of tissue hypoxia (extensive skin mottling, anuria, neurological impairment, elevated blood lactate…) despite adequate fluid loading; severely depressed left ventricle ejection fraction (<25%) with low cardiac output (defined as aortic velocity-time integral <8 cm and sustained hypotension despite infusion of very high-dose catecholamines (epinephrine >1 μg/kg/min or dobutamine >20 μg/kg/min with norepinephrine >1 μg/kg/min). However, because most ECMO systems were implanted in other hospitals, it was impossible to precisely verify that all patients satisfied all these criteria. Patients implanted with VA-ECMO for refractory cardiac arrest under CPR were excluded from this study.

ECMO implantation

The detailed surgical procedure for femoral–femoral VA-ECMO placement was described previously [16, 17, 21]. Briefly, trained cardiovascular surgeons performed all procedures at the

bedside or in the cardiac angiography room because of patient's hemodynamic instability. Femoral vessels were cannulated after limited cut-down using the Seldinger technique and an additional 7F catheter was systematically inserted distally into the femoral artery to prevent severe leg ischemia. For highly unstable patients diagnosed with refractory cardiogenic shock in other hospitals, our institution's Mobile Circulatory Assistance Unit traveled rapidly to primary-care hospitals with a portable ECMO system, installed the device before refractory multiorgan failure or cardiac arrest took hold, and then transported the patient to our tertiary-care center [22].

Patient management

The detailed management of patients under VA-ECMO was described previously [13, 14, 18, 20,21]. Briefly, pump speed was adjusted to obtain blood flow at 4–5 L/min, although at these flow rates there is a risk of poor left ventricle unloading with the possibility of further left ventricle-function deterioration. Intravenous unfractionated heparin was given to maintain the activated partial thromboplastin time at 1.5–2-times normal. When a pulsatile arterial waveform had been maintained for at least 24 h, an ECMO-weaning trial was undertaken as described elsewhere [21]. Therapeutic hypothermia (32–34°C) was initiated during the first 24 h post-cardiac arrest, according to the ILCOR guidelines [12]. Patients who could not be weaned-off VA-ECMO because of persistent heart failure underwent comprehensive predictive neurological work-ups, including clinical examination and electroencephalography (see online supplement). When neurological prognosis was favorable, patients were bridged to a long-term left ventricle assist device or cardiac transplantation, whereas patients with predicted poor neurological outcomes were weaned-off VA-ECMO during withdrawal of life-sustaining therapies.

Outcome variables

Main outcome variables were 28-day, hospital and 12-month mortality rates. Secondary outcome measures included survival to VA-ECMO weaning, number of patients bridged to a long-term left ventricle assist device or cardiac transplantation, times on VA-ECMO and on mechanical ventilation, duration of ICU stay, cause of mortality and multiple organ donations. Survivors to hospital discharge were contacted by phone 1-year post-cardiac arrest to evaluate neurological outcomes using the Cerebral Performance Category score [24].

Statistical analyses

Results are expressed as number (%), continuous variables as mean (standard deviation, SD) or median [interquartile range, IQR] and compared using Student's *t*-test or Wilcoxon's rank test. Categorical variables were compared with χ^2 tests. Patients' demographic, clinical and biological characteristics were tested in univariable analyses for association with hospital mortality. Continuous variables were transformed into categorical variables (by defining the best thresholds after analyzing mortality in each corresponding-variable quartile). Thereafter, multiple logistic-regression analyses using backward-stepwise variable elimination were run (with the variable-exit threshold set at $P>0.10$). Factors achieving $P\leq0.10$ in our univariable analyses and parameters previously reported to be strongly associated with death were entered into the multivariable model. All potential explanatory variables included in the multivariable analyses were subjected to collinearity analysis with a correlation matrix. Variables associated with one another were not included in the model. Model goodness-of-fit was assessed with the determination coefficient (R^2). $P<0.05$ defined statistical significance. Analyses were computed with IBM SPSS Statistics v22.0 software (IBM Corp, Armonk, NY).

Ethics

In accordance with the ethical standards of our hospital's institutional review board, the Committee for the Protection of Human Subjects, informed consent was not obtained for demographic, physiological and hospital-outcome data analyses because this observational study did not modify existing diagnostic or therapeutic strategies. However, patients and/or relatives were informed about the anonymous data collection and that they could decline inclusion. The National Commission for Informatics and Liberties (CNIL) approved this study (no. 1950673).

Results

Study population

Among the 954 VA-ECMO–treated patients in our ICU, 94 implanted for refractory cardiogenic shock post-cardiac arrest were included (Fig. 1). Their characteristics are reported in Table 1 and Table E1 (online supplement). Most patients had no or few comorbidities but were severely ill, as assessed by the high simplified acute physiology score II (SAPS II) and sequential organ failure assessment (SOFA) score. Median left ventricle ejection fraction was 15% [10–20%] (87/94 assessable) and aortic velocity-time integral was 7 [5–9] cm (67/94 assessable). Median cardiac arrest-to-VA-ECMO-implantation interval was 7.4 [3.3–14] h and median ECMO-support duration was 4 [2–6] days. VA-ECMO was implanted by our institution's Mobile Unit surgeon at another hospital in 60 (64%) patients, in our ICU in 17 (18%), in the catheterization lab in 14 (15%) and by another institution's surgeon at another hospital in three (3%) patients. Median cardiac arrest-to-VA-ECMO-implantation interval was similar for patients implanted by the Mobile Unit vs. the others (7.9 [3.9–18.5] vs. 5.4 [3.9–11.1] h, respectively, $P = 0.08$).

Outcomes

Respective 28-day, hospital and 12-month survival rates were 32%, 28% and 27% (Table 2). Fifty-five (59%) patients died on VA-ECMO, 33 (35%) were successfully weaned, four (4%) were bridged to a left ventricle assist device and two (2%) to heart transplantation. Causes of death were multiorgan failure for 45 (65%) patients, brain death for 11 (16%), post-anoxic encephalopathy for 10 (14%) and recurrent-cardiac arrest for three (4%; one after day 28) (Figure E1, online supplement). The 25 (27%) 1-year survivors had good neurological outcomes (cerebral performance category 1). Among the 11 patients with confirmed brain death, five became multiple organ donors. Forty-seven (50%) patients received an intra-aortic balloon pump (Table 2); vascular complications and outcomes were similar for patients with or without a pump (Table E1, online supplement).

Comparisons between survivors and non-survivors

The 26 survivors to hospital discharge and 68 non-survivors were comparable for age, sex, body mass index, comorbidities, cardiac arrest cause and place of occurrence, duration of resuscitation and median left ventricle ejection fraction before VA-ECMO implantation (Tables 1 and E1). Survivor's first rhythm was more frequently ventricular fibrillation, their aortic velocity-time integral pre-VA-ECMO was higher and their cardiac arrest-to-VA-ECMO-implantation intervals were longer. Non-survivors had higher SAPS II, SOFA and out-of-hospital cardiac arrest scores, higher rates of neurological and renal failures at ICU admission, higher arterial blood lactate, alanine aminotransferase and serum creatinine levels, lower prothrombin activity and urinary output on the ECMO-implantation day. According to multivariable analyses (Table 3), independent predictors of hospital mortality were international normalized ratio (INR) >2.4 (odds ratio (OR) 4.9; 95% confidence interval (CI) 1.4–17.2), admission SOFA score >14 (OR 5.3;

95% CI 1.7–16.5) and shockable rhythm (OR 0.3; 95% CI 0.1–0.9). The Survival After Veno-arterial Extracorporeal membrane oxygenation (SAVE) score [15] was not independently associated with outcome (see online supplement).

Comparable results were obtained when analyzing factors associated with 1-year mortality: INR and admission SOFA score were independent predictors of 1-year mortality (Tables E3 and E4 in the online supplement).

Figure 2 shows the Kaplan–Meyer survival-probability curves according to SOFA-score quartiles, and Figures E1 and E2 for all patients and according to pre-ECMO SOFA scores (online supplement). Only 10% of patients with pre-ECMO SOFA scores >14 survived; almost all deaths occurred during the first 24 h, whereas patients with pre-ECMO SOFA scores ≤14 had 50% 1-year survival.

Discussion

This large cohort of patients with refractory cardiogenic shock post-cardiac arrest showed that VA-ECMO was an effective rescue technique, with 27%1-year survival; all survivors had favorable neurological outcomes. When analyzing survival according to disease severity at ECMO initiation, 50% of patients with admission SOFA scores ≤14 survived, whereas only 10% with pre-ECMO multiorgan failure (i.e., SOFA scores >14) survived, raising the question of futility for this population. Interestingly, most patients died early of multiorgan failure. Because we included a wide variety of patients (i.e., in- or out-of-hospital cardiac arrest of various causes), we analyzed a subgroup of patients with out-of-hospital cardiac arrest of coronary origin and found comparable results: one-third survived at 1 year, and survival poor for the most severely ill (see online supplement).

Few data are available on the potential usefulness of circulatory support for patients in cardiogenic shock after return of spontaneous circulation post-cardiac arrest; however, post-cardiac arrest myocardial dysfunction contributes to the low survival rate after in- and out-of-hospital cardiac arrests. In a retrospective study on 205 in-hospital and out-of-hospital cardiac arrest patients, 33% died of cardiovascular failure and multiorgan failure [25]. In another out-of-hospital cardiac arrest cohort, 73/165 (44%) patients suffered from hemodynamic instability with significant left ventricle dysfunction (median left ventricle ejection fraction, 32%) and 8% of the total (19.2% of the 73 with hemodynamic instability) died of early shock [26]. In a more recent study on 1152 cardiac arrests, 789 (68%) developed post-cardiac arrest shock, with 73% mortality; the etiology of shock was not reported but it is highly probable that some patients had pure cardiogenic shock, some pure vasoplegia and others both [27]. Some data indicate that this phenomenon is responsive to therapy and reversible [26, 28].

However, myocardial dysfunction persists in some patients and may lead to cardiogenic shock refractory to conventional medical therapies (fluid resuscitation and inotropic drugs). Mechanical circulatory support could be considered at that time until myocardial recovery or to bridge patients with predicted favorable neurological outcomes toward long-term assist device or heart transplantation. Intra-aortic balloon pumps have been evaluated in the setting of cardiogenic shock, with 45% of patients post-cardiac arrest resuscitation, but results were disappointing [29]. The Impella percutaneous left ventricle assist device has also been proposed to treat refractory cardiogenic shock post-cardiac arrest but with limited data [30, 31]. VA-ECMO has been extensively investigated for e-CPR for refractory cardiac arrest but with discordant findings [18–20].

However, no studies have specifically investigated the possible VA-ECMO usefulness and risk factors associated with mortality in patients with refractory cardiogenic shock post-

cardiac arrest, as most of the studies that focused on VA-ECMO for refractory cardiogenic shock mixed patients with or without cardiac arrest and even refractory cardiac arrest [30, 31]. In the most recent [32], among 138 patients implanted with VA-ECMO for acute myocardial infarction-related cardiogenic shock in two French ECMO centers, 79 (57%) suffered cardiac arrest pre-VA-ECMO implantation, including 19 (14%) with implantation during CPR; 65 (47%) survived to discharge. Factors independently associated with mortality were age >60 years, female sex, body mass index >25 kg/m^2, Glasgow Coma Score <6, serum creatinine >150 µmol/L, elevated serum arterial lactate and prothrombin activity <50%. In the Extracorporeal Life Support Organization cohort of 3846 refractory cardiogenic shock patients, 1240 (32%) had experienced pre-ECMO cardiac arrest; 456 (37%) of them survived and were discharged [15]. Again, long-term follow-up and neurological outcomes were not available. According to their multivariable analysis, cardiac arrest was independently associated with poorer survival. Although our cohort's survival to discharge seems to be slightly lower than that of cardiogenic shock patients without prior cardiac arrest, we reported long-term survival and 1-year neurological outcomes, information often lacking in earlier publications. Moreover, we were able to identify factors associated with mortality in this specific population, whereas other studies mixed patients put on ECMO for cardiogenic shock, post-cardiac arrest cardiogenic shock or refractory cardiac arrest.

Our findings support VA-ECMO feasibility for extremely severe patients with refractory cardiogenic shock post-cardiac arrest, with 27% 1-year survival and good neurological outcomes, comparable to those of patients not requiring ECMO implantation [12]. Patient selection (reflected partly by their low mean age) may have played a role in this outcome. Moreover, our 1-year survivors' good neurological outcomes are partly explained by selective pressure: those with severe neurological injury died early (12% had initial poor neurological outcome prediction and care was withdrawn) and hospital survivors with severe brain injury

usually die early after hospital discharge. However, patients with severe multiorgan failure have very poor prognoses and, in our experience, survival of patients with pre-ECMO ICU-admission SOFA scores >14 was very low, raising the question of futility. This crucial decision might be addressed by survival-predictive models, which aim to help clinicians select patients who are more likely to survive on ECMO [15, 32]. For acute myocardial infarction, the ENCOURAGE score, which integrates extracardiac organ failure, showed good performance to predict survival in this context [32]. In our population, ENCOURAGE and SAVE scores seem less accurate than the SOFA score for our patients, since multivariable analyses retained only the SOFA score as being associated with hospital and 1-year mortality. This lack of association is probably explained by almost all patients being in the high-risk classes of both scores, with low survival probability.

Notably, ECMO is not an obstacle to care withdrawal: seven of our patients could not be weaned-off ECMO and had dismal neurological prognoses. Their ECMO was removed during care withdrawal. Strikingly, cardiac arrest variables (witnessed status, bystander CPR, low-flow and no-flow times…) and other traditional post-arrest predictors (SAPS II score, blood lactate level, acute renal failure or out-of-hospital cardiac arrest score) were not independently associated with mortality. We have no clear explanation for these findings, but it is highly possible that due to our population's specifics, patient survival mostly reflected shock intensity (and the related organ failures) rather than "traditional" cardiac arrest parameters or scores. Although not statistically significant herein, cardiac-arrest-to-ECMO-start interval could also be an important factor to consider for patient selection, with longer times being associated with more severe multiorgan failure.

This study has several limitations. First, it is a retrospective, monocenter-cohort analysis of information collected prospectively. Second, included patients might not reflect the global

cardiogenic shock population post-cardiac arrest resuscitation, the cardiogenic shock post-cardiac arrest frequency or the number of refractory shock patients requiring VA-ECMO. Indeed, most patients were admitted to other hospitals' ICUs and referred to us for VA-ECMO assistance. Moribund, elderly or highly comorbid patients may not have been considered for ECMO or may have been rejected because of obvious futility. Third, despite our ICU's strict ECMO-implantation criteria, we are not sure that all criteria were fulfilled by all the patients included. Indeed, because most of our patients (63/94, 67%) were put on ECMO in another hospital, data on pre-ECMO echocardiography, blood pressure and catecholamine use were not always entered in the medical charts, meaning all these criteria could not be verified. However, because our policy is to implant VA-ECMO only in patients with cardiogenic shock (and not those with vasoplegia and hyperkinetic state), it is highly probable that all patients had severe cardiogenic shock with hypotension, tissue hypoxia, low cardiac output and high inotrope doses. Moreover, post-ECMO echocardiography showed left ventricle ejection fraction <25% with aortic velocity-time integral <8 cm in all patients. Fourth, we mixed patients with different cardiac arrest causes. However, when the analysis was restricted to patients with out-of-hospital cardiac arrest due to acute coronary syndrome, the same results were obtained. Fifth, circulatory failure in our cohort reflected left ventricular dysfunction (i.e. cardiogenic shock). Thus, our results cannot be generalized to patients with refractory post-cardiac arrest syndrome and preserved (or moderately decreased) cardiac output and vasoplegia. Lastly, we would have liked to have a control group with cardiogenic shock post-cardiac arrest for comparison; however, the severity of our patients' cardiogenic shock made it impossible to match our cases with controls.

CONCLUSION

In this retrospective cohort of severely ill patients who received VA-ECMO for refractory

cardiogenic shock post-cardiac arrest resuscitation, 27% were alive at 1 year with good neurological outcomes. VA-ECMO might be considered a rescue therapy for patients with refractory cardiogenic shock post-cardiac arrest. Patients with multiorgan failure (defined as SOFA score >14), high INR (>2.4) and no shockable rhythm at the time of implantation had poorer outcomes, raising the question of the futility of this technique for such patients.

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Table 1. Main characteristics of all venoarterial extracorporeal membrane oxygenation–treated patients at ICU admission and comparisons between hospital survivors and non-survivors

Characteristic	Entire Cohort (*n* = 94)	Survivors (*n* = 26)	Non-Survivors (*n* = 68)	*P*
Age (y)	50.8±11.5	49.96±10	51.1±12.1	0.6
Male sex	71 (76)	20 (76.9)	51 (75)	0.8
Body mass index (kg/m^2)	26.2 [23.4–29.3]	25.8 [23.7–28.1]	26.1 [23.4–29.4]	0.9
McCabe & Jackson score for comorbidity	1 [0–2]	0.5 [0–2]	1 [0–2]	0.7
SAPS II	82 [77–88]	77 [67.5–83]	84 [79–89]	0.002
SOFA score	13 [15–17]	13 [12–14]	16 [14–18]	<0.0001
Organ failure[a]				
Cardiovascular system	94 (100)	26 (100)	68 (100)	–
Lung	94 (100)	26 (100)	68 (100)	–
Brain	91 (97)	24 (92.3)	67 (98.5)	0.01
Kidney	48 (51)	5 (19.2)	43 (63.2)	<0.0001
Hematological	6 (6)	1 (3.8)	5 (7.4)	0.5
Liver	2 (2)	0	2 (2.9)	0.3
Out-of-hospital cardiac arrest score [2]	41.3 [30.8–50.9]	32.4 [24.7–42.6]	43.9 [33.9–51.9]	0.001
Etiology of cardiac arrest				
Myocardial infarction	66 (70)	19 (73.1)	47 (69.1)	0.7
Acute decompensation of chronic cardiomyopathy	8 (9)	3 (11.5)	5 (7.4)	0.5

Pulmonary embolism	4 (4)	2 (7.7)	2 (2.9)	0.3
Drug intoxication	3 (3)	0	3 (4.4)	0.2
Anaphylactic shock	3 (3)	2 (7)	1 (1.5)	0.1
Miscellaneous[b]	10 (11)	0 (0)	10 (14.7)	0.04
Witnessed cardiac arrest	88 (94)	25 (96)	63 (93)	0.5
Attempted defibrillation	56 (60)	21 (80.8)	35 (51.5)	0.01
Bystander-attempted CPR	76 (81)	21 (80.8)	55 (80.9)	0.9
No flow (min)	0 [0–5]	0 [0–3.5]	0 [0–5]	0.9
Low flow (min)	30 [15–43]	27.5 [10–40]	30 [16–45]	0.3
Out-of-hospital cardiac arrest	78 (83)	22 (85)	56 (82)	0.7
Shockable rhythm	56 (60)	21 (81)	35 (52)	0.02
Cardiac arrest-to-VA-ECMO interval (h)	7.4 [3.3–14]	10.7 [4.1–18.8]	6.3 [3–13]	0.07
ECMO implanted by mobile team	60 (64)	15 (58)	45 (66)	0.5
Therapeutic hypothermia	75 (80)	19 (73)	56 (82)	0.3
Pre-ECMO echocardiographic findings				
Left ventricular ejection fraction[c] (%)	15 [10–20]	15 [10–20]	15 [10–20]	0.3
Aortic velocity-time integral[d] (cm)	7 [5–9]	8 [6–10]	6 [5–8]	0.06
SAVE-score risk class [15]				0.007
I	0	0	0	
II	0	0	0	
III	6 (6)	1 (4)	5 (7)	
IV	28 (30)	14 (54)	14 (21)	
V	60 (64)	11 (42)	49 (72)	

Abbreviations: *SAPS* simplified acute physiology score, *SOFA* sequential organ failure assessment, *CPR* cardiopulmonary resuscitation, *VA-ECMO* venoarterial extracorporeal membrane oxygenation, *SAVE* Survival after VA-ECMO

Continuous variables are expressed as mean ± SD or median [IQR] and compared using Student's *t*-test or Wilcoxon's rank test. Categorical variables are expressed as *n* (%) and were compared with χ^2 tests.

[a] Deemed present when the corresponding SOFA score was >2.

[b] Miscellaneous causes of cardiac arrest: hypoxic cardiac arrest and/or potassium disorders: 2 each; and 1 each: near drowning, myocarditis, subarachnoid hemorrhage, amniotic fluid embolism, postpartum hemorrhage or idiopathic cardiac arrhythmia.

[c] Available for 87 patients (27 survivors and 59 non-survivors).

[d] Available for 67 patients (25 survivors and 42 non-survivors).

1

Table 2. Outcome measures for all 94 VA-ECMO–treated patients

Outcome measure	Value
VA-ECMO duration (days)	4 [2–6]
Intensive care unit length of stay (days)	4 [1–13]
Mechanical ventilation duration (days)	4 [2–11]
ECMO complications	
Limb ischemia	14 (15)
Fasciotomy	4 (4)
Amputation	1 (1)
Bleeding	24 (26)
Infection	17 (18)
Mechanical support during ECMO	
Intra-aortic balloon pump	47 (50)
Impella®	2 (2)
VA-ECMO weaning	
Yes	33 (35)
No	61 (65)
Died on ECMO	55 (59)
Left ventricular assist device	4 (4)
Heart transplantation	2 (2)
28-Day survival	30 (32)
Hospital survival	26 (28)
12-Month survival	25 (27)

Cause of death (*n*=69)	
Multiorgan failure	45 (65)
Brain death	11 (16)
Post-anoxic encephalopathy	10 (14)
Cardiac arrest recurrence	3 (4)
Multiple organ donation[a]	5 (5)

Abbreviations: *VA-ECMO* venoarterial extracorporeal membrane oxygenation

Continuous variables are expressed as median [IQR] and categorical variables as *n* (%).

[a] Reasons for refusing organ donation: 3 with persistent multiorgan failure, and 1 each with family refusal, pregnancy or liver transplantation.

1 **Table 3.** Univariable and multivariable analyses of factors associated with hospital mortality

Factor	Univariable analysis OR [95% CI]	*P*	Multivariable analysis OR [95% CI]	*P*
Arterial lactate >11.5, mmol/L	4.7 [1.7–12.7]	0.003		
International normalized ratio >2.4	7.8 [2.4–25.3]	0.0006	4.9 [1.4–17.2]	0.01
Renal failure at ICU admission[a]	7.2 [2.4–21.5]	0.0004		
Pre-VA-ECMO SOFA score >14	7.5 [2.6–21.3]	0.0002	5.3 [1.7–16.5]	0.004
SAPS II >82	3.4 [1.3–9.3]	0.01		
Shockable rhythm	0.3 [0.1–0.7]	0.01	0.3 [0.1–0.9]	0.04

Abbreviations: *INR* international normalized ratio, *VA-ECMO* venoarterial-extracorporeal membrane oxygenation, *SOFA* sequential organ failure assessment, *SAPS* simplified acute physiology score

[a] Defined as a renal SOFA score of 3 or 4.

The following variables were included in the multivariable model: arterial lactate >11.5 mmol/L, INR >2.4, pre-VA-ECMO SOFA score >14 and shockable rhythm. SAPS II and renal failure at ICU admission were not included in the final model because they were strongly associated with the SOFA score. Model $R^2 = 0.26$.

2

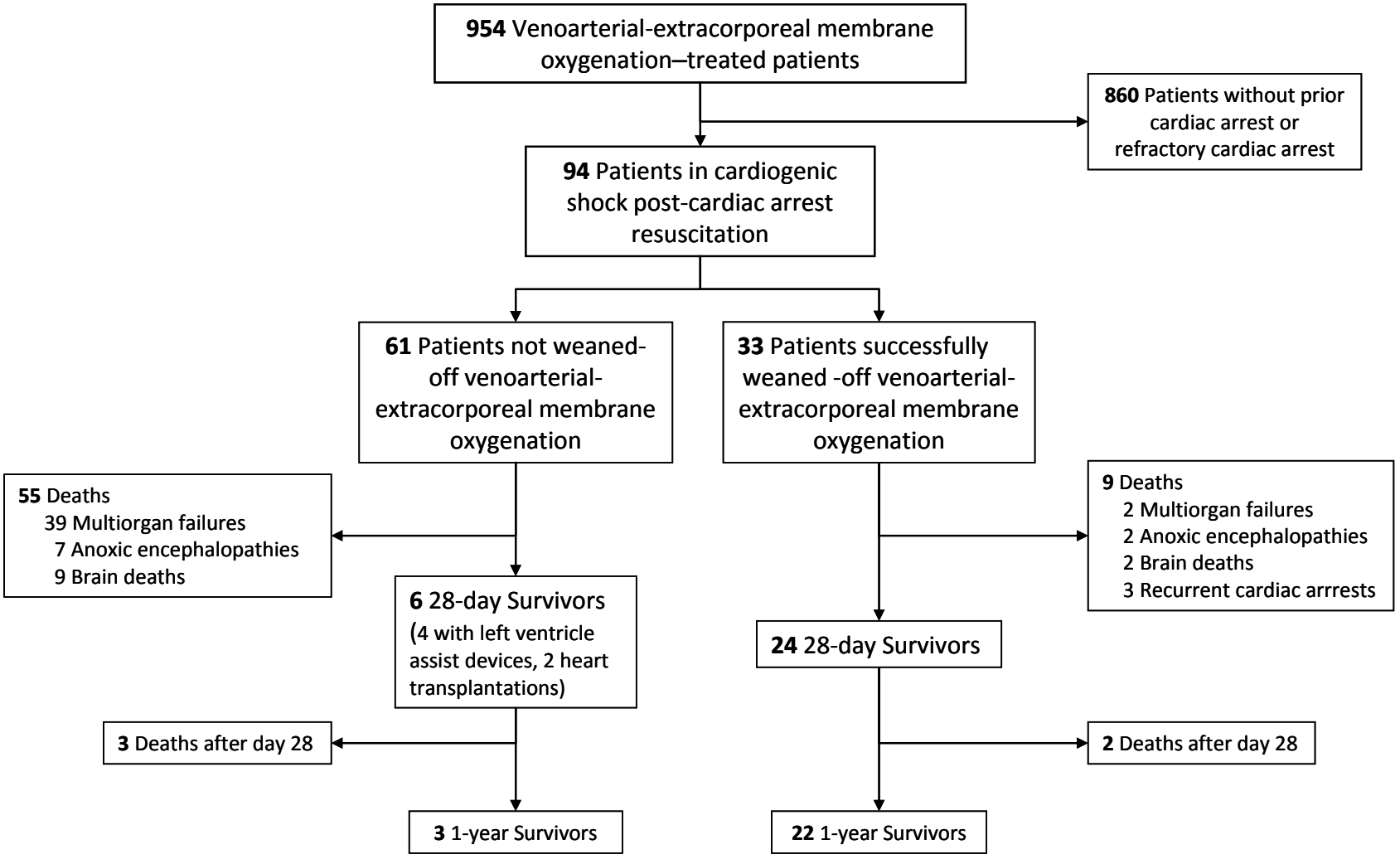
Figure legends

Fig. 1 Flow-chart of the study

Fig. 2 Kaplan–Meier probability of survival curves according to Sequential Organ Failure Assessment score quartile at admission

Fig. 3 Cause of death (neurological injury or multiorgan failure) according to the time between extracorporeal membrane oxygenation start and death

Fig 1


954 Venoarterial-extracorporeal membrane oxygenation–treated patients
860 Patients without prior cardiac arrest or refractory cardiac arrest
94 Patients in cardiogenic shock post-cardiac arrest resuscitation
61 Patients not weaned-off venoarterial-extracorporeal membrane oxygenation
33 Patients successfully weaned -off venoarterial-extracorporeal membrane oxygenation
55 Deaths
39 Multiorgan failures
7 Anoxic encephalopathies
9 Brain deaths
9 Deaths
2 Multiorgan failures
2 Anoxic encephalopathies
2 Brain deaths
3 Recurrent cardiac arrrests
6 28-day Survivors
(4 with left ventricle assist devices, 2 heart transplantations)
24 28-day Survivors
3 Deaths after day 28
2 Deaths after day 28
3 1-year Survivors
22 1-year Survivors

1 Fig 2

2

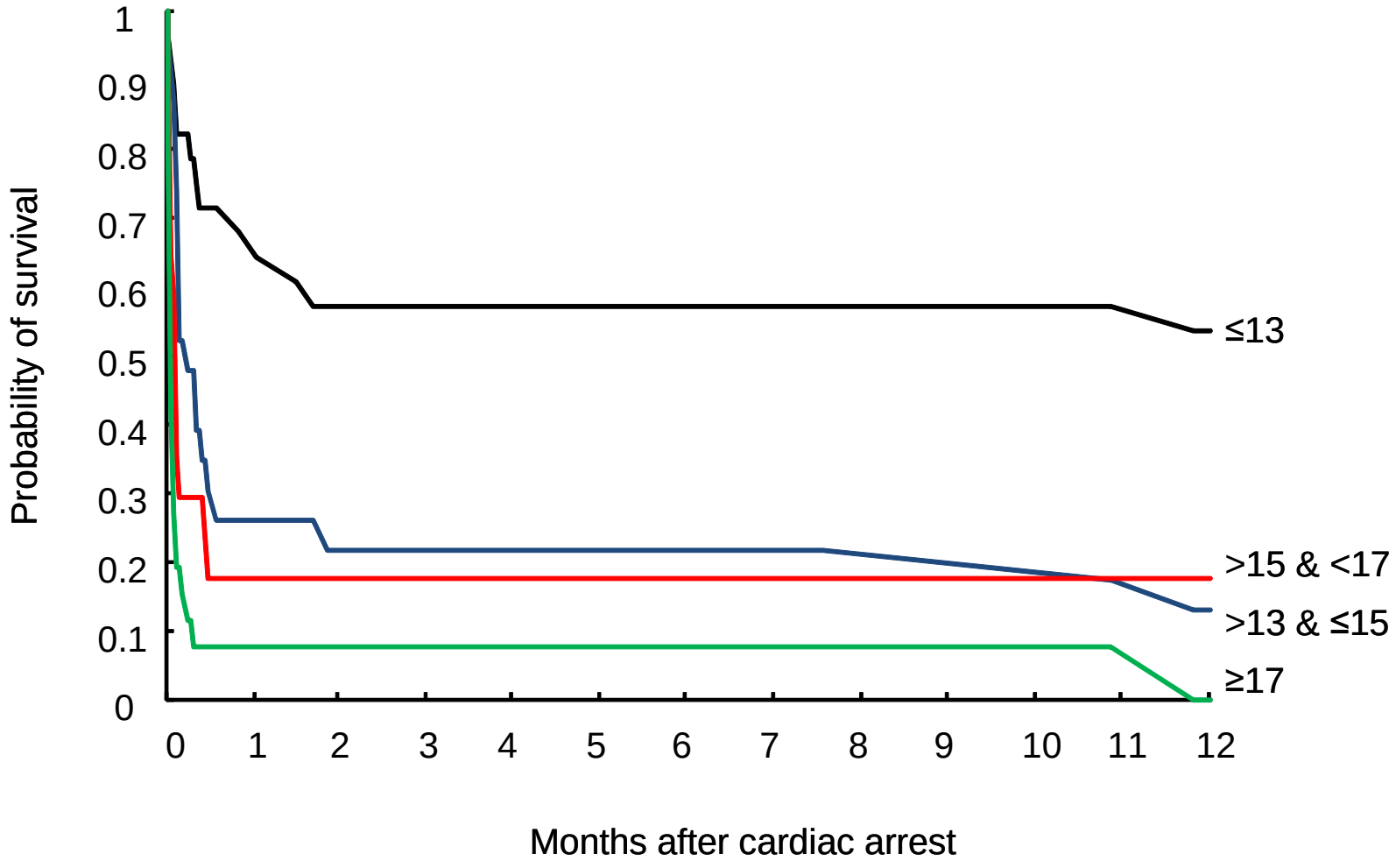
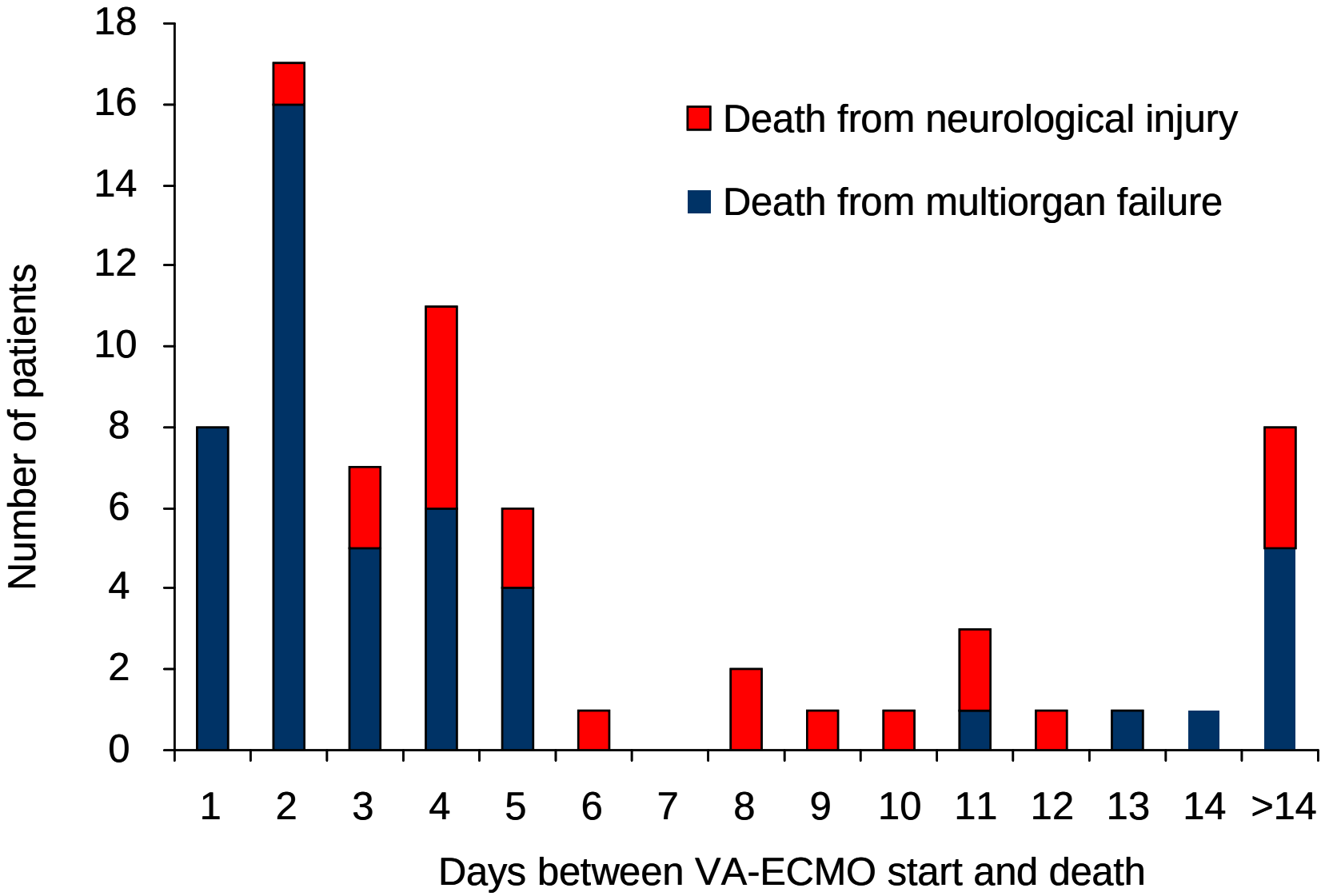

Probability of survival
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 1 2 3 4 5 6 7 8 9 10 11 12
Months after cardiac arrest
≤13
>15 & <17
>13 & ≤15
≥17

Fig 3


Death from neurological injury
Death from multiorgan failure
Number of patients
0
2
4
6
8
10
12
14
16
18
1
2
3
4
5
6
7
8
9
10
11
12
13
14
>14
Days between VA-ECMO start and death