Prognostic Significance of Arterial Lactate Levels at Weaning from Postcardiotomy Venoarterial Extracorporeal Membrane Oxygenation

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Abstract: Background: The outcome after weaning from postcardiotomy venoarterial extracorporeal membrane oxygenation (VA-ECMO) is poor. In this study, we investigated the prognostic impact of arterial lactate levels at the time of weaning from postcardiotomy VA. Methods: This analysis included 338 patients from the multicenter PC-ECMO registry with available data on arterial lactate levels at weaning from VA-ECMO. Results: Arterial lactate levels at weaning from VA-ECMO (adjusted OR 1.426, 95%CI 1.157–1.758) was an independent predictor of hospital mortality, and its best cutoff values was 1.6 mmol/L (<1.6 mmol/L, 26.2% vs. ≥ 1.6 mmol/L, 45.0%; adjusted OR 2.489, 95%CI 1.374–4.505). When 261 patients with arterial lactate at VA-ECMO weaning ≤2.0 mmol/L were analyzed, a cutoff of arterial lactate of 1.4 mmol/L for prediction of hospital mortality was identified (<1.4 mmol/L, 24.2% vs. ≥1.4 mmol/L, 38.5%, p = 0.014). Among 87 propensity score-matched pairs, hospital mortality was significantly higher in patients with arterial lactate ≥1.4 mmol/L (39.1% vs. 23.0%, p = 0.029) compared to those with lower arterial lactate. Conclusions: Increased arterial lactate levels at the time of weaning from postcardiotomy VA-ECMO increases significantly the risk of hospital mortality. Arterial lactate may be useful in guiding optimal timing of VA-ECMO weaning.

Keywords: extracorporeal membrane oxygenation; cardiac surgery; postcardiotomy; venoarterial; ECMO; VA-ECMO

1. Introduction

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is an effective salvage therapy for postcardiotomy cardiogenic shock refractory to inotropes and intra-aortic balloon pump support [1]. Recent pooled results demonstrated that one third of patients survived to discharge using postcardiotomy VA-ECMO, although 23% of patients died early after weaning from postcardiotomy VA-ECMO [2]. The causes underlying such a high postweaning mortality have not been thoroughly investigated. The identification of risk factors underlying failure to recover after weaning from postcardiotomy VA-ECMO are of clinical importance to establish a protocol for discontinuation of this therapy in patients with unrecoverable end-organ failure as well as to develop strategies to improve the early outcome of postcardiotomy VA-ECMO. Increased levels of arterial lactate before and during ECMO have been shown to predict the outcome of these patients [2–7]. In this study, we investigated whether arterial lactate levels at the time of weaning from VA-ECMO is a prognostic factor for weaned patients and could be useful in the decision-making process of the timing of VA-ECMO discontinuation.

2. Methods

2.1. Study Population

The PC-ECMO registry is a multicenter retrospective study that gathered data on consecutive patients who underwent VA-ECMO after adult cardiac surgery at 19 cardiac surgery centers in Belgium, Czech Republic, Finland, France, Italy, Germany, Saudi Arabia, Sweden, and the United Kingdom, from January 2010 to March 2018. The study is registered in Clinicaltrials.gov (Identifier: NCT03508505) and the main results of this series are reported elsewhere [7]. The institutional review board or the regional ethics review board of each participating center approved this study. Data was collected retrospectively into a dedicated access datasheet with pre-specified variables and underwent checking of its quality.

Consecutive patients aged over 18 years who required mechanical circulatory support with VA-ECMO for cardiopulmonary failure occurring during the index hospitalization after cardiac surgery, i.e., surgery on the coronary arteries, heart valves, ascending aorta/aortic arch and/or ventricular wall and septum, grown-up congenital heart diseases, and chronic thromboembolic pulmonary
hypertension, were included in this registry. Cardiopulmonary failure in these patients was considered
not responsive to inotropes and/or intra-aortic balloon pump. Patients who received any ECMO therapy
before cardiac surgery or VA-ECMO after heart transplantation or implantation of a ventricular assist
device were excluded from this registry. Furthermore, patients who underwent heart transplantation
or implantation of a ventricular assist device while on VA-ECMO were excluded from the present
analysis. For the purpose of this study, we included only patients who were considered safely weaned
from VA-ECMO per treatment protocol and with available data on arterial lactate levels immediately
before weaning from VA-ECMO.

2.2. Outcomes

The outcome measures of the present study were hospital mortality after weaning from VA-ECMO,
i.e., all-cause death during the index hospitalization, and 30-day mortality. Specific causes of death
were not considered as outcome measures because most often multiple conditions led to early death
after weaning from VA-ECMO.

2.3. Statistical Methodology

Statistical analyses were performed using SPSS v. 25.0 (IBM Corporation, Armonk, NY, USA) and
Stata v. 15.1 (StataCorp LLC, College Station, TX, USA) statistical software. Continuous variables are
reported as mean and standard deviation, and categorical variables as counts and percentages. Risk
estimates are reported as odds ratio (OR) and hazard ratio (HR) with their 95% confidence interval (CI).
Arterial lactate clearance was estimated as the difference of the pre-VAECMO arterial lactate level and
the VA-ECMO weaning arterial lactate level. The arterial lactate clearance/duration of the VA-ECMO
ratio was also considered as a covariate of interest. The Mann–Whitney U, chi-square, the Fisher’s exact,
linear-by-linear association tests, and receiver operating characteristics curve (ROC) analysis with
estimation of the area under the curve (AUC) were used for univariate analysis. The Youden’s test was
used to identify the best cutoff value of arterial lactate at weaning from VA-ECMO in predicting hospital
death. The DeLong’s test was used for comparative analyses of ROC curves. Multilevel mixed-effects
logistic regression was employed to identify independent predictors of hospital mortality avoiding bias
related to any interinstitutional difference. In fact, multilevel models provide a valuable way to identify
independent predictors of poor outcome taking into account interinstitutional differences in terms of
the referral pathway, treatment strategy, and institutional performance. Regression models included
multiple risk factors preceding the initiation of VA-ECMO, with \( p < 0.1 \) for hospital mortality in the
univariate analysis (Table 1). Furthermore, the impact of arterial lactate at weaning from VA-ECMO
on hospital mortality was adjusted for the PC-ECMO score [7]. Once pre-VA-ECMO arterial lactate
was dichotomized, 1-to-1 propensity score matching analysis was performed to reduce the effect of
confounding covariates using the psmatch2 Stata module with a caliper width of 0.2 of the standard
deviation of the logit, i.e., 0.1. A propensity score was estimated with non-parsimonious logistic
regression, including all covariates listed in Table 2, except the type of surgery and arterial lactate and
pH levels at the time of VA-ECMO weaning. Standardized differences lower than 0.10 were considered
as an adequate balance between the matched cohorts. The McNemar test was used to assess the
difference in all-cause hospital mortality in the propensity score-matched pairs. Mortality at 30 days
after weaning from VA-ECMO was evaluated also by the Kaplan–Meier method with the log-rank test
and the Cox proportional hazards method. A \( p < 0.05 \) was set for statistical significance.
Table 1. Patients’ data and predictors of hospital mortality after weaning from postcardiotomy venoarterial extracorporeal membrane oxygenation.

| Baseline covariates | Overall Series 388 Patients | Survivors 221 Patients | Deaths 117 Patients | Univariate Analysis p-Value | Univariate Analysis OR, 95%CI | Mixed-Effects Multivariate Analysis OR, 95%CI |
|---------------------|----------------------------|------------------------|---------------------|------------------------------|-------------------------------|---------------------------------|
| Age (years)         | 61.1 ± 13.3                | 59.5 ± 13.5            | 61.4 ± 12.6         | 0.001                        | 1.029, 1.010–1.049            | 1.058, 1.030–1.086            |
| Female gender       | 108 (32.0)                 | 62 (27.9)              | 46 (39.7)           | 0.028                        | 1.696, 1.058–2.723            |                                |
| eGFR (mL/min/1.73 m²) | 69 ± 29                   | 71 ± 30                | 64 ± 27             | 0.013                        | 0.993, 0.982–0.999            |                                |
| Dialysis            | 11 (3.3)                   | 7 (3.2)                | 4 (3.5)             | 1.000                        | 1.092, 0.313–3.809            |                                |
| Anemia              | 154 (45.6)                 | 94 (42.3)              | 60 (51.7)           | 0.100                        | 1.459, 0.929–2.291            |                                |
| Diabetes            | 88 (26.0)                  | 58 (26.1)              | 30 (25.9)           | 0.958                        | 0.986, 0.591–1.646            |                                |
| Arterial lactate at weaning from VA-ECMO (mmol/L) | 7.34 ± 0.55 | 7.34 ± 0.56 | 7.33 ± 0.53 | <0.0001 | 1.331, 1.140–1.555 | 1.426, 1.157–1.758 |
| VA-ECMO immediately after surgery | 207 (61.2) | 135 (60.8) | 72 (62.1) | 0.822 | 1.055, 0.655–1.674 |                                |
| Central cannulation | 105 (31.1)                 | 56 (25.2)              | 49 (42.2)           | 0.001                        | 2.168, 1.346–3.493            |                                |
| Arterial lactate at start of VA-ECMO (mmol/L) | 6.1 ± 4.0 | 5.9 ± 4.0 | 6.3 ± 3.8 | 0.215 | 1.024, 0.968–1.083 |                                |
| Arterial pH at start of VA-ECMO | 7.31 ± 0.12 | 7.31 ± 0.11 | 7.30 ± 0.13 | 0.900 | 0.739, 0.109–4.982 |                                |
| Arterial lactate at weaning from VA-ECMO (mmol/L) | 1.9 ± 1.6 | 1.6 ± 1.2 | 2.4 ± 2.2 | <0.0001 | 1.331, 1.140–1.555 | 1.426, 1.157–1.758 |
| Arterial pH at weaning from VA-ECMO | 7.34 ± 0.55 | 7.34 ± 0.56 | 7.33 ± 0.53 | <0.0001 | 1.331, 1.140–1.555 | 1.426, 1.157–1.758 |
| Duration of VA-ECMO (days) | 8.1 ± 6.3 | 7.6 ± 5.9 | 8.9 ± 6.7 | 0.067 | 1.033, 0.997–1.070 | 1.063, 1.018–1.111 |

Continuous variables are reported as the mean ± standard deviation. Categorical variables are reported as counts and percentages. Anemia is defined as baseline hemoglobin concentration <12.0g/L in women and <13.0 g/L in men. OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate according to the Modification of Diet in Renal Disease equation; IABP, intra-aortic balloon pump; CABG, coronary artery bypass grafting; GUCH, grown-up congenital disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation. Clinical variables are according to the EuroSCORE II definition criteria.
Table 2. Data of unmatched and propensity score-matched patients with arterial lactate at postcardiomyotomy VA-ECMO weaning less or higher than 1.4 mmol/L in the subgroup with normal lactate level or mild hyperlactatemia.

| Baseline covariates          | Unmatched Patients | Propensity Score Matched Patients |
|------------------------------|--------------------|----------------------------------|
|                              | Lactate <1.4 mmol/L | Lactate ≥1.4 mmol/L | Standardized Differences | Lactate <1.4 mmol/L | Lactate ≥1.4 mmol/L | Standardized Differences |
|                              | 157 Patients       | 104 Patients       |                        | 87 Patients       | 87 Patients       |                        |
| Age (years)                  | 61.2 ± 13.5        | 59.2 ± 12.9        | 0.154                  | 60.6 ± 15.3       | 60.5 ± 12.7       | 0.013                  |
| Female gender                | 47 (29.9)          | 33 (31.7)          | 0.039                  | 27 (31.0)         | 27 (31.0)         | 0.000                  |
| eGFR (mL/min/1.73 m²)        | 72 ± 31            | 67 ± 32            | 0.164                  | 68 ± 30           | 69 ± 33           | 0.037                  |
| Dialysis                     | 7 (4.5)            | 3 (2.9)            | 0.085                  | 3 (3.4)           | 3 (3.4)           | 0.000                  |
| Anemia                       | 67 (42.7)          | 52 (50.0)          | 0.147                  | 45 (51.7)         | 40 (46.0)         | 0.115                  |
| Diabetes                     | 42 (26.8)          | 30 (28.8)          | 0.047                  | 26 (29.9)         | 26 (29.9)         | 0.000                  |
| Recent myocardial infarction | 36 (22.9)          | 25 (24.0)          | 0.026                  | 19 (21.8)         | 20 (23.0)         | 0.027                  |
| Prior stroke                 | 7 (4.5)            | 10 (9.6)           | 0.202                  | 7 (8.0)           | 7 (8.0)           | 0.000                  |
| Atrial fibrillation          | 30 (19.1)          | 25 (24.0)          | 0.120                  | 18 (20.7)         | 20 (23.0)         | 0.056                  |
| Pulmonary disease            | 18 (11.5)          | 16 (15.4)          | 0.115                  | 15 (17.2)         | 13 (14.9)         | 0.063                  |
| Extrapluric arteriopathy     | 16 (10.2)          | 13 (12.5)          | 0.073                  | 11 (12.6)         | 11 (12.6)         | 0.098                  |
| Active endocarditis          | 16 (10.2)          | 18 (17.3)          | 0.208                  | 14 (16.1)         | 11 (12.6)         | 0.098                  |
| Prior cardiac surgery        | 31 (19.7)          | 29 (27.9)          | 0.192                  | 25 (28.7)         | 22 (25.3)         | 0.078                  |
| Coronary artery disease      | 68 (43.3)          | 41 (39.4)          | 0.079                  | 38 (43.7)         | 36 (41.4)         | 0.047                  |
| Left ventricular ejection fraction ≤50% | 96 (61.1) | 65 (62.5) | 0.028                  | 52 (58.9)         | 56 (64.4)         | 0.095                  |
| Critical preoperative state  | 52 (33.1)          | 46 (44.2)          | 0.229                  | 33 (37.9)         | 33 (37.9)         | 0.000                  |
| Ventricular arrhythmia       | 6 (3.8)            | 8 (7.7)            | 0.167                  | 5 (5.7)           | 6 (6.9)           | 0.047                  |
| Preoperative IABP            | 14 (8.9)           | 10 (9.6)           | 0.024                  | 7 (8.0)           | 8 (9.2)           | 0.040                  |
| Stroke/unconsciousness       | 2 (1.3)            | 5 (4.8)            | 0.207                  | 2 (2.3)           | 1 (1.1)           | 0.088                  |
| Emergency procedure          | 35 (22.3)          | 33 (31.7)          | 0.214                  | 24 (27.6)         | 21 (24.1)         | 0.079                  |
| PC-ECMO score                | 3.1±2.0           | 3.4±2.4            | 0.153                  | 3.4±2.2           | 3.3±2.2           | 0.074                  |
| EuroSCORE II (%)             | 12.9±15.3         | 16.2±17.6          | 0.199                  | 15.3±16.6         | 14.6±17.4         | 0.042                  |

Operative data

- Any CABC: 77 (49.0) vs. 44 (28.0) (P = 0.026)
- Aortic valve repair: 1 (0.6) vs. 0 (0.0) (P = 0.000)
- Mitral valve replacement: 40 (25.3) vs. 25 (24.0) (P = 0.000)
- Mitral valve repair: 16 (10.2) vs. 17 (16.3) (P = 0.000)
- Tricuspid valve replacement: 5 (3.2) vs. 1 (0.0) (P = 0.000)
- Tricuspid valve repair: 18 (11.5) vs. 21 (17.7) (P = 0.000)
- Aortic valve repair: 27 (17.2) vs. 14 (23.5) (P = 0.000)
- Aortic arch replacement: 1 (0.6) vs. 2 (9.0) (P = 0.000)
- Surgery for GUCH disease: 3 (1.9) vs. 4 (3.8) (P = 0.000)
- Repair of septum or ventricle: 3 (1.9) vs. 4 (3.8) (P = 0.000)
- Pulmonary thromboendarterectomy: 2 (1.3) vs. 3 (2.9) (P = 0.000)
- Other major cardiac surgery: 4 (2.5) vs. 2 (1.9) (P = 0.000)
- Aortic cross-clamp time (min): 120 ± 71 vs. 121 ± 79 (P = 0.000)
- Cardiopulmonary bypass time (min): 212 ± 115 vs. 211 ± 131 (P = 0.000)

VA-ECMO data

- VA-ECMO immediately after surgery: 94 (59.9) vs. 59 (56.7) (P = 0.000)
- Central cannulation: 40 (25.5) vs. 32 (30.8) (P = 0.000)
- Arterial lactate at start of VA-ECMO: 5.4 ± 3.6 vs. 6.8 ± 4.2 (P = 0.000)
- Arterial pH at start of VA-ECMO: 7.3 ± 0.12 vs. 7.30 ± 0.12 (P = 0.000)
- Arterial lactate at weaning from VA-ECMO: 7.4 ± 0.22 vs. 7.34 ± 0.58 (P = 0.000)
- Arterial pH at weaning from VA-ECMO: 7.4 ± 0.22 vs. 7.34 ± 0.58 (P = 0.000)
- Duration of VA-ECMO (days): 8.4 ± 6.5 vs. 8.9 ± 6.5 (P = 0.000)

Continuous variables are reported as the mean ± standard deviation. Categorical variables are reported as counts and percentages. Anemia is defined as baseline hemoglobin concentration <12.0 g/L in women and <13.0 g/L in men. eGFR, estimated glomerular filtration rate according to the Modification of Diet in Renal Disease equation; IABP, intra-aortic balloon pump; CABC, coronary artery bypass grafting; GUCH, grown-up congenital disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation. Clinical variables are according to the EuroSCORE II definition criteria.
3. Results

3.1. Characteristics of the Study Cohort

The PC-ECMO registry included 781 consecutive patients and hospital mortality was 64.3%. Mortality on VA-ECMO occurred in 362 patients (46.4%). Among 419 patients who were believed to be safely weaned from VA-ECMO, 140 patients (33.4%) died during the index hospital stay. Data on the arterial lactate level before and at weaning from VA-ECMO was available in 355 patients. Seventeen patients underwent heart transplantation or implantation of a ventricular assist device from VA-ECMO and were excluded from the present analysis. Overall, 338 patients were the subjects of this study and their baseline characteristics, operative data, and VA-ECMO-related data are summarized in Table 1. In these patients, the mean VA-ECMO therapy duration was 8.1 ± 6.3 days (median 6.0 days, interquartile range 7.0 days, range 0.5–39.0 days; 5 lowest outliers 0.5–0.8 days; 5 highest outliers 31.0–39.0 days).

3.2. Predictive Performance of Arterial Lactate at VA-ECMO Weaning

The AUC of pre-VA-ECMO arterial lactate was 0.541 (95%CI 0.476–0.606) and that of arterial lactate at weaning from VA-ECMO was 0.629 (95%CI 0.567–0.691) (DeLong test, \( p = 0.032 \)). Arterial lactate clearance (AUC 0.521, 95%CI 0.454–0.588) and arterial lactate clearance/duration of VA-ECMO ratio (AUC 0.549, 95%CI 0.483–0.615) were not associated with increased hospital mortality.

Mixed-effects logistic regression showed that arterial lactate at weaning from VA-ECMO \( ( p = 0.001, \text{adjusted OR} 1.426, 95\% \text{CI} 1.157–1.758; \text{Likelihood-ratio test for model vs. logistic regression}, p < 0.0001) \) was an independent predictor of hospital mortality when adjusted for risk factors with \( p < 0.1 \) in the univariate analysis (Table 1). Similarly, arterial lactate at weaning from VA-ECMO was predictive of hospital mortality (adjusted OR 1.341, 95%CI 1.100–1.635) when adjusted for the PC-ECMO score.

The crude rates of hospital mortality along increasing arterial lactate levels at weaning from VA-ECMO are summarized in Figure 1 (linear-by-linear association test, \( p < 0.0001 \)). The Youden’s test identified a cutoff of arterial lactate of 1.6 mmol/L for the prediction of hospital mortality (arterial lactate <1.6 mmol/L 26.2% vs. arterial lactate ≥1.6 mmol/L 45.0%, \( p < 0.0001 \), sensitivity 57%, specificity 65%). When adjusted for participating centers and risk factors with \( p < 0.1 \) in the univariate analysis, arterial lactate at weaning from VA-ECMO ≥1.6 mmol/L was still predictive of hospital mortality (adjusted OR 2.489, 95%CI 1.374–4.505). Similarly, arterial lactate at weaning from VA-ECMO ≥1.6 mmol/L was predictive of hospital mortality (adjusted OR 2.094, 95%CI 1.201–3.651) when adjusted for the PC-ECMO score. Thirty-day mortality after weaning from VA-ECMO was 21.0% in patients with arterial lactate <1.6 mmol/L and 41.1% in those with arterial lactate ≥1.6 mmol/L (log-rank test, \( p < 0.0001 \); adjusted HR 2.245, 95%CI 1.416–3.560).
3.3. Predictive Performance of Mild Hyperlactatemia at VA-ECMO Weaning

The overall study population included a number of patients with arterial lactate at VA-ECMO weaning >2.0 mmol/L. In order to avoid bias of excessively high arterial lactate levels, we assessed the prognostic performance of arterial lactate levels in the subgroup with mild hyperlactatemia as defined by arterial lactate at VA-ECMO weaning ≤2.0 mmol/L (261 patients). The hospital mortality of this subgroup of patients was 30.2%.

The AUC of pre-VA-ECMO arterial lactate was 0.529 (95%CI 0.452–0.606) and that of arterial lactate at weaning from VA-ECMO was 0.578 (95%CI 0.504–0.652) (DeLong test, \( p = 0.325 \)). The Youden’s test identified a cutoff of arterial lactate of 1.4 mmol/L for the prediction of hospital mortality (arterial lactate <1.4 mmol/L, 24.2% vs. arterial lactate ≥1.4 mmol/L, 38.5%, \( p = 0.014 \), sensitivity 51%, specificity 65%).

Propensity score matching resulted in 87 pairs with balanced baseline characteristics and duration of VA-ECMO (Table 2). Hospital mortality was significantly higher in patients with arterial lactate ≥1.4 mmol/L (34 patients, 39.1% vs. 20 patients, 23.0%, McNemar’s test, \( p = 0.029 \)) compared to those with arterial lactate <1.4 mmol/L. These findings were confirmed also when arterial lactate ≥1.4 mmol/L was adjusted for postoperative renal replacement (OR 1.846, 95%CI 1.068–3.193). Among propensity score-matched pairs, 30-day mortality after weaning from VA-ECMO was 17.4% in patients with arterial lactate at VA-ECMO weaning <1.4 mmol/L and 33.8% in those with arterial lactate ≥1.4 mmol/L (Log-rank test, \( p = 0.016 \); HR 2.100, 95%CI 1.126–3.919) (Figure 2).
We speculate that patients with mild hyperlactatemia after VA-ECMO therapy, in the absence of irreversible end-organ injury, may need prolonged mechanical circulatory support and treatment of underlying causes of hyperlactatemia. In the absence of suboptimal oxygen delivery and severe renal failure, pulmonary complications are frequent causes of increased blood lactate levels [9] and VA-ECMO should not be discontinued until resolution of pulmonary failure. The same may apply to other severe conditions underlying hyperlactatemia. Since a mild increase in arterial lactate has been shown to increase the risk of death in critically ill patients [10], achieving a normal level of lactate before discontinuation of cardiopulmonary support therapies is a reasonable goal as shown in other subsets of critically ill patients [11].

Arterial lactate before starting VA-ECMO is widely recognized as a predictor of poor outcome [2–7], still, to the best of our knowledge, no data exists on the prognostic value of arterial lactate at the time of weaning from VA-ECMO. Similarly, the clearance of arterial lactate, even when adjusted for the duration of this salvage therapy, was also not associated with an increased risk of early mortality.

Figure 2. Kaplan–Meier estimates of 30-day all-cause mortality in propensity score matched pairs with arterial lactate levels <1.4 mmol/L versus 1.4 to 2.0 mmol/L at the time of weaning from postcardiotomy venoarterial extracorporeal membrane oxygenation (Log-rank test, \( p = 0.016 \)).

4. Discussion

This study demonstrated that there is a substantial hospital mortality after weaning from postcardiotomy VA-ECMO and most of these patients die during the first five days after discontinuation of VA-ECMO therapy (Figure 2). In the absence of a standardized VA-ECMO weaning protocol [8], the present results suggest that treatment strategies at the time of discontinuation of this salvage therapy should be improved. In particular, there is a need for objective parameters indicating when and how to intervene to improve the cardiopulmonary and metabolic status of these critically ill patients and thereby to optimize the timing of weaning from VA-ECMO. In this setting, arterial lactate is an independent predictor of early mortality and may potentially guide the decision-making process before discontinuation of mechanical circulatory support. Importantly, analysis of the subset of patients with arterial lactate \( \leq 2.0 \) mmol/L at the time of discontinuation of VA-ECMO showed that even a mild increase of lactate, i.e., \( \geq 1.4 \) mmol/L, is associated with a two-fold risk of early mortality. Such a risk was observed in propensity score-matched pairs with similar duration of VA-ECMO (Table 2). We speculate that patients with mild hyperlactatemia after VA-ECMO therapy, in the absence of irreversible end-organ injury, may need prolonged mechanical circulatory support and treatment of underlying causes of hyperlactatemia. In the absence of suboptimal oxygen delivery and severe renal failure, pulmonary complications are frequent causes of increased blood lactate levels [9] and VA-ECMO should not be discontinued until resolution of pulmonary failure. The same may apply to other severe conditions underlying hyperlactatemia. Since a mild increase in arterial lactate has been shown to increase the risk of death in critically ill patients [10], achieving a normal level of lactate before discontinuation of cardiopulmonary support therapies is a reasonable goal as shown in other subsets of critically ill patients [11].
The reason for this resides in the complexity of lactate metabolism and the heterogeneity of causes underlying its increased production and/or decreased removal [12,13].

5. Limitations

The retrospective nature is a limitation of the present study. Secondly, arterial lactate levels were measured using different laboratory methods and this may introduce a significant bias, which we attempted to mitigate using multilevel mixed-effects regression analysis. Thirdly, arterial lactate levels might have been affected by patients’ conditions and treatment methods, such as renal replacement therapy, use of certain drugs, poor nutritional status, and therapies for acid-base abnormalities [12,13]. In such cases, the level of arterial lactate does not reflect the metabolic state of the patient at weaning from VA-ECMO.

6. Conclusions

This multicenter study showed that increases in arterial lactate at the time of weaning from postcardiotomy VA-ECMO are associated with an increased risk of hospital mortality. Further studies are needed to confirm these findings and to evaluate whether arterial lactate may be a useful biomarker to guide the optimal timing of VA-ECMO weaning.

Author Contributions: Conceptualization, F.B., G.M., and M.D.; Data curation, A.F., T.J., A.L. (Artur Lichtenberg), K.J., G.G., S.Z., V.G.R., A.P., K.B., A.L. (Antonio Loforte), A.L. (Andrea Lechiancole), D.S., M.P. (Marek Pol), C.S., M.P. (Matteo Pettinari), K.M., K.A., Z.E.D., N.S., H.W., A.M.D. and T.F.; Formal analysis and methodology, F.B., A.F. and M.D.; Writing—original draft, F.B.; Writing—review rewriting, F.B., A.F., G.M., T.F. and M.D. 

Funding: This study was performed without external financial support.

Conflicts of Interest: The authors declare that they do not have any conflicts of interest related to this study.

References

1. Rastan, A.J.; Dege, A.; Mohr, M.; Doll, N.; Falk, V.; Walther, T.; Mohr, F.W. Early and late outcomes of 517 consecutive adult patients treated with extracorporeal membrane oxygenation for refractory postcardiotomy cardiogenic shock. J. Thorac. Cardiovasc. Surg. 2010, 139, 302–311. [CrossRef] [PubMed]
2. Biancari, F.; Perrotti, A.; Dalén, M.; Guerrieri, M.; Fiore, A.; Reichart, D.; Tauriainen, T. Meta-Analysis of the outcome after postcardiotomy venoarterial extracorporeal membrane oxygenation in adult patients. J. Cardiothorac. Vasc. Anesth. 2018, 32, 1175–1182. [CrossRef] [PubMed]
3. Wang, L.; Wang, H.; Hou, X. Clinical outcomes of adult patients who receive extracorporeal membrane oxygenation for postcardiotomy cardiogenic shock: A systematic review and meta-analysis. J. Cardiothorac. Vasc. Anesth. 2018, 32, 2087–2093. [CrossRef] [PubMed]
4. Park, S.J.; Kim, S.P.; Kim, J.B.; Jung, S.H.; Choo, S.J.; Chung, C.H.; Lee, J.W. Blood lactate level during extracorporeal life support as a surrogate marker for survival. J. Thorac. Cardiovasc. Surg. 2014, 148, 714–720. [CrossRef] [PubMed]
5. Debaty, G.; Babaz, V.; Durand, M.; Gaide-Chevronnay, L.; Fournel, E.; Blancher, M.; Albaladejo, P. Prognostic factors for extracorporeal cardiopulmonary resuscitation recipients following out-of-hospital refractory cardiac arrest. A systematic review and meta-analysis. Resuscitation 2017, 112, 1–10. [CrossRef] [PubMed]
6. Fux, T.; Holm, M.; Corbascio, M.; Lund, L.H.; van der Linden, J. Venoarterial extracorporeal membrane oxygenation for postcardiotomy shock: Risk factors for mortality. J. Thorac. Cardiovasc. Surg. 2018, 156, 1894–1902. [CrossRef] [PubMed]
7. Biancari, F.; Dalén, M.; Fiore, A.; Ruggieri, V.G.; Saeed, D.; Jönsson, K.; Loforte, A. Multicenter study on postcardiotomy venoarterial extracorporeal membrane oxygenation. J Thorac. Cardiovasc. Surg. 2019, in press. [CrossRef] [PubMed]
8. Vasques, F.; Romitti, F.;Gattinoni, L.; Camporota, L. How I wean patients from veno-venous extra-corporeal membrane oxygenation. Crit. Care 2019, 23, 1–3. [CrossRef] [PubMed]
9. Rishu, A.H.; Khan, R.; Al-Dorzi, H.M.; Tamim, H.M.; Al-Qahtani, S.; Al-Ghamdi, G.; Arabi, Y.M. Even mild hyperlactatemia is associated with increased mortality in critically ill patients. *Crit. Care* 2013, 17, R197. [CrossRef] [PubMed]

10. De Backer, D.; Creteur, J.; Zhang, H.; Norrenberg, M.; Vincent, J.L. Lactate production by the lungs in acute lung injury. *Am. J. Respir. Crit. Care Med.* 1997, 156, 1099–1104. [CrossRef] [PubMed]

11. Jansen, T.C.; van Bommel, J.; Schoonderbeek, F.J.; Sleeswijk Visser, S.J.; van der Klooster, J.M.; Lima, A.P.; Willemsen, S.P.; Bakker, J. LACTATE study group. Early lactate-guided therapy in intensive care unit patients: A multicenter, open-label, randomized controlled trial. *Am. J. Respir. Crit. Care Med.* 2010, 182, 752–761. [CrossRef] [PubMed]

12. Vincent, J.L.; Quintairos, E.; Silva, A.; Couto, L., Jr.; Taccone, F.S. The value of blood lactate kinetics in critically ill patients: A systematic review. *Crit. Care* 2016, 20, 257. [CrossRef] [PubMed]

13. Wardi, G.; Brice, J.; Correia, M.; Liu, D.; Self, M.; Tainter, C. Demystifying lactate at emergency department. *Ann. Emerg. Med.* 2019, in press.

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