Venoarterial extracorporeal membrane oxygenation for postcardiotomy shock: Risk factors for mortality

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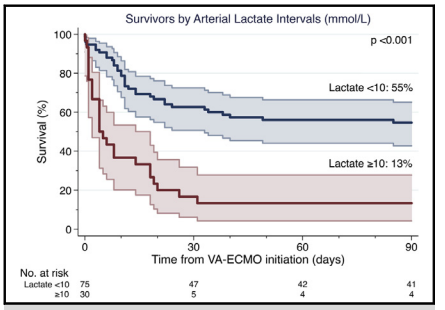
ABSTRACT

Objectives: Refractory postcardiotomy cardiogenic shock is associated with a high mortality, and venoarterial extracorporeal membrane oxygenation can offer acute cardiopulmonary life support. The aim of this study was to identify pre–venoarterial extracorporeal membrane oxygenation risk factors of 90-day mortality.

Methods: We retrospectively analyzed 105 consecutive patients supported with venoarterial extracorporeal membrane oxygenation due to refractory postcardiotomy cardiogenic shock. The association between preimplant variables and all-cause mortality at 90 days was analyzed with univariable and multivariable logistic regression.

Results: Main surgical subgroups were single noncoronary artery bypass grafting (29%), isolated coronary artery bypass grafting (20%), and 2 and 3 concomitant surgical procedures (31% and 20%, respectively). The median age of patients was 62 years (interquartile range, 52-68 years), and 76% were men. Cardiopulmonary resuscitation was performed in 30% of patients before venoarterial extracorporeal membrane oxygenation initiation. The median duration of venoarterial extracorporeal membrane oxygenation was 7 days (interquartile range, 3-14). The 90-day overall mortality was 57%, and in-hospital mortality was 56%. Forty-seven percent of patients died on venoarterial extracorporeal membrane oxygenation, 51% of patients were successfully weaned, 1% of patients were bridged to heart transplantation, and 1% of patients were bridged to left ventricular assist device. Multivariable logistic regression analysis identified arterial lactate (odds ratio per unit, 1.22; 95% confidence interval, 1.07-14.0; $P = .004$) and ischemic heart disease (odds ratio, 7.87; 95% confidence interval, 2.55-24.3; $P < .001$) as independent risk factors of 90-day mortality.

Conclusions: In patients with postcardiotomy cardiogenic shock, ischemic heart disease and level of arterial lactate before venoarterial extracorporeal membrane oxygenation initiation were identified as independent pre–venoarterial extracorporeal membrane oxygenation risk factors of 90-day mortality. These risk factors are easily available for pre–venoarterial extracorporeal membrane oxygenation risk prediction and may improve patient selection for this resource-intensive therapy. (J Thorac Cardiovasc Surg 2018;156:1894-902)



The 90-day survival in patients with PCS related to lactate intervals at initiation of VA-ECMO.

Central Message

In patients with refractory PCS, lactate and IHD were independent predictors of 90-day mortality after initiation of VA-ECMO, whereas age, type of surgery, EuroSCORE II, CBP duration, or AMI were not.

Perspective

VA-ECMO offers reasonable 90-day survival in selected patients with refractory PCS and should be initiated before profound hyperlactatemia occurs, especially in patients with IHD. The correlation between duration of VA-ECMO and in-hospital mortality indicates that weaning should be individualized and delayed until cardiopulmonary parameters are fully optimized.

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Abbreviations and Acronyms

AIC = Akaike information criterion
AMI = acute myocardial infarction
BIC = Bayesian information criterion
CABG = coronary artery bypass grafting
CPB = cardiopulmonary bypass
euroSCORE = European System for Cardiac Operative Risk Evaluation
IHD = ischemic heart disease
IQR = interquartile range
OR = odds ratio
PCS = postcardiotomy cardiogenic shock
RPCS = refractory postcardiotomy cardiogenic shock
VAD = ventricular assist device
VA-ECMO = venoarterial extracorporeal membrane oxygenation

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Postcardiotomy cardiogenic shock (PCS), defined as low cardiac output syndrome with evidence of tissue hypoperfusion and end-organ dysfunction despite adequate preload, affects 0.2% to 6% of patients who undergo cardiothoracic surgery.[1-3] PCS is a life-threatening complication with mortality rates between 50% and 80%[4-6] and includes the inability to wean from cardiopulmonary bypass (CPB) in the operating room or deterioration of myocardial function during the first postoperative days. Between 70% and 90% of the patients who cannot be easily separated from CPB because of PCS can be weaned from CPB by support of inotropes, vasopressors, and intra-aortic balloon pumps, and an estimated two thirds of these patients will recover hemodynamically without the need for other mechanical circulatory support.[7,8] In comparison, PCS refractory to intravascular volume loading, pharmacologic, and intra-aortic balloon pump support occurs postoperatively in 0.5% to 1.5%[7] of patients and will inexorably lead to death unless more efficient circulatory support is initiated.

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) can temporarily provide partial or complete cardiopulmonary support in patients with refractory PCS (RPCS) as a bridge to myocardial recovery, heart transplantation, long-term ventricular assist device (VAD), or other interventions.[9-11] VA-ECMO is initiated in 0.6% to 2.9% of patients after routine cardiothoracic surgery.[11-18] Despite VA-ECMO support, the in-hospital mortality rate is 53% to 84%[6,18-22] and is influenced by patient characteristics and surgical case mix.[11,13,16] Previous studies have focused on a combination of preoperative, surgical, and on–VA-ECMO (ie, during support) variables to identify risk factors for mortality.[12-14,16-18,23,24] However, it is problematic to include on–VA-ECMO factors if the specific aim is to identify preimplant risk factors to facilitate early risk prediction to better use and prioritize this technique for appropriate patients with RPCS. Thus, the aim was to identify independent pre–VA-ECMO risk factors for 90-day mortality in an unselected population with RPCS supported by VA-ECMO.

MATERIALS AND METHODS

Study Population

We retrospectively reviewed the medical records of 105 consecutive patients who received VA-ECMO support for RPCS between September 2006 and April 2015 at our institution. The Regional Ethics Review Board approved this study (Project No. 2008/1695-31 and 2012/119-32). There are no universal criteria or specific indications for initiation of VA-ECMO support in RPCS. Our unit considers VA-ECMO as a salvage therapy due to inability to wean from CPB or the development of poor hemodynamics and evidence of persistent tissue hypoperfusion in the early postoperative period, despite adequate intravascular volume loading and pharmacologic support, when there is potential for recovery, heart transplantation, or left VAD implantation. No short-term VADs were used for RPCS during the period of this study because the likelihood of death was considered extremely high without VA-ECMO providing sufficient biventricular support. The VA-ECMO circuit, implantation technique, and patient management during VA-ECMO are not the scope of this study and have been described.[9,10,24]

Data Collection

The patients were included in the study irrespective of locality or timing of VA-ECMO initiation, that is, intraoperatively or postoperatively in the intensive care unit. Patients' characteristics, surgical procedure, and clinical and laboratory data at VA-ECMO initiation (ie, just before cannulation) were together with complications and outcome data obtained from the medical records. Patients were subdivided into 4 mutually exclusive cardiac surgical subgroups according to the European System for Cardiac Operative Risk Evaluation (euroSCORE) II classification: single noncoronary artery bypass grafting (non-CABG), isolated CABG, and 2 and 3 concomitant surgical procedures. Type of cannulation and complications were presented for descriptive purposes but not included in the statistical analysis because they were not pre–VA-ECMO factors.

Baseline Definitions

Ischemic heart disease (IHD) was defined as a history of myocardial infarction, angina pectoris, percutaneous coronary intervention/CABG, or when prior coronary angiography had shown evidence of coronary artery disease according to multidisciplinary conferences, chronic renal failure as the estimated preoperative glomerular filtration rate of less than 60 mL/min/1.73 m^2 present for more than 3 months (in accordance with the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines 2012), number of inotropes and vasopressors as the total number of intravenous inotropes and vasopressors (epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, levosimendan), pre–VA-ECMO data as the latest clinical

and laboratory data just before VA-ECMO cannulation, and data defined "prior" refers to data previous to the current medical event/admission. Cardiopulmonary resuscitation included all cardiopulmonary resuscitation episodes from the time of the current hospital admission: preoperative (before CPB) and postoperative until initiation of VA-ECMO.

Statistical Analysis

The descriptive analysis compared pre–VA-ECMO variables between survivors and nonsurvivors at 90 days after VA-ECMO initiation. Categoric variables were presented as numbers and percentages, and compared with the chi-square, likelihood ratio, or Fisher exact tests. Non-normally distributed continuous variables were expressed as median and interquartile range (IQR), and compared with the Mann–Whitney *U* test. Logistic regression was used to assess the impact of pre–VA-ECMO variables on likelihood for death at 90 days after VA-ECMO initiation. Variables identified as being significant in the univariable analysis were subjected to multicollinearity analysis by using the Spearman rho correlation coefficient before multivariable logistic regression analysis. Five variables, none with missing data, were included in the multivariable logistic regression model to determine the independent associations between pre–VA-ECMO implant variables and 90-day mortality. To assess the impact of nonlinearity on the logistic regression analysis, the continuous variables included in the model were transformed by using restricted cubic splines with both 3 and 4 knots (default placements). Logistic regression was subsequently performed with the categoric variables included in the 2 spline models with 3 and 4 knots, respectively. The acquired Akaike information criterion (AIC) and Bayesian information criterion (BIC) values were then compared with the corresponding AIC and BIC values of the original model. Goodness of fit was verified by the Hosmer–Lemeshow test. Cumulative survival curves for 90-day follow-up were generated using the Kaplan–Meier method, and arbitrary chosen subgroups were compared using the log-rank test. All statistical analyses were performed with SPSS version 23 for Windows (IBM SPSS Statistics, New York, NY).

RESULTS

No patients were lost to follow-up, and there were no VA-ECMO device-related deaths. Pre–VA-ECMO variables and comparison between survivors and nonsurvivors at 90 days after VA-ECMO initiation are summarized in Table 1. Median age was 62 years (IQR, 52-68), which was significantly lower in survivors (60 years; IQR, 49-66) compared with nonsurvivors (65 years; IQR, 54-69; $P = .017$). Of the surgical subgroups, only isolated CABG differed significantly between survivors and nonsurvivors, with a 90-day mortality of 86%. Acute myocardial infarction (AMI) and IHD were present in 27% and 57% of the patients with an 82% and 77% 90-day mortality, respectively. Median left ventricular ejection fraction, mean arterial pressure, and arterial pH just before cannulation were significantly lower among nonsurvivors compared with survivors, whereas the inverse relationship was significant for age, euroSCORE II, prior CABG, arterial lactate, alanine aminotransferase, and total number of inotropes and vasopressors (epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, levosimendan).

Eight variables were found significantly associated with 90-day mortality by univariable logistic regression: age, isolated CABG, AMI, IHD, left ventricular ejection fraction, mean arterial pressure, arterial pH, and lactate (Table E1). There were strong correlations between arterial pH and lactate (rho $= -0.713$; $P < .001$), AMI and IHD (rho $= 0.522$; $P < .001$), CABG and IHD (rho $= 0.433$; $P < .001$), and CABG and AMI (rho $= 0.829$; $P < .001$), respectively. Arterial pH, AMI, and CABG, the latter 2 being included in the variable IHD, were all 3 excluded from the model, leaving 5 variables in the model (Table 2). We favored exclusion of pH and not lactate, because the latter is a more robust variable less sensitive to the influence of $PaC0_2$ and administration of buffer solutions in the acute setting.

When assessing AIC, our original model had a value of 102, compared with 105 (3 knots) and 104 (4 knots). The corresponding BIC values were 118, 131 (3 knots), and 141 (4 knots), respectively. Because of similar values in both AIC and BIC, the approach of nonlinearity through splines did not seem to affect the logistic regression analysis in a problematic way, which supports the use of the model without transformations and facilitates clinical interpretation. The model was statistically significant, chi-square $(5, n = 105) = 52.911$; $P < .001$, indicating that the model was able to distinguish between survivors and nonsurvivors at 90 days. Chi-square for Hosmer–Lemeshow test was 2.952 with a significance level of P of .937, thereby further supporting that the overall fit of the model was good. The model as a whole explained between 39.6% (Cox and Snell R^2) and 53.1% (Nagelkerke R^2) of the variance of 90-day mortality and overall correctly classified 80.0% of the cases. The sensitivity of the model was 85% (true positives) and specificity was 73.3% (true negatives), giving positive and negative predictive values of 81% and 79%, respectively.

In multivariable logistic regression, only 2 of the independent variables made a unique statistical significant contribution to the model (Table 2). The most significant risk factor being presence of IHD (odds ratio [OR], 7.87; 95% confidence interval, 2.55-24.3; $P < .001$), followed by arterial lactate (OR per mmol/L increase: 1.22; 95% confidence interval, 1.07-1.40, $P = .004$). Outcome data including events after initiation of VA-ECMO and causes of death within 90 days are presented in Table 3. The median duration of VA-ECMO was 7 days (IQR, 3-14). Death during VA-ECMO occurred in 47% (n = 49) of the patients, 51% (n = 54) were successfully weaned, 2% (n = 2) did not tolerate weaning, 1% (n = 1) were bridged to heart transplantation, and 1% (n = 1) were bridged to left VAD. The in-hospital mortality was 56% (n = 59), and 44% (n = 46) were discharged home. The median number of days from initiation of VA-ECMO to discharge home was 64 (IQR, 41-105; range 13-212). The primary end point overall 90-day mortality after initiation of VA-ECMO was 57% (n = 60). The overall mortality at 24, 48, and 72 hours,

TABLE 1. Comparison of pre–venoarterial extracorporeal membrane oxygenation characteristics between survivors and nonsurvivors at 90 days after venoarterial extracorporeal membrane oxygenation initiation

Pre–VA-ECMO characteristics	MD (%)	All patients (n = 105)	Survivors (n = 45)	Nonsurvivors (n = 60)	*P* value
Male gender	0	80 (76)	33 (41)	47 (59)	.552
Age (y)	0	62 (52-68; 18-77)	60 (49-66; 18-72)	65 (54-69; 23-77)	**.017**
≥65 (y)	0	42 (40)	13 (31)	29 (69)	**.044**
Weight (kg)	0	80 (72-93; 45-143)	84 (74-93; 45-143)	78 (72-94; 56-130)	.441
BMI (kg/m^2)	0	26.2 (23.7-29.8)	26.5 (23.6-30.2)	25.9 (23.7-29.5)	.669
euroSCORE II score	0	7.32 (2.82-25.03; 0.62-77.53)	4.82 (2.19-21.97; 0.62-43.52)	10.04 (3.53-28.43; 0.92-78.53)	**.046**
euroSCORE II critical preoperative state	0	38 (36)	16 (42)	22 (58)	.907
euroSCORE II type of cardiac surgical subgroup					
Single non-CABG	0	30 (29)	16 (53)	14 (47)	.170
Isolated CABG	0	21 (20)	3 (14)	18 (86)	**.003**
2 procedures*	0	33 (31)	16 (49)	17 (51)	.582
3 procedures*	0	21 (20)	10 (48)	11 (52)	.622
euroSCORE II urgency of surgery					
Elective	0	48 (46)	25 (52)	23 (48)	.080
Urgent	0	19 (18)	8 (42)	11 (58)	.942
Emergency	0	27 (26)	9 (33)	18 (67)	.246
Salvage	0	11 (11)	3 (27)	8 (73)	.345
Type of cardioplegia					
No cardioplegia	0	14 (13)	7 (50)	7 (50)	.562
Antegrade cardioplegia	0	43 (41)	17 (40)	26 (60)	.817
Antegrade + retrograde cardioplegia	0	43 (41)	19 (44)	24 (56)	.819
Retrograde cardioplegia	0	5 (4.8)	2 (40)	3 (60)	1.00
Crossclamp time (min)	2.9	122 (59-198; 21-359)	136 (84-201; 24-359)	98 (55-193; 21-291)	.162
CPB time (min)	2.9	222 (172-283; 35-568)	217 (185-275; 35-556)	227 (167-287; 81-568)	.869
From CPB direct to VA-ECMO in the OR	0	51 (49)	21 (41)	30 (59)	.735
AMI	0	28 (27)	5 (18)	23 (82)	**.002**
IHD	0	60 (57)	14 (23)	46 (77)	**<.001**
Smoking	0	54 (51)	20 (37)	34 (63)	.215
Hypertension	0	51 (49)	20 (39)	31 (61)	.464
Valvular heart disease	0	72 (69)	34 (47)	38 (53)	.182
Congestive heart failure	0	32 (31)	14 (44)	18 (56)	.903
Diabetes mellitus	0	17 (16)	5 (29)	12 (71)	.221
Atrial fibrillation	0	26 (25)	9 (35)	17 (65)	.328
Dyslipidemia	0	36 (34)	13 (36)	23 (64)	.313
Prior myocardial infarction†	0	20 (19)	6 (30)	14 (70)	.197
Prior PCI†	0	11 (10)	3 (27)	8 (73)	.345
Prior cardiac surgery†	0	28 (27)	10 (36)	18 (64)	.372
Prior CABG†	0	12 (11)	2 (17)	10 (83)	**.040**
Renal failure	0	14 (13)	4 (29)	10 (71)	.246
Hypertrophic cardiomyopathy	0	14 (13)	4 (29)	10 (71)	.246
Endocarditis	0	8 (7.6)	5 (62)	3 (38)	.243
Primary graft failure after HTX	0	7 (6.7)	4 (57)	3 (43)	.232
Acute pulmonary embolism	0	2 (1.9)	1 (50)	1 (50)	1.00

(Continued)

TABLE 1. Continued

Pre–VA-ECMO characteristics	MD (%)	All patients (n = 105)	Survivors (n = 45)	Nonsurvivors (n = 60)	*P* value
LVEF (%)‡	0	25 (13-50)	33 (18-55)	15 (0-29)	**<.001**
<20 (%)	0	50 (48)	12 (24)	38 (76)	**<.001**
MAP (mm Hg)‡	0	50 (40-64)	60 (49-68)	47 (40-60)	**.001**
<50 (mm Hg)	0	44 (42)	11 (25)	33 (75)	**.002**
Arterial pH‡	0	7.26 (7.13-7.32; 6.75-7.49)	7.29 (7.18-7.35; 6.84-7.46)	7.22 (7.09-7.31; 6.75-7.49)	**.009**
Arterial lactate (mmol/L)‡	0	7.0 (3.2-11.5; 0.7-28.0)	4.0 (2.0-8.6; 0.7-14.7)	8.0 (5.4-14.9; 0.7-28.0)	**<.001**
<5 (mmol/L)	0	39 (37)	25 (64)	14 (36)	–
5-9.9 (mmol/L)	0	36 (34)	16 (44)	20 (56)	–
10-14.9 (mmol/L)	0	16 (15)	4 (25)	12 (75)	–
≥15 (mmol/L)	0	14 (13)	0 (0)	14 (100)	**<.001**
Hemoglobin (g/L)‡		93 (86-106)	94 (85-109)	93 (86-104)	.964
WBC (10^9/L)	0	10.8 (7.2-15.7)	10.4 (7.2-16.7)	11.2 (7.2-14.8)	.568
Platelets (10^9/L)	0	161 (95-234)	157 (108-228)	161 (87-240)	.991
Creatinine (μmol/L)	0	120 (92-169)	110 (79-159)	124 (95-189)	.103
GFR MDRD (mL/min/1.73 m^2)	0	55 (37-73)	62 (41-89)	53 (33-70)	.074
ALT (μkat/L)	5.7	0.82 (0.40-2.11)	0.69 (0.34-1.32)	1.06 (0.54-2.80)	**.041**
Pre–VA-ECMO interventions					
Acute PCI	0	7 (6.7)	2 (29)	5 (71)	.696
Hemodialysis	0	24 (23)	10 (42)	14 (58)	.893
CPR	0	31 (30)	12 (39)	19 (61)	.578
Intra-aortic balloon pump	0	5 (4.8)	1 (20)	4 (80)	.389
No. of inotropes and vasopressors§	0	3 (2-4)	2 (2-3)	3 (2-4)	**.046**
Retrieval from external hospital	0	24 (23)	8 (33)	16 (67)	.283
VA-ECMO insertion period					
2006-2010	0	55 (52)	19 (35)	36 (65)	–
2011-2015	0	50 (48)	26 (52)	24 (48)	.071

Bold indicates statistical significance. Categoric variables are presented as n (%) and compared with the chi-square, likelihood ratio, or Fisher exact test. Continuous variables are presented as median (IQR; range) and compared with the Mann–Whitney *U* test. *VA-ECMO*, Venoarterial extracorporeal membrane oxygenation; *MD*, missing data; *BMI*, body mass index; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *CABG*, coronary artery bypass grafting; *CPB*, cardiopulmonary bypass; *OR*, operating room; *AMI*, acute myocardial infarction; *IHD*, ischemic heart disease; *PCI*, percutaneous coronary intervention; *HTX*, heart transplantation; *LVEF*, left ventricular ejection fraction; *MAP*, mean arterial pressure; *WBC*, white blood cell count; *GFR MDRD*, glomerular filtration rate modification of diet in renal disease; *ALT*, alanine aminotransferase; *CPR*, cardiopulmonary resuscitation. *Number of surgical interventions on the heart (euroSCORE II classification). †Before current medical event/admission. ‡Just before cannulation. §Epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, and levosimendan.

and 7 and 30 days were 11%, 11%, 15%, 25%, and 51%, respectively. Multiple organ failure was the main cause of death both on VA-ECMO (49%, 24 of 49 deaths) and within 90 days after its initiation (59%, 29 of 49 deaths).

The main complications after VA-ECMO initiation are provided in Figure E1, with the most frequent being renal failure necessitating hemodialysis (70%), reexploration (68%), pneumonia (61%), sepsis (24%), and ischemic stroke (16%). In patients with peripheral (76%, n = 80) and central cannulation (24%, n = 25), the 90-day mortality was 51% and 76%, respectively. Distal perfusion catheter was used in 90% (n = 72) of patients with peripheral

TABLE 2. Factors associated with mortality within 90 days after venoarterial extracorporeal membrane oxygenation initiation

Variables	MD (%)	Univariable logistic regression		Multivariable logistic regression	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (y)	0	1.04 (1.01-1.07)	**.017**	1.04 (0.99-1.09)	.058
IHD	0	7.28 (3.05-17.4)	**<.001**	7.87 (2.55-24.3)	**<.001**
LVEF (%)*	0	0.96 (0.94-0.98)	**<.001**	0.98 (0.95-1.01)	.112
MAP (mm Hg)*	0	0.96 (0.94-0.99)	**.007**	0.98 (0.95-1.04)	.243
Arterial lactate (mmol/L)*	0	1.21 (1.10-1.33)	**<.001**	1.22 (1.07-1.40)	**.004**

Bold indicates statistical significance. *MD*, Missing data; *OR*, odds ratio; *CI*, confidence interval; *IHD*, ischemic heart disease; *LVEF*, left ventricular ejection fraction; *MAP*, mean arterial pressure. *Just before cannulation.

TABLE 3. Outcomes

Variables	MD (%)	All patients (n = 105)
VA-ECMO duration		
Days	0	7 (3-14; 1-55)
Single non-CABG (n = 30)	0	8 (4-25)
Isolated CABG (n = 21)	0	6 (2-11)
2 procedures* (n = 33)	0	9 (5-17)
3 procedures* (n = 21)	0	5 (3-11)
VA-ECMO destination		
Death during VA- ECMO	0	49 (47)
Successful weaning	0	54 (51)
VA-ECMO to heart transplantation	0	1 (1.0)
VA-ECMO to LVAD	0	1 (1.0)
90-d mortality	0	60 (57)
Single non-CABG (n = 30)	0	14 (47)
Isolated CABG (n = 21)	0	18 (86)
2 procedures* (n = 33)	0	17 (52)
3 procedures* (n = 21)	0	11 (52)
In-hospital mortality	0	59 (56)
Single non-CABG (n = 30)	0	13 (43)
Isolated CABG (n = 21)	0	18 (86)
2 procedures* (n = 33)	0	17 (52)
3 procedures* (n = 21)	0	11 (52)
Discharge to home	0	46 (44)
Single non-CABG (n = 30)	0	17 (57)
Isolated CABG (n = 21)	0	3 (14)
2 procedures* (n = 33)	0	16 (49)
3 procedures* (n = 21)	0	10 (48)
Days from VA-ECMO initiation to discharge home	0	64 (41-105; 13-212)
CPC score at discharge to home	0	46 (44)
CPC 1-2	0	46 (100)
CPC 3-4	0	0 (0)
Main cause of death during VA-ECMO	0	49 (47)
Multiple organ failure	0	24 (23)
Neurologic†	0	9 (8,6)
Cardiac‡	0	7 (6.7)
Bleeding§	0	7 (6.7)
Miscellaneous‖	0	2 (1.9)
Main cause of death within 90 d	0	60 (57)
Multiple organ failure	0	29 (28)
Neurologic†	0	12 (11)
Cardiac‡	0	8 (7.6)
Bleeding§	0	7 (6.7)
Miscellaneous‖,¶	0	4 (3.8)

Categoric and continuous variables are presented as n (%) and median (IQR); range), respectively. *MD*, Missing data; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation; *CABG*, coronary artery bypass grafting; *LVAD*, left ventricular assist device; *CPC*, cerebral performance category. *Number of surgical interventions on the heart (euroSCORE II classification). †Stroke, fatal anoxia, brain death. ‡Sudden cardiac arrest, arrhythmia, myocardial infarction, heart failure. §Lung, gastrointestinal, and retroperitoneal bleeding. ‖Iatrogenic air entry into the ECMO circuit (n = 1), aortic dissection at cannulation (n = 1). ¶Massive pulmonary embolus (n = 1), pulmonary embolus, and ischemic colitis (n = 1).

cannulation. Figure 1, *A*, depicts the cumulative Kaplan–Meier survival curves until 90 days after initiation of VA-ECMO related to arterial lactate intervals, indicating that an arterial lactate level 10 mmol/L or greater (90.1 mg/dL) had severely worse outcome ($P < .001$). All patients with an arterial lactate level 15 mmol/L or greater (135 mg/dL) died within 20 days after VA-ECMO initiation. There was a significant difference in the cumulative 90-day survival between patients with and without IHD, 23% and 69%, respectively ($P < .001$) (Figure 1, *B*).

Of the 4 euroSCORE II cardiac surgical subgroups, isolated CABG, even if not being an independent risk factor of 90-day mortality, had the worst prognosis with a sharp decrease in survival during the first 15 days, after which survival leveled out to 14% at 90 days after VA-ECMO initiation ($P < .001$). In contrast, the other 3 cardiac surgical subgroups, single non-CABG and 2 and 3 concomitant surgical procedures had a 90-day survival of approximately 50%.

DISCUSSION

The main finding of this study was the identification of 2 independent pre–VA-ECMO risk factors for 90-day mortality in patients with RPCS, arterial lactate level, and IHD (Video 1). Furthermore, the 90-day and in-hospital mortality rates were 57% and 56%, respectively, the latter being one of the lowest rates reported in unselected patients with RPCS.

Previous outcome studies have not focused specifically on pre–VA-ECMO risk factors for outcome, but rather on a combination of preoperative, surgical, and on–VA-ECMO (ie, during support) factors. However, to include on–VA-ECMO factors (ie, after cannulation) will obviously be problematic when the aim is to predict outcome at initiation of VA-ECMO (ie, just before cannulation). Furthermore, to focus merely on preoperative and intraoperative factors may be suitable only in patients who cannot be weaned from CPB, that is, bridged directly from CPB to VA-ECMO, because 11% to 65% of patients[11,13,14,16,17,24] were weaned from CPB and transferred to the intensive care unit before VA-ECMO was initiated because of hemodynamic deterioration after a varying number of hours or days.[11,13,14,16,17,23]

In the largest single-center study involving 517 patients with RPCS by Rastan and colleagues,[13] only 40% were bridged directly from CPB to VA-ECMO. Numerous preoperative, surgical, and on–VA-ECMO factors were analyzed, whereby several independent risk factors for in-hospital mortality were identified. However, factors between weaning from CPB and start of VA-ECMO in the patients weaned from CPB were not included in their analysis, thereby blinding identification of specifically pre–VA-ECMO risk factors

in the majority (60%) of patients. Likewise, the second largest single-center study by Papadopoulos and colleagues,[25] including 360 patients with PCS, identified 7 independent risk factors for in-hospital mortality, although type of cannulation, an on–VA-ECMO risk factor, was included in their analysis. Consequently, in addition to preoperative and surgical factors, we retrospectively identified several complementary variables after surgery until the start of VA-ECMO. To our knowledge, our study is the first to specifically focus on identifying pre–VA-ECMO risk factors for 90-day mortality in an unselected patient population with RPCS.

We identified 2 significant independent risk factors associated with 90-day mortality. First, lactate had an OR of 1.22 per mmol/L, implying progressively worse outcomes with increasing lactate levels. High lactate levels at the end of cardiac surgery due to an imbalance between oxygen demand and supply ultimately leading to tissue hypoxia and organ failure have been described as an independent risk factor of negative outcome after cardiac surgery.[26-28] The physiologic background is that lactate is a metabolic end product of anaerobic glycolysis, which is produced by the reduction of pyruvate and primarily removed by the liver. Lactate is considered to be a marker of tissue perfusion, which is affected by both macro- and microcirculation, whereas routine hemodynamic parameters have been suggested to be unreliable. On the basis of our daily practice, we divided the study population into 4 chosen subgroups of lactate with arbitrary cutoff levels of less than 5 mmol/L, 5 to 9.9 mmol/L, 10 to 14.9 mmol/L, and 15 mmol/L or greater (Table 1) to facilitate clinical interpretation of lactate as a strong and significant risk factor. In addition, the cutoff level of 10 or greater was chosen (Figure 1) because it corresponded to a specificity of 91% (receiver operating characteristic survival of 9%), implying that a lactate level of 10 identified more than 90% of the patients who died in our study population. A cutoff level of 15 mmol/L would have identified 100% of nonsurvivors and at the same time raised the question if ECMO out of ethical reasons should be offered to patients with an approximately 100% expected mortality. Moreover, our finding of arterial lactate as an independent pre–VA-ECMO risk factor of mortality after cardiac surgery is compatible with the findings of Park and colleagues,[14,29] who in 2 studies including 115 and 93 patients, respectively, identified blood lactate before initiation of extracorporeal life support (ie, VA-ECMO) as an independent risk factor of in-hospital mortality (OR per unit lactate, 1.19 and 1.13, respectively). Likewise, Papadopoulos and colleagues[25] found that a pre–VA-ECMO serum lactate level of greater than 120 mg/dL (>13.3 mmol/L) adversely affected in-hospital survival (OR, 2.6), as did Rastan and colleagues,[13] who found that a lactate level greater than 4 mmol/L in the operating room and greater than 10 mmol/L immediately after VA-ECMO initiation were significant risk factors of in-hospital mortality (OR, 2.21 and 2.65, respectively). Furthermore, an important feature that strengthens the impact of arterial lactate as a risk factor was that we were able to identify specific intervals of arterial lactate indicating progressively worse outcomes as illustrated in Figure 1, *A*, and Table 1, which to our knowledge is the first time to be reported in RPCS in a pre–VA-ECMO setting.

The second independent risk factor, IHD, was the only organ-specific risk factor of mortality, which is supported by previous studies indicating that patients with IHD have worse expected outcome compared with patients without IHD[11,30] (Figure 1, *B*). Obviously, all patients who received planned CABG had IHD. These factors were highly correlated in the multicollinearity analysis. However, not all patients with IHD received grafts unless there was significant and graftable stenosis, whereby IHD had a higher prevalence than CABG. Thus, we kept IHD and excluded CABG from the model. In addition to the significant correlation between IHD and CABG, AMI correlated significantly with IHD and was removed from the model, besides being included in the definition of IHD. Our analysis further demonstrated that none of the 4 euroSCORE II cardiac surgical subgroups, cardioplegic route, or time

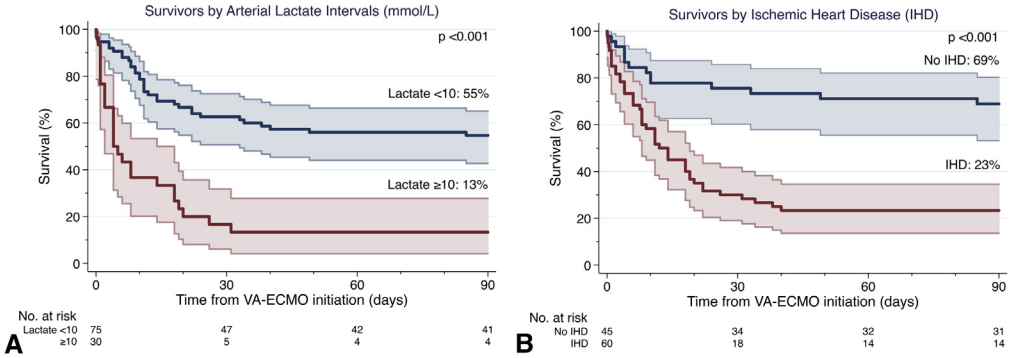

FIGURE 1. Kaplan–Meier survival curves until 90 days after initiation of VA-ECMO support related to (A) arterial lactate intervals and (B) presence of IHD, with 95% confidence intervals, at initiation of VA-ECMO in 105 patients with RPCS. *VA-ECMO*, Venoarterial extracorporeal membrane oxygenation.

VIDEO 1. A video of Matthias Corbascio, MD, PhD, one of the authors, explaining the importance and relevance of the article for the readers of the *Journal*. Video available at: https://www.jtcvs.org/article/S0022-5223(18)31487-9/fulltext.

on CPB independently predicted 90-day mortality (Table E1), although isolated CABG had a significantly worse outcome at 90 days compared with the other surgical subgroups (Table 1). Thus, the extent of tissue hypoperfusion in RPCS, as indicated by lactate levels and the presence of IHD, appeared to be more important than other variables that otherwise affect postoperative outcomes, such as patient characteristics, comorbidities, type of surgical procedure, cardioplegic route, aortic crossclamp, and CPB time. In contrast to several other studies,[11-14,16,17,21,24,25,31] age did not reach significance in our multivariable analysis. This could be a type II error, but more likely suggests that in previous less-adjusted analyses age was important, whereas in our analysis, age was neutralized by the many other covariates in the model and risk more directly reflected by severity of hypoperfusion and thus lactate increase.

Our primary end point mortality within 90 days after VA-ECMO initiation was chosen over 30-day mortality because 6.7% of the patients (7/105) had VA-ECMO support 30 days or more (up to 55 days). Also, the Kaplan–Meier survival curves flattened out before reaching 90 days, indicating that an extension beyond 90 days would not add further clarity to midterm outcome. Given the nonproportional hazards with early high risk, we preferred logistic regression for categoric vital status at 90 days rather than Cox regression for time-dependent outcomes analyses. Moreover, we preferred the outcome variable mortality at 90 days to the alternative alive at hospital discharge because the former includes a specific time span and not a subjectively decided point of time for discharge from the hospital.

Our in-hospital mortality rate was 56%, which to our knowledge is one of the lowest single-center mortality rates reported in an unselected population with RPCS supported with VA-ECMO. In comparison, previous studies have reported in-hospital mortality rates of 53.4% to 76.3%.[11,13,19,25] Our incidence of postcardiotomy VA-ECMO was 1.3%, which is in the midrange of other reported studies (0.6%-2.9%) and almost equal to the large studies by Rastan and colleagues,[13] 1.3%, and Doll and colleagues,[11] 1.2%. Nonetheless, outcomes are overall poor, which highlights the need to rigorously identify risk factors and develop tools to optimize selection of appropriate patients with RPCS who profit from VA-ECMO.

We successfully weaned 51% of our patients from VA-ECMO compared with between 31% and 63.5% in previous studies.[11,13,21,25] However, comparisons of studies are challenging because of nonreporting of data and lack of a clear definition over what is to be regarded as successful in terms of survival time after weaning.[13,24] Besides comparing patient characteristics, weaning, and bridging rates, the reported rate of successful weaning should also be related to the number of patients discharged alive without having been bridged to heart transplantation or VAD, regardless of having survived weaning with an arbitrary defined number of hours or days.

Study Limitations

This retrospective observational study with heterogeneous surgical patients did not allow for randomization or include a matched control cohort. However, its heterogeneity reflects the clinical reality in patients with RPCS and provides for external validity (generalizability) of our findings.

CONCLUSIONS

In patients with RPCS, arterial lactate level and presence of IHD were independent pre–VA-ECMO risk factors of 90-day mortality. These variables are easily available and may facilitate early prediction of outcome and improve use of VA-ECMO in these critically ill patients. Our data suggest that VA-ECMO should be considered before profound hyperlactatemia occurs, especially in patients with IHD. In contrast, age, type of cardiac surgery, euroSCORE II, and CPB duration did not predict outcome independently.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: extracorporeal life support, extracorporeal membrane oxygenation, ischemic heart disease, lactate, postcardiotomy cardiogenic shock

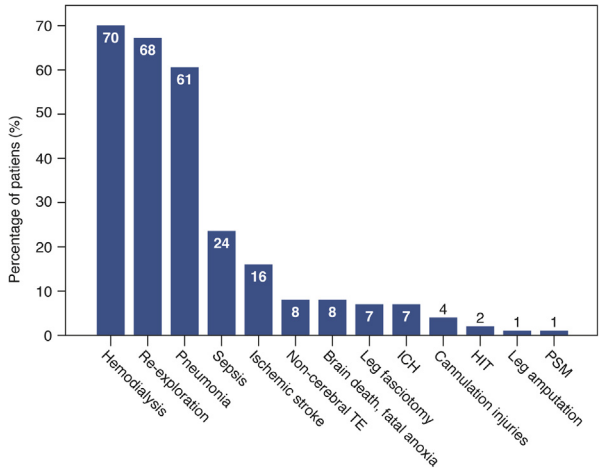

FIGURE E1. Main complications after initiation of venoarterial extracorporeal membrane oxygenation support in 105 patients with refractory postcardiotomy cardiogenic shock. *TE*, Thromboembolism; *ICH*, intracranial hemorrhage; *HIT*, heparin induced thrombocytopenia; *PSM*, poststernotomy mediastinitis.

TABLE E1. Factors associated with mortality within 90 days after venoarterial extracorporeal membrane oxygenation initiation

Variables	MD (%)	Univariable logistic regression		Multivariable logistic regression	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Male sex	0	1.32 (0.53-3.24)	.552	—	—
Age (y)	0	1.04 (1.01-1.07)	.017	1.04 (0.99-1.09)	.058
Age ≥65 y vs. <65 y	0	2.30 (1.01-5.23)	.046	—	—
Weight (kg)	0	1.00 (0.98-1.02)	.970	—	—
BMI (kg/m^2)	0	0.99 (0.92-1.07)	.800	—	—
euroSCORE II	0	1.03 (0.99-1.05)	.071	—	—
euroSCORE II critical preoperative state	0	1.05 (0.47-2.35)	.907	—	—
euroSCORE II type of cardiac surgery					
Single non-CABG	0	0.55 (0.24-1.30)	.173	—	—
Isolated CABG	0	6.00 (1.64-21.9)	.007	—	—
2 procedures*	0	0.72 (0.31-1.64)	.431	—	—
3 procedures*	0	0.62 (0.30-2.05)	.622	—	—
euroSCORE II urgency of surgery					
Elective	0	0.50 (0.23-1.09)	.081	—	—
Urgent	0	1.04 (0.38-2.84)	.942	—	—
Emergency	0	1.71 (0.69-4.28)	.249	—	—
Salvage	0	2.15 (0.54-8.63)	.279	—	—
Type of cardioplegia					
No cardioplegia	0	Reference	—	—	—
Antegrade cardioplegia	0	1.53 (0.46-5.14)	.492	—	—
Antegrade + retrograde cardioplegia	0	1.26 (0.38-4.23)	.705	—	—
Retrograde cardioplegia	0	1.50 (0.19-11.93)	.702	—	—
Cross clamp time (min)	2.9	0.997 (0.99-1.00)	.206	—	—
CPB time (min)	2.9	1.00 (0.99-1.00)	.738	—	—
From CPB direct to VA-ECMO in the operating room	0	1.14 (0.53-2.48)	.735	—	—
Acute myocardial infarction	0	4.97 (1.71-14.4)	.003	—	—
Ischemic heart disease	0	7.28 (3.05-17.4)	<.001	7.87 (2.55-24.3)	<.001
Smoking	0	1.64 (0.75-3.56)	.216	—	—
Hypertension	0	1.334 (0.62-2.90)	.464	—	—
Valvular heart disease	0	0.56 (0.24-1.32)	.184	—	—
Congestive heart failure	0	0.95 (0.41-2.20)	.903	—	—
Diabetes mellitus	0	2.00 (0.65-6.16)	.227	—	—
Atrial fibrillation	0	1.58 (0.63-3.97)	.330	—	—
Dyslipidemia	0	1.53 (0.67-3.50)	.314	—	—
Previous* myocardial infarction	0	1.98 (0.69-5.64)	.202	—	—
Previous† PCI	0	2.15 (0.54-8.63)	.279	—	—
Previous† cardiac surgery	0	1.50 (0.61-3.67)	.374	—	—
Previous† CABG	0	4.30 (0.89-20.7)	.069	—	—
Renal failure	0	2.05 (0.60-7.02)	.253	—	—
Hypertrophic cardiomyopathy	0	2.05 (0.60-7.02)	.253	—	—
Endocarditis	0	0.42 (0.10-1.86)	.254	—	—
Primary graft failure after HTX	0	0.54 (0.12-2.54)	.435	—	—
LVEF (%)‡	0	0.96 (0.94-0.98)	<.001	0.98 (0.95-1.01)	.112
<20 vs. ≥20 (%)	0	4.75 (2.04-11.1)	<.001	—	—

(Continued)

TABLE E1. Continued

Variables	MD (%)	Univariable logistic regression		Multivariable logistic regression	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
MAP (mm Hg)‡	0	0.96 (0.94-0.99)	.007	0.98 (0.95-1.04)	.243
<50 vs. ≥50 (mm Hg)	0	3.78 (1.62-8.83)	.002	—	—
Laboratory values					
Arterial pH‡	0	0.03 (0.00-0.53)	.017	—	—
Arterial lactate (mmol/L)‡	0	1.21 (1.10-1.33)	<.001	1.22 (1.07-1.40)	.004
Hemoglobin (g/L)‡	0	0.998 (0.98-1.02)	.851	—	—
WBC (10^9/L)	0	0.97 (0.93-1.02)	.269	—	—
Platelets (10^9/L)	0	0.999 (0.99-1.00)	.576	—	—
Creatinine (μmol/L)	0	1.00 (0.99-1.01)	.686	—	—
GFR MDRD (mL/min/1.73m^2)	0	0.99 (0.97-1.00)	.051	—	—
ALT (μkat/L)	5.7	1.00 (0.97-1.04)	.923	—	—
Pre-VA-ECMO interventions	0				
Acute PCI	0	1.96 (0.36-10.6)	.436	—	—
Hemodialysis	0	1.07 (0.42-2.68)	.893	—	—
CPR	0	1.27 (0.54-3.00)	.579	—	—
No. of inotropes and vasopressors§	0	1.42 (0.99-2.04)	.055	—	—
Retrieval from external hospital	0	1.68 (0.65-4.37)	.286	—	—
VA-ECMO insertion period, 2011-2015 vs. 2011-2015	0	0.45 (0.22-1.07)	.073	—	—

MD, Missing data; *OR*, odds ratio; *CI*, confidence interval; *BMI*, body mass index; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *CABG*, coronary artery bypass grafting; *CPB*, cardiopulmonary bypass; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation; *PCI*, percutaneous coronary intervention; *HTX*, heart transplantation; *LVEF*, left ventricular ejection fraction; *MAP*, mean arterial pressure; *WBC*, white blood cell counts; *GFR MDRD*, glomerular filtration rate modification of diet in renal disease; *ALT*, alanine aminotransferase; *CPR*, cardiopulmonary resuscitation. *Number of surgical interventions on the heart (euroSCORE II classification). †Before current medical event or admission. ‡Just before cannulation. §Epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, and levosimendan.