Duration of Veno-Arterial Extracorporeal Membrane and Mortality in Postcardiotomy Cardiogenic Shock

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Abstract

Background and Aim: The optimal duration of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in patients

affected by postcardiotomy cardiogenic shock (PCS) remains controversial. We aimed to investigate the impact of VA-ECMO duration on hospital outcomes. Methods: Data on PCS patients receiving VA-ECMO were retrieved from the multicentre PC-ECMO registry. Patients were stratified according to different duration of VA-ECMO therapy: [?]3 days, 4-7 days, 8-10 days, and >10 days. Results: A total of 725 patients with a mean age of 62.9±12.9 years were included. The mean duration of VA-ECMO was 7.1±6.3 days (range: 0-39 days), and 39.4% patients were supported for [?]3 days, 29.1% for 4-7 days, 15.3% for 8-10 days, and finally 20.7% for >10 days. A total of 391 (53.9%) patients were successfully weaned from VA-ECMO while 134 (34.3%) died prior to discharge. Multivariable logistic regression showed that prolonged duration of VA-ECMO therapy (4-7 days, adjusted rate 53.6%, odds ratio [OR] 0.28, 95% confidence interval [CI] 0.18-0.44; 8-10 days, adjusted rate 61.3%,OR 0.51, 95% CI 0.29-0.87; and >10 days, adjusted rate 59.3%,OR 0.49, 95% CI 0.31-0.81) was associated with lower risk of mortality compared with VA-ECMO lasting [?]3 days (adjusted rate 78.3%). Patients requiring VA-ECMO therapy for 8-10 days (OR 1.96, 95% CI 1.15-3.33) and >10 days (OR 1.85, 95% CI 1.14-3.02) had significantly higher mortality compared to those on VA-ECMO for 4-7 days. Conclusions: PCS patients weaned from VA-ECMO after 4 to 7 days of support had significantly lower mortality compared with those with shorter or longer mechanical support.

Introduction

In patients affected by postcardiotomy cardiogenic shock (PCS) following cardiac surgery, the use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has increased steadily in the last decades [1-3]. However, the complications and mortality rates associated with this mechanical support remain high [1-5]. In this context, prolonged VA-ECMO support with the risk of ECMO-induced complications is inversely associated with cardiopulmonary recovery and survival [1,3-5]. However, the optimal duration of VA-ECMO remains controversial, and the available evidence in PCS patients is limited [1,3,4-9]. We report the results of the large multicentre "Postcardiotomy Veno-arterial Extracorporeal Membrane Oxygenation" (PC-ECMO) study, analysing the impact of VA-ECMO duration on hospital mortality and early complications.

Material and Methods

Patient population, Study Design and Outcome Measures

The PC-ECMO registry is a multicenter observational study enrolling patients undergoing VA-ECMO following adult cardiac surgery at 19 centers from Belgium, Czech Republic, Finland, France, Germany, Italy, Saudi Araba, Sweden, and the United Kingdom from January 2010 to March 2018. The present study is registered in Clinicaltrials.gov (Identifier: NCT03508505), and its detailed protocol with definition criteria have been previously published [5]. Briefly, patients aged [?]18 years who required VA-ECMO for PCS following cardiac surgery were included. Exclusion criteria encompassed patients with preoperative VA-ECMO, patients with descending thoracic aorta repair, or those receiving VA-ECMO after implantation of ventricular assist device or heart transplantation. Patients without baseline data on arterial lactate level at the start of VA-ECMO were also excluded from the present analysis because of its impact on patient outcome. The primary end-point was in-hospital mortality. The study complies with the Strengthening the Reporting of Observational Studies in Epidemiology reporting requirements for observational studies (Supplemental Table 1) [10].

Statistical analysis

Statistical analysis was performed using the SPSS statistical software v. 25.0 (IBM Corporation, Armonk, NY, USA), and Stata v. 15.1 (StataCorp LLC, College Station, Texas, USA). Covariates and outcomes were reported as counts and percentages, and as mean and standard deviation or median and interquartile range (IQR). The Kruskal-Wallis test and the linear-by-linear association test were used for univariate analysis. The risk-adjusted mortality rates over different VA-ECMO interval durations were estimated using the direct standardization method employing the*dstdize* module of Stata, and the patient population were stratified according to different duration of VA-ECMO therapy: [?]3 days, 4-7 days, 8-10 days, and >10 days [3,7]. The impact of VA-ECMO duration on hospital mortality was also adjusted for the PC-ECMO score [4], multiple covariates and participating centers in logistic regression analysis. A $P < .05$ was set for statistical significance.

Results

Among the 781 patients of the PC-ECMO registry, 56 patients (7.2%) were excluded from the present analysis because of lack of data on arterial lactate levels before starting VA-ECMO support. A total of 725 patients over 2378 days of VA-ECMO were included in the final analysis. Their mean age was 62.9 ± 12.9 years (range: 18.4-86.7 years), and 232 (32.0%) were female. The mean duration of VA-ECMO was 7.1 ± 6.3 days (median: 5.0 days; range: 0-39 days), and 39.4% patients were supported for [?]3 days, 29.1% for 4-7 days, 15.3% for 8-10 days, and 20.7% for > 10 days (Figure 1). The different groups of VA-ECMO duration exhibited similar baseline, demographic and operative characteristics (Table 1). However, VA-ECMO duration [?]3 days was associated with a higher metabolic derangement, as expressed by the arterial lactate level before VA-ECMO institution (8.2+-5.4 vs 6.5+-4.3 vs 6.1+-4.0 vs 6.1+-4.0, $P < .0001$) (Figure 2).

A total of 391 (53.9%) patients were successfully weaned from VA-ECMO and, among those, 134 (34.3%) died prior to discharge. Hospital survival increased from 8.1% on day 1 to 55% on day 5. Multivariable logistic regression adjusted for the PC-ECMO score and participating centers showed that prolonged duration of VA-ECMO therapy (4-7 days, adjusted rate 53.6%, odds ratio [OR] 0.28, 95% confidence interval [CI] 0.18-0.44; 8-10 days, adjusted rate 61.3%, OR 0.51, 95% CI 0.29-0.87; and >10 days, adjusted rate 59.3%, OR 0.49, 95% CI 0.31-0.81) was associated with a lower risk of mortality compared with VA-ECMO lasting [?]3 days (adjusted rate 78.3%) (Figure 3).

However, patients requiring VA-ECMO therapy for 8-10 days (adjusted OR 1.955, 95% CI 1.149-3.326) and >10 days (adjusted OR 1.854, 95%CI 1.139-3.020) had a significantly increased risk of hospital mortality compared to those who were on VA-ECMO therapy for 4-7 days. In addition, VA-ECMO support longer than 7 days was associated with a significantly increased risk of re-exploration for bleeding, blood transfusion requirements, renal failure requiring renal replacement therapy, deep sternal wound infection, bloodstream infection and pneumonia (Table 2).

Discussion

Our data showed that in patients affected by PCS following cardiac surgery, the duration of VA-ECMO support is associated with increased mortality. Patients weaned from VA-ECMO after 4 to 7 days had significantly lower mortality compared with patients with shorter or longer mechanical support, even when adjusted for confounding. In addition, VA-ECMO support longer than 7 days was associated with a significantly increased risk of complications, including re-exploration for bleeding, blood transfusion, renal failure requiring renal replacement therapy, deep sternal wound infection, bloodstream infection and pneumonia.

Evidence from the Extracorporeal Life Support Organisation (ELSO) registry also showed that short duration of VA-ECMO is associated with high mortality. In this large registry that included 2699 VA-ECMO patients, survival increased up to day 4 and then decreased from day 4 to 12, with no significant change thereafter [1]. However, the study encompassed a mixed cohort of patients with only a minority of them undergone cardiac surgery, a limitation shared with previous studies [1-3,8,9]. On the other hand, the absence of clear guidelines on VA-ECMO weaning is the testament that this aspect is still poorly addressed [1-3]. In addition, data on survival with longer VA-ECMO runs are limited [1,3,4,9]. To our knowledge, the present analysis is the largest to date in evaluating the impact of VA-ECMO duration in adult patients affected by PCS following cardiac surgery. Distelmaier et al. [4] firstly addressed the impact of VA-ECMO duration on survival in 354 cardiovascular surgery patients, observing that longer VA-ECMO runs were associated with higher mortality even 2-years after hospital discharge [4]. More recently, Wang et al. [3] enrolled 166 PCS patients following coronary bypass surgery. More than 60% of patients received VA-ECMO for 3–6 days and had significantly lower mortality than those who were supported by VA-ECMO for < 3 days or [?] 7 days [3].

Our data are consonant with previous studies, suggesting that in PCS patients following cardiac surgery VA-ECMO support longer than 7 days can be challenged, considering the associated early and late higher mortality. In this cohort of patients, the risks of complications appear to overcome the cardiopulmonary advantage exerted by the VA-ECMO support. Bloodstream infections have been demonstrated to be associated with longer VA-ECMO runs, occurring in 27.7% of treated patients [11,12]. Therefore, it is not

surprising that longer VA-ECMO runs are associated with a higher risk of bloodstream infection along with an increased rate of blood transfusions and organ failure [11,12]. Among other complications, administration of large volumes of blood transfusion and renal failure requiring renal replacement therapy are potentially fatal conditions in longer VA-ECMO runs, particularly in PCS patients with an underlying severe cardiac dysfunction [13,14]. Similarly, our data confirmed that shorter VA-ECMO runs ([?]3 days) are also associated with significantly higher mortality. Although we did not detect a higher rate of lethal haemorrhage in this patient group that has been previously suggested as main cause of the increased early mortality [15,16], the underlying primary cardiac condition seemed to play a major role in the survival of those patients [3,17]. Cardiopulmonary failure leading to multiorgan failure appeared to predominate over ECMO treatment. The hyperlactatemia observed in patients under VA-ECMO [?]3 days suggest a significant metabolic derangement in these patients. In this context, arterial lactate level may be useful in guiding the appropriate timing of VA-ECMO discontinuation, thereby avoiding futile prolonged support [19].

The results observed in our series are relevant considering the unsolved issue of balancing a fruitful VA-ECMO duration against a vain support especially in light of the uniquely high level of resources involved [19]. In addition, due to the lack of defined guidelines and indications, the duration of ECMO support is often based on arbitrary limits [1]. Data derived from ELSO registry over a 10-year period indicates that 52% of patients on VA-ECMO are discontinued from support because of irreversible organ failure [1]. Therefore, when cardiopulmonary recovery cannot be successfully achieved within 7 days, other therapeutic options should be considered, including ventricular assist device implantation or heart transplantation [1,7,19].

Certainly, our study is not exempted from limitations. First, our series is subjected to the limitations of all observational analyses, including selection bias and unmeasured confounding. Second, the present analysis is conditional to in-hospital survival only, and our data do not allow an assessment of the outcomes after weaning and discharge from the hospital. Third, a trend in the survival of patients with very long ECMO duration ($>$ 15 days) may not be fully detected due to the small number of remaining individuals, with insufficient statistical power. Lastly, we cannot account for the surgeon and anaesthetist's experience as well as for the differences in local policies of ECMO weaning. Despite these limitations, our cohort is currently the largest in evaluating the impact of VA-ECMO duration in the PCS setting.

In conclusion, in PCS following cardiac surgery, patients weaned from VA-ECMO after 4 to 7 days of support had significantly lower mortality compared with those with shorter or longer mechanical support. The present data can contribute to identifying the most ideal duration of VA-ECMO support, supporting clinicians in deriving more accurate prognostic models and timely weaning strategies.

Disclosures

The investigators have no conflicts of interest to disclose.

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Biancari and Mariscalco, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Baseline and operative data.

Outcomes	**VA-ECMO duration**	**VA-ECMO duration**	**VA-ECMO duration**	**VA-ECMO duration**	**VA-ECMO duration**
	[?]3 days 253 pts	**4-7 days 211 pts**	**8-10 days 111 pts**	**>10 days 150 pts**	***P*-values**
Baseline characteristics	Baseline characteristics	Baseline characteristics	Baseline characteristics	Baseline characteristics	Baseline characteristics

Outcomes	VA-ECMO duration	VA-ECMO duration	VA-ECMO duration	VA-ECMO duration	VA-ECMO duration
Age (years)	64.1±12.3	62.6±13.1	63.3±11.9	61.1±14.2	0.23
Female	82 (32.4)	61 (28.9)	40 (36.0)	49 (32.7)	0.70
Body mass index (kg/m^2)	27±5	27±5	27±5	28±6	0.86
eGFR (mL/min/1.73 m^2)	67±29	70±33	70±31	68±29	0.47
Haemoglobin (g/L)	125±21	126±20	128±25	123±23	0.39
Dialysis	13 (5.2)	8 (3.8)	3 (2.7)	7 (4.7)	0.65
Diabetes	55 (21.7)	46 (21.8)	32 (28.8)	46 (30.7)	0.023
Coronary artery disease	110 (43.5)	97 (46.0)	47 (42.3)	65 (43.3)	0.87
Stroke	21 (8.3)	16 (7.6)	6 (5.4)	11 (7.3)	0.55
Extracardiac arteriopathy	44 (17.4)	38 (18.0)	14 (12.6)	12 (8.0)	0.007
Pulmonary disease	39 (15.4)	28 (13.3)	15 (13.5)	21 (14.0)	0.68
Atrial fibrillation	60 (23.7)	52 (24.6)	31 (27.9)	34 (22.7)	0.97
Prior cardiac surgery	65 (25.7)	44 (20.9)	25 (22.5)	43 (28.7)	0.57
Prior myocardial infarction	79 (31.2)	70 (33.2)	44 (39.6)	53 (35.3)	0.23
LVEF [?]50%	140 (55.3)	129 (61.1)	62 (56.9)	95 (63.3)	0.18
Active endocarditis	36 (14.2)	25 (11.8)	10 (9.0)	12 (8.0)	0.039
Type A aortic dissection	32 (12.6)	10 (4.7)	8 (7.2)	7 (4.7)	0.006
Emergency procedure	77 (30.4)	53 (25.1)	29 (26.1)	43 (28.7)	0.66
Critical preoperative state	84 (33.2)	77 (36.5)	38 (34.2)	59 (39.3)	0.28
Preoperative stroke/unconsciousness	14 (5.5)	5 (2.4)	2 (1.8)	5 (3.3)	0.18
PC-ECMO score[a]	4.5±2.5	3.7±32.4	3.7±2.4	3.6±2.2	<0.0001
EuroSCORE II, score (%)	16.6±18.2	16.4±18.5	11.9±11.9	15.7±17.8	0.48
Operative data	Operative data	Operative data	Operative data	Operative data	Operative data
ACC time (minutes)	140±137	120±73	117± 87	131±86	0.07
CPB time (minutes)	248±133	209±113	192±112	233±123	<0.0001
Coronary surgery	127 (50.2)	101 (47.9)	55 (49.5)	70 (46.7)	0.56

Outcomes	VA-ECMO duration	VA-ECMO duration	VA-ECMO duration	VA-ECMO duration	VA-ECMO duration
Aortic procedures	62 (24.5)	37 (17.5)	18 (16.2)	29 (19.3)	0.15
Aortic valve replacement/repair	76 (30.0)	62 (29.4)	30 (27.0)	39 (26.0)	0.34
Mitral valve surgery	84 (33.2)	83 (39.3)	32 (28.8)	52 (34.7)	0.85
Tricuspid valve surgery	29 (11.5)	26 (12.3)	22 (19.8)	15 (10.0)	0.77
Other major procedures	21 (8.3)	18 (8.5)	11 (9.9)	20 (13.3)	0.10
VA-ECMO inserted immediately after surgery	161 (63.6)	119 (56.4)	68 (61.3)	87 (58.0)	0.36
Central arterial cannulation	84 (33.2)	64 (30.3)	32 (28.8)	43 (28.7)	0.30
Arterial lactate before VA-ECMO, mmol/L	8.2±5.4	6.5±4.3	6.1±4.0	6.1±4.0	<0.0001

Note : Continuous data are presented as mean ± standard deviation; categorical variables as number (percent).

Abbreviations: ACC, aortic cross clamp; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

[a]PC-ECMO score is based on the following risk factors: age (60-69 tears, [?]70 years – points 2 or 4, respectively), female gender (points 1), prior cardiac surgery (points 1), arterial lactate [?]6 mmol/L (points 2), aortic arch surgery (points 4), and preoperative stroke/unconsciousness (points 5) [please see ref. 5].

Table 3. In-hospital outcomes.

Outcomes	VA-ECMO duration	VA-ECMO duration	VA-ECMO duration	VA-ECMO duration	VA-ECMO duration
	[?]3 days 253 pts	**4-7 days 211 pts**	**8-10 days 111 pts**	**>10 days 150 pts**	***P*-values**
Hospital mortality	198 (78.3)	113 (53.6)	68 (61.3)	89 (59.3)	<0.0001
Mortality on VA-ECMO	175 (69.2)	67 (31.8)	43 (38.7)	49 (32.7)	<0.0001
Heart transplantation or VAD	3 (1.2)	7 (3.3)	6 (5.4)	9 (6.0)	0.005
Stroke/global brain ischemia	36 (14.2)	50 (23.8)	27 (24.3)	27 (18.1)	0.22
New dialysis	100 (40.5)	106 (51.0)	68 (61.3)	103 (71.0)	<0.0001

Outcomes	VA-ECMO duration	VA-ECMO duration	VA-ECMO duration	VA-ECMO duration	VA-ECMO duration
Pneumonia	53 (20.9)	77 (36.5)	49 (44.1)	87 (58.0)	<0.0001
Deep sternal wound infection	2 (0.8)	6 (2.8)	3 (2.7)	15 (10.0)	<0.0001
Blood stream infection	35 (13.8)	52 (24.6)	34 (30.6)	54 (36.0)	<0.0001
Reoperation for intrathoracic bleeding/tamponade	95 (37.5)	82 (39.0)	48 (43.2)	82 (54.7)	<0.0001
RBC transfusion > 10 units	158 (62.5)	139 (65.9)	77 (69.4)	121 (80.7)	<0.0001
RBC units transfused (units)	16.6±14.9	21.0±21.0	22.6± 18.5	34.4±27.9	<0.0001
Intensive care unit stay (days)	7.1±10.8	19.5±20.4	21.3±19.3	28.4±17.7	<0.0001
Hospital stay (days)	9.3±13.5	30.0±32.4	32.6±37.2	40.6±38.9	<0.0001

Note : Continuous data are presented as mean ± standard deviation; categorical variables as number (percent).

Abbreviations: RBC, red blood cell; VAD, ventricular assist device; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

Figure legend

Figure 1. Number of patients who died and survived to hospital discharge according to the duration of postcardiotomy VA-ECMO.

Figure 2. Medial lactate level at the start, during and at weaning from VA-ECMO. P -values are from Kruskal-Wallis' test. Data is from 409 patients with complete data on arterial lactate.

Figure 3. Risk-adjusted hospital and on VA-ECMO mortality rates according to the duration of postcardiotomy VA-ECMO.

Supplemental Table I. STROBE Statement for observational studies.

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title o (*b*) Provide in the abstract an informative and balanced summary of wh
Introduction	*Introduction*	*Introduction*
Background/rationale	2	Explain the scientific background and rationale for the investigation bei
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods	*Methods*	*Methods*
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of

	Item No	Recommendation
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If appl
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for c
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of samplin
		(*e*) Describe any sensitivity analyses
Results	*Results*	*Results*
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers p
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, s
		(b) Indicate number of participants with missing data for each variable
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted es
		(*b*) Report category boundaries when continuous variables were categori
		(*c*) If relevant, consider translating estimates of relative risk into absolu
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions
Discussion	*Discussion*	*Discussion*
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential
Interpretation	20	Give a cautious overall interpretation of results considering objectives, li
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information	*Other information*	*Other information*
Funding	22	Give the source of funding and the role of the funders for the present stu