Journal of Critical Care 71 (2022) 154044

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Patterns of oxygen debt repayment in cardiogenic shock patients sustained with extracorporeal life support: A retrospective study

Yuri M. Ganushchak [a,*], Eva R. Kurniawati [a], Iwan C.C. van der Horst [b], Sander M.J. van Kuijk [c], Patrick W. Weerwind [a,d], Roberto Lorusso [a,d], Jos G. Maessen [a,d]

[a] Department of Cardiothoracic Surgery, Maastricht University Medical Center, Maastricht, the Netherlands
[b] Department of Intensive Care, Maastricht University Medical Center, Maastricht, the Netherlands
[c] Clinical Epidemiology and Medical Technology Assessment (KEMTA), Maastricht University Medical Center+, Maastricht, the Netherlands
[d] Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, the Netherlands

ARTICLE INFO

Available online xxxx

Keywords:
Cardiogenic shock
Extracorporeal life support
Oxygen debt
Oxygen debt repayment schedule

ABSTRACT

Cardiogenic shock is the most frequent kind of shock in cardiac intensive care, and cardiac dysfunction and hypoxia are often seen in critically ill patients. Inadequate organ and tissue perfusion and hypoxia result in anaerobic metabolism with hyperlactatemia and oxygen debt accumulation. However, the role of accumulated oxygen debt in the course of cardiogenic shock and hypoxia has not been clearly described. Here, we first described the existence of several patterns of oxygen debt repayment in cardiogenic shock patients maintained by an extracorporeal life support system. Oxygen debt was computed from the lactate concentration at five time points, covering the first 26 h of ECLS. Patterns representing basic pathophysiological processes were independent of the cause of the primary insult. Groups of patients classified into specific patterns differed in terms of survival rate from 51.5% to only 4.6%. It is very important that the initial group not predetermine the fate of the patient and may change in the course of treatment due to 'between-cluster migration'. We believe that our finding of different patterns of oxygen debt repayment in cardiogenic shock patients may offer new insights for a more rational, goal-directed treatment of highly morbid conditions such as hypoxia and cardiogenic shock.

1. Introduction

Cardiogenic shock is the most frequent type of shock in cardiac intensive care, and cardiac dysfunction is often seen in critically ill patients [1]. Cardiogenic shock is an emergency involving a complex, highly morbid and vicious cycle of cardiac and systemic decompensation. It includes a complex and diverse disorder involving end-organ hypoperfusion, hypoxic endothelial damage, acute coagulopathy, and multisystem organ failure [2]. Inadequate organ and tissue perfusion results in hypoxia and activation of anaerobic metabolism [3-5]. In addition to anaerobic glycolysis, adrenergic stimulation due to the accompanying severe stress response can increase aerobic lactate production [6,7].

Elevated arterial lactic acid levels are associated with in-hospital and 30-day mortality rates independent of treatment mode [7-16]. However, focus on lactate concentration and its clearance erodes the understanding of the shock state's major physiological underpinnings [17]. Lactate concentration is merely a metabolic correlate of the pathophysiological process known as *oxygen debt*. Translating lactate concentration (mmol/l) to the deficit in oxygen consumption (mlO2) creates an important quantitative descriptor of the severity of the shock process [18]. A better understanding of the mechanisms underlying oxygen debt accumulation and recovery, also known as *repayment*, may be a useful guide in treating shock [17,18].

Archibald Hill originally introduced the term *'oxygen debt'* in 1928 as the additional oxygen that must be taken into the body after vigorous exercise to restore all systems to their normal states [19]. In clinical practice, unlike the physiological increase in metabolic requirements during vigorous exercise, the disparity between the metabolic requirements and the level of oxygen delivery is caused by a decrease in oxygen delivery beyond its critical level [17]. Therefore, oxygen debt is the accumulation of an oxygen deficit over time and represents [18] both the severity of shock and the time spent in the shock state. Animal and clinical studies have demonstrated a direct association of total oxygen debt and mortality [18,20,21]. Furthermore, the severity of end-organ and tissue damage increase with the period of oxygen debt and, in case of failure, the period to repay the oxygen debt [18,22]. Therefore, timely oxidation of unmetabolized substrates (i.e., an oxygen debt repayment schedule)

* Corresponding author at: Department of Cardiothoracic Surgery, Maastricht University Medical Center, P. Debyelaan 25, PO Box 5800, 6202 AZ Maastricht, the Netherlands.
E-mail address: y.ganushchak@mumc.nl (Y.M. Ganushchak).

https://doi.org/10.1016/j.jcrc.2022.154044

is an essential factor determining the severity of ongoing damage and outcome [17].

Our retrospective study aims to demonstrate the possible differences in the compensation of metabolic disorder patterns caused by cardiogenic shock in terms of oxygen debt in patients supported by extracorporeal life support (ECLS). It also examines the dependence between the treatment outcome of this group of patients and the oxygen debt repayment schedule.

2. Material and methods

2.1. Study population and design

Between January 2013 and December 2017, all consecutive patients undergoing venoarterial ECLS (v-a ECLS) in a single academic center were included retrospectively. No exclusion criteria were applied. Moreover, there was no formal consent applied due to the retrospective nature of the study. All methods were performed in accordance with the relevant guidelines and regulations. The study was approved as a study to which the Medical Research Involving Human Subjects Act (WMO) does not apply, and the need for informed consent was waived by the local ethical committee (Medisch-Ethische Toetsingscommissie Academisch Ziekenhuis Maastricht/Universiteit Maastricht, decision METC 2020–1440).

2.2. Data collection

The clinical, laboratory, intervention, and outcome data were collected at treatment time during the support using Extracorporeal Life Support Organization (ELSO) forms and the computer database. Additional information was extracted by reviewing hospital records. The following clinical data were evaluated at the following time points: before ECLS initiation and after 2, 8, 14, 20, and 26 h of ECLS: ECLS flow, mean arterial pressure (MAP), lactate concentration, and norepinephrine infusion rate.

Oxygen debt was computed from lactate concentration using the following linear regression equation [21]:

$$\text{Oxygen debt } (ml/\text{kg}) = -25.26 + 13.06 \text{ x } [\text{lactate}](\text{mmol/l})^{*} \quad (1)$$

* Calculated only when lactate ≥2.0 mmol/l.

Total oxygen debt is the result of the multiplication of the oxygen debt computed in eq. 1 by the patient's body weight. The changes in oxygen debt were evaluated over the following intervals: pre-ECLS – 2 h (T1), 2–8 h (T2), 8–14 h (T3), 14–20 h (T4), and 20–26 h (T5).

2.3. Study outcomes

Six-month survival was used as an outcome parameter and controlled via the Municipal Personal Records Database.

2.4. Statistical analysis

The sociodemographic and clinical characteristics were analyzed using descriptive statistics, including percentages for categorical variables and continuous variables and the mean ± standard deviation (SD) for normally distributed parameters.

A two-step cluster analysis algorithm was used for initial stratification. The *Z*-scores of total oxygen debt before the start of ECLS and after 2 h of support were selected for detecting primary subgroups of patients with similar patterns of oxygen debt and repayment dynamics.

The oxygen debt parameters after the T1 period generated the initial set of centers for the K-means clustering procedure in a sequential period between 2 and 8 h of support (T2). The algorithm then proceeded by repeating the K-means clustering procedure, where the generated cluster centers at the end of each study period were used as initial cluster centers for the next (sequential) period until the end of the 26-h study period.

The migration of patients between clusters was tracked at each time interval. Analysis of variance (ANOVA) was used to examine the clusters' differences in clinical and laboratory parameters at each time interval. The Pearson chi-square test was used to assess the distribution of patients in clusters by categorical variables. Tests were considered statistically significant at the 95% confidence interval (p-value ≤0.05). Statistical analyses were performed using SPSS version 23 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. General characteristics

During the study period, a total of 153 patients were included with an average age of 61.5 ± 12.3 years; the majority of patients were male (66%).

The distribution of the causes of cardiogenic shock in patients sustained by an extracorporeal life support device is presented in Fig. 1a. A total of 106 patients died. The etiology of cardiogenic shock was not associated with six-month mortality in patients sustained by ECLS (Fig. 1b, X^2 (8, $N = 153$) = 14.53, $p = 0.069$). Independent of the etiology of cardiogenic shock, 82.4% of patients received peripheral cannulation, and 14.4% had central arterial cannulation and peripheral venous cannulation. The decision to start the ECLS within 8 h after the event was made in 97.8% of survivors versus 76.6% of nonsurvivors (X^2 (1, $N = 153$) = 10.63, $p = 0.001$). Furthermore, in 41.5% of patients in the nonsurvivor group, ECLS was discontinued during the first 24 h due to *prognosis infausta*. That is why the duration of ECLS in the group of nonsurvivors was lower than that in the group of six-month survivors (79.0 ± 93.7 h compared to 150.0 ± 137.9 h, respectively, $p < 0.0001$).

The duration of ECLS was associated with six-month survival (150.0 ± 137.9 h in the survivor group compared to 79.0 ± 93.7 h, $p < 0.0001$). Discontinuation of ECLS during the first 24 h due to *prognosis infausta*, was decided in 44 (41.5%) out of all patients who died during the six-month follow-up period.

3.2. Cluster analysis

Two-step cluster analysis based on the oxygen debt amount at the start of ECLS and after two hours of support (as a mark of repayment) generated three clusters (Cluster 1, Cluster 2, and Cluster 3, respectively). The K-means cluster procedure repeated at each time interval, as described in the methods section, allowed the tracing of the changes in oxygen debt and the distribution of patients in clusters (Fig. 2). During the first 2 h of ECLS, the patients in Cluster 1 demonstrated an increase in oxygen debt (1491 ± 1556 ml pre-ECLS and 2331 ± 2272 ml after 2 h of ECLS, $p = 0.016$) followed by a statistically significant decrease in oxygen debt at each time interval (Fig. 2). We observed a higher prevalence of postcardiotomy in patients in Cluster 1 after the initial classification (Fig. 3a, $p = 0.002$). However, after 2 h of ECLS support, the differences in the distributions by the cause of cardiogenic shock between clusters were not statistically significant (Fig. 3b, $p = 0.19$). Fig. 4 presents the migration of patients between clusters during the first 26 h of circulatory support. During this time, seven patients from Cluster 1 were successfully weaned and survived during the six-month follow-up period. The migration of patients with more effective oxygen debt repayment to Cluster 1 as well as the reverse migration of patients with a delay in repayment increased the survival rate in this cluster from 46.1% as observed after two hours of support to 51.5% after 26 h of support and was counterbalanced by a decrease in the survival rate in Cluster 2 from 26.5% to 15.8%. Only one patient assigned to Cluster 3 survived for six months. The observed rise in the survival rate in Cluster 3 from 4.8% after two hours of support to 12.5%

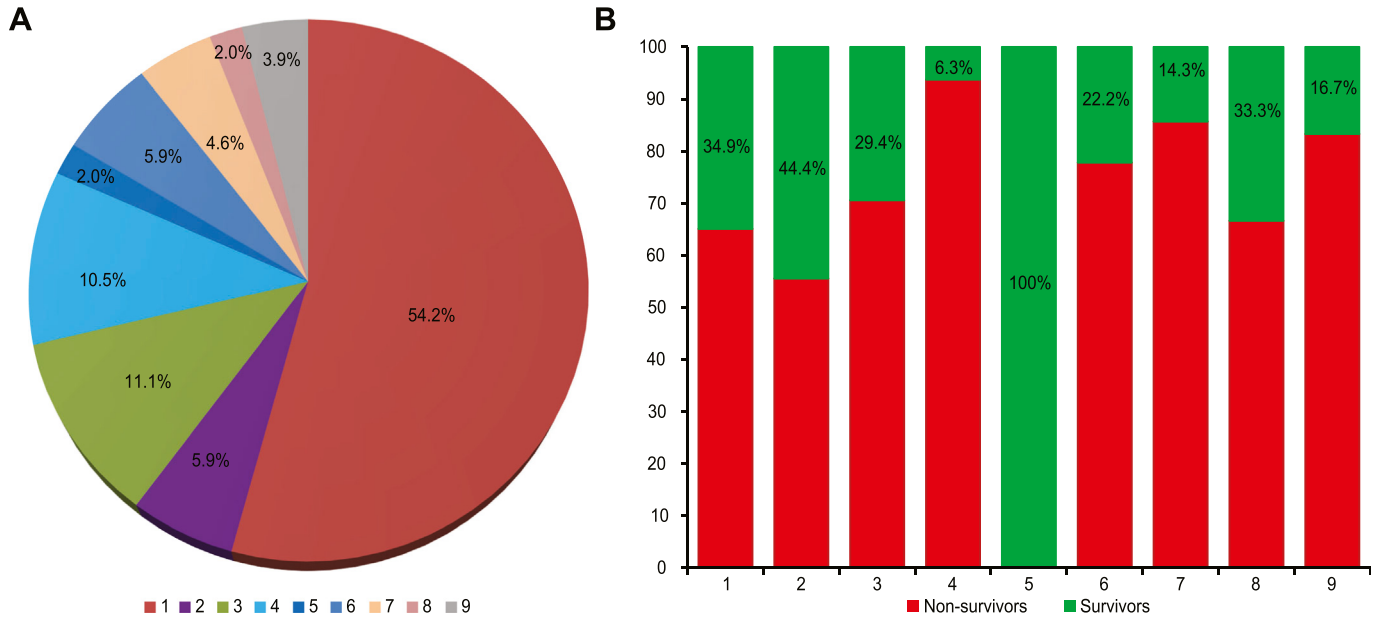

Fig. 1. a) Causes of cardiogenic shock in the patient cohort; (b) survival rate by etiology of cardiogenic shock (χ^2 (8, $N = 153$) = 14.532, $p > 0.05$).

was caused by a decrease in the total number of patients in Cluster 3 from 21 to 8 at the end of the 26-h observation period (Fig. 5 a, b).

The frequency of initiation of ECLS during 8 h after the event in the initial clusters did not differ statistically between clusters (90.6% in Cluster 1, 79.4% in Cluster 2, and 86.7% in Cluster 3, $p = 0.30$).

The MAP in the clusters during the observation period is shown in Fig. 6a. The patients assigned to Cluster 3 had lower MAP values despite the higher doses of noradrenaline infusion throughout all study periods (Fig. 6b). The average ECLS machine flow was 4.2 ± 0.8 l/min in all clusters and did not differ between clusters and time periods.

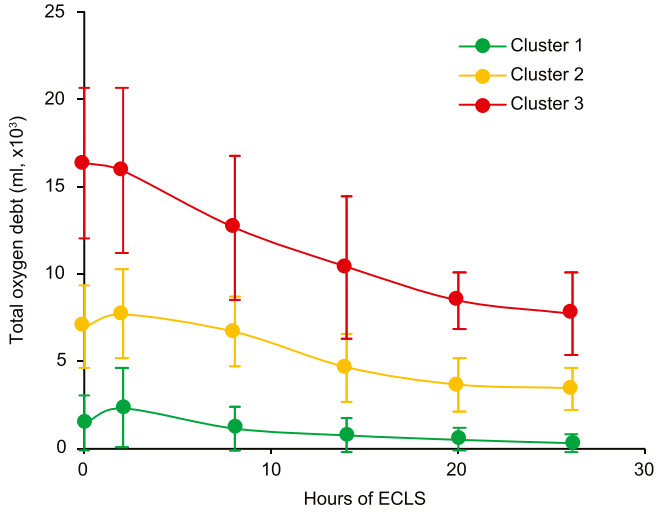

Fig. 2. Cluster center shifts in five time periods. Statistically significant shifting of cluster centers occurred at T1 (0–2 h: cluster 1 – $F(1,126) = 5.95$, $p = 0.016$); at T2 (2–8 h: cluster 1 – $F(1,136) = 14.64$, $p < 0.0001$ and cluster 3 – $F(1,36) = 5.04$, $p = 0.031$); at T3 (8–14 h): cluster 1 – $F(1,145) = 4.59$, $p = 0.034$ and cluster 2 – $F(1,61) = 17.09$, $p < 0.0001$); and at T4 (14–20 h: cluster 2 – $F(1,55) = 4.63$, $p = 0.036$). No significant changes in the cluster centers occurred at T5 (20–26 h).

4. Discussion

To our knowledge, this is the first attempt to describe the patterns of tissue perfusion disorder in patients with cardiogenic shock in terms of oxygen debt accumulation and repayment and its impact on short-term survival.

The initial two-step cluster analysis algorithm based on the total oxygen debt and its dynamics defined three clusters in our study group (Fig. 2). These clusters, along with sequential clustering, exposed three distinct patterns of initial oxygen debt and repayment in our patients. The cluster analysis methods used in combination in our study have been successfully reported and are increasingly appearing in clinical studies [23-26]. Interested readers can study the principles and algorithms of cluster analysis elsewhere [27].

It is well established that accumulated oxygen debt due to a disproportion between the oxidative requirement and the level of oxygen delivery without timely repayment leads to multiple organ failure and mortality [17]. Maintenance and fast restoration of oxygen delivery sufficient to facilitate adequate cellular metabolism are fundamental in sustaining organ function. The early improvement of tissue perfusion by all means, including mechanical circulatory support [7,28-33] and a rapid decrease or normalization of lactate levels, is critical for survival [7,34-38].

Our findings support the relevance and positive impact of an early start of ECLS. The ECLS provided to the patients included in our study was initiated during the first 8 h after the insult in 97.8% of patients who survived a six-month observation period versus 76.4% of nonsurvivors. However, a relatively high number of nonsurvivors who were started on ECLS within 8 h in nonsurvivors questions the importance of this factor as the primary determinant of the outcome. Furthermore, the distribution of patients who were started on ECLS within 8 h across clusters was not statistically significant despite a substantial difference in mortality rates. This can be explained by the fact that our study's initial classification was based on the total oxygen debt, which is the accumulation of oxygen deficit over time and embodies both the severity of shock and time spent in the shock state [17,18].

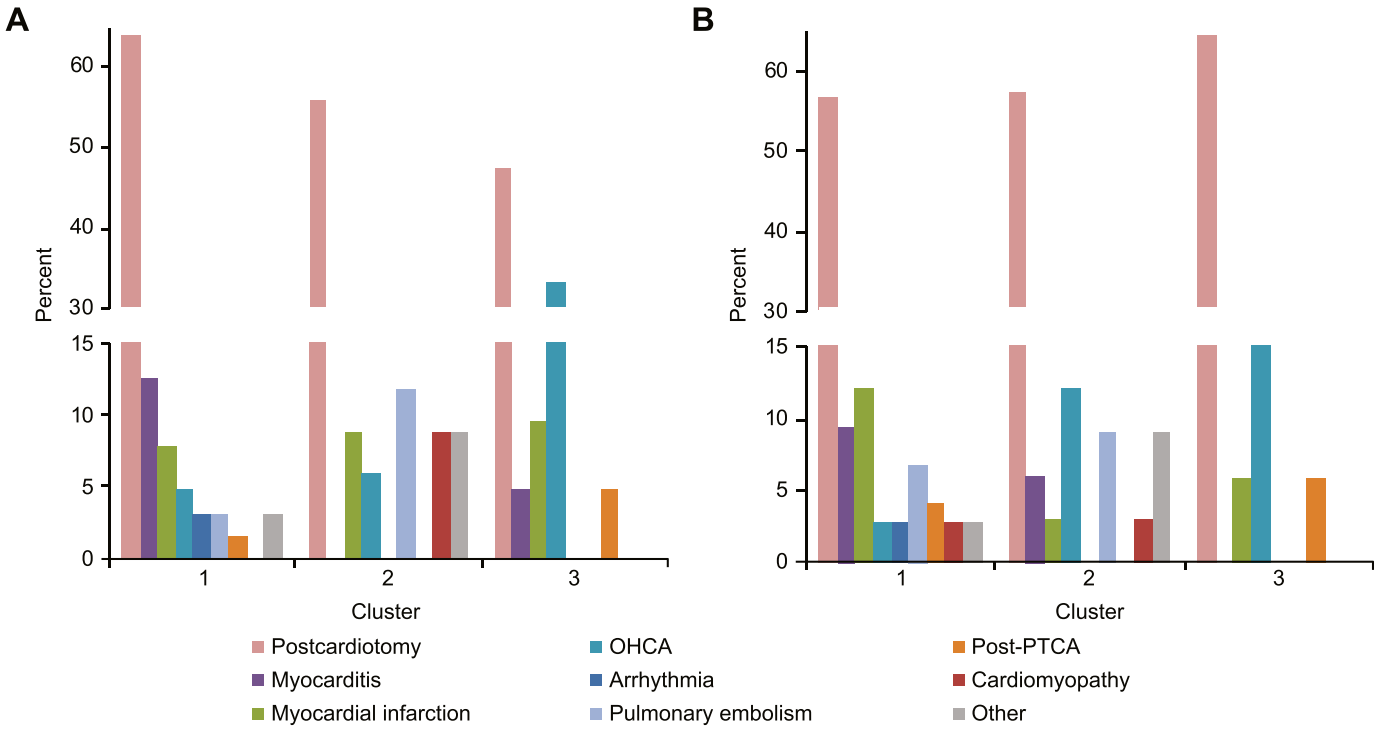

Fig. 3. Distribution of patients by etiology of cardiogenic shock in clusters. (a) Initial classification. There were significant differences in the distribution of patients by etiology of CS in clusters (χ^2 (16, $N = 119$) = 37.756, $p = 0.002$), which disappeared after 2 h (b) of support (χ^2 (16, $N = 124$) = 20.642, $p > 0.05$). OHCA: out-of-hospital cardiac arrest; PTCA: percutaneous coronary angioplasty.

The total oxygen debt during the first 26 h of ECLS and its repayment patterns were derived from serial measurements of lactate concentration at the study time points. As a quantitative metric, this variable more adequately represents the metabolic state of the patient [17] than the lactate concentration in arterial blood alone. The linear regression equation used in our study was based on the animal hemorrhagic shock model described by Dieter Rixen et al. in 2001 [21]. However, the equivalence of metabolic acidosis and accumulated oxygen debt permits quantification of the severity of the ischemic shock process in both animals and humans [18,39]. The total oxygen debt was computed as oxygen debt times the body weight of the patient and indicates the additional oxygen that must be taken into the body to restore all systems to their normal states. Considering the prognostic importance of lactate clearance and absolute lactate levels [40], we used oxygen debt

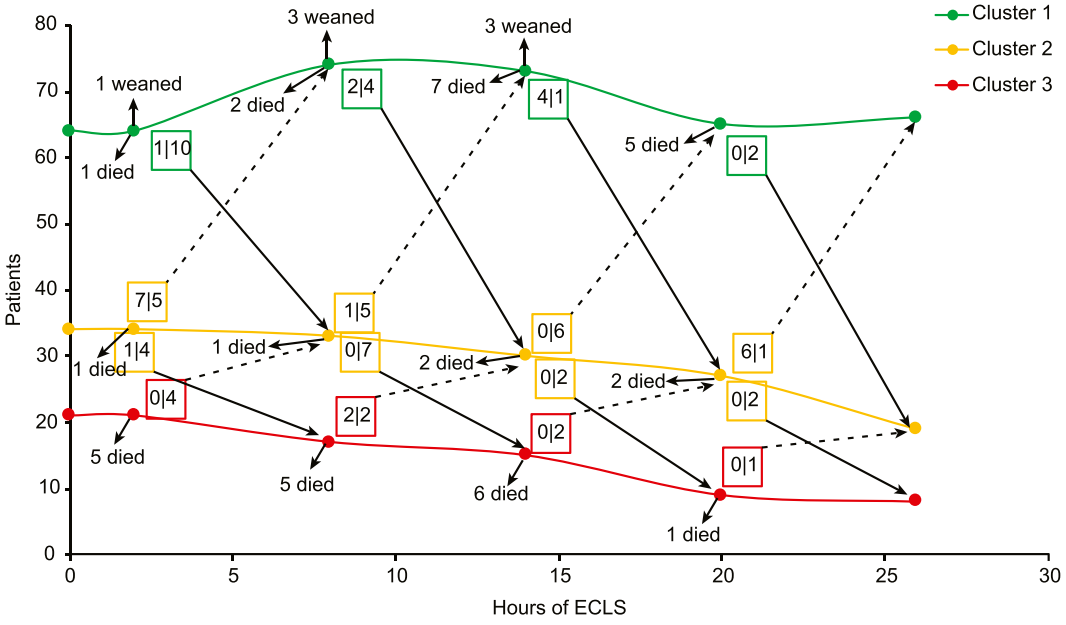

Fig. 4. Patient migration over the course of extracorporeal life support. The colored text boxes present the number of migrated patient survivors | nonsurvivors. Patient migration occurred throughout the entire 26-h observation period. Only patients from the first cluster were successfully weaned during the first 26 h of support and survived for 6 months.

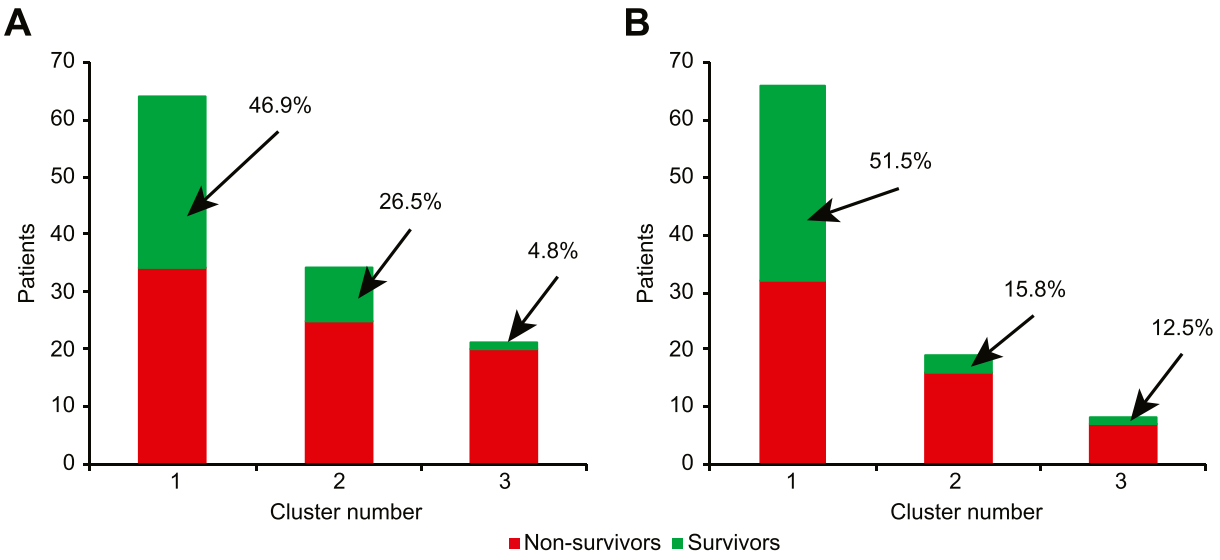

Fig. 5. Six-month survival in clusters. Bars represent total number of patients in the cluster. Labels are the 6-month survival rate in patients assigned to the clusters initially (a) and at the end of the observation period (b). The distribution of *survivors* | *nonsurvivors* in the clusters was statistically significant throughout all ECLS observation periods. In the shown examples, $\chi 2$ (2, N = 119) = 13.66 (p < 0.0001) after initial classification (a) and χ^2 (2, N = 93) = 10.71 (p = 0.005) after 26 h of support (b).

at the start and end of the period as variables for the clustering procedure. Therefore, the clustering procedure was affected by the initial value of the debt and its repayment efficiency.

The distribution of patients by the etiology of cardiogenic shock was statistically significant after the initial cluster step. The observed high percentage of postcardiotomy patients in Cluster 1 with the lowest initial oxygen debt (Fig. 3a) can be explained by the continuous observation and treatment of these patients from the end of surgery until the start of ECLS. The percentage of patients with 'Out of Hospital Circulatory Arrest' in Cluster 3 with the highest accumulated oxygen debt (Fig. 3a) could be expected by the severity of the condition and commonly longer time between insult and starting ECLS. This difference by etiological factor disappears after 2 h of support (Fig. 3b). Although we did not find a statistically significant relationship between the etiology of cardiogenic shock and six-month survival (Fig. 1b, p = 0.069), the effect of the initial insult and reversibility of myocardial damage is self-explanatory. However, our data showed that timely and effective oxygen debt repayment could prevent slippage into a *vicious cycle* of injury, cardiac and systemic decompensation, and further injury and decompensation. The survival rate was significantly higher in patients initially assigned to Cluster 1 (with accumulated oxygen debt of approximately 1500 ml), and it further increased due to the migration of patients over the course of the 26-h ECLS observation period.

Patients in Cluster 1 and Cluster 2 had significantly higher mean arterial pressures (Fig. 6a) and required lower norepinephrine infusion rates (Fig. 6b) than patients assigned to Cluster 3. The cardiogenic shock stages defined by the SCAI Consensus Statement Classification [41,42] could be imposed onto the clusters derived for our population The patients in Cluster 3 most likely had stage E ("Extremis") or refractory cardiogenic shock with relatively low mean arterial pressure and nonsignificant in time intervals of decreasing (repayment) oxygen debt despite the use of ECLS and the high rate of norepinephrine infusion (Fig. 6a and b). Cluster 2 consisted of patients who most likely had stage D ("Deteriorating") or a mixture of the last three SCAI shock stages. These patients readily migrated to Cluster 1 or Cluster 3 (Fig. 4). Most of our patients were assigned to Cluster 1. Presumably, these patients were in stage C ("Classic") of cardiogenic shock. These patients required a lower infusion rate of norepinephrine to maintain a mean arterial pressure of approximately 70 mmHg (Fig. 6a, b). However, an observed significant elevation of oxygen debt after 2 h of circulatory support (Fig. 2) suggests further deterioration, but we believe that the rising lactate with increasing total blood flow with the initiation of ECLS could be explained by lactate washout from previously hypoperfused tissues [43]. Furthermore, this cluster's patients demonstrated a steady decrease in total oxygen debt during each following time interval until the end of the observation period (Fig. 2). From this perspective, the absence of an oxygen debt rise after 2 h of support in Cluster 3 is a sign of vasoplegia and washing out of the substrates of anaerobic metabolism to the circulation before the start of ECLS. This suggestion is supported by the highest amount of oxygen debt accumulated (Fig. 2) and persistent hypotension despite the highest infusion rate of norepinephrine throughout the ECLS observation period (Fig. 6a, b).

However, the accumulation of total oxygen debt, even more than 15,000 ml (Cluster 3), does not mean inevitable death. Timely and effective repayment of oxygen debt can prevent irreversible damage. Four patients migrated from Cluster 3 to Cluster 2 after eight to 14 h of support (Fig. 4). Two of these patients migrated further to Cluster 1 after 20 to 26 h of support and survived until the end of the six-month observation period.

We realize that the amount of *'total oxygen debt'*, as computed using a linear regression equation based on animal models of hemorrhagic shock, can differ from the actual 'debt'. However, the universal character of the pathophysiological mechanisms of oxygen debt accumulation and repayment and the robust linear relation of debt with lactate concentration permit us to use this value as an indicator of the severity and duration of the shock. Furthermore, the application of the oxygen debt theory to cardiogenic shock patients sustained by ECLS combined with cluster analysis allowed us to better describe and understand the patterns of end-organ hypoperfusion recovery and the mechanisms of its failure. The failure of massive oxygen debt repayment in the intensive care unit could be related to the persisting of abnormal microcirculatory perfusion despite normal oxygen delivery values [44]. However, one of the most challenging problems in the treatment of patients with severe circulatory shock is that the burden of accumulated oxygen debt must be repaid by timely increasing oxygen delivery above baseline levels to restore metabolic function and prevent ongoing organ injury at the cellular level [17,18,20,39]. Therefore, returning oxygen delivery to only normal basal levels after an accumulation of oxygen debt is insufficient to prevent subsequent organ injury [17]. Mechanical circulatory support devices, especially with peripheral cannulation, cannot cover the required increase in oxygen delivery.

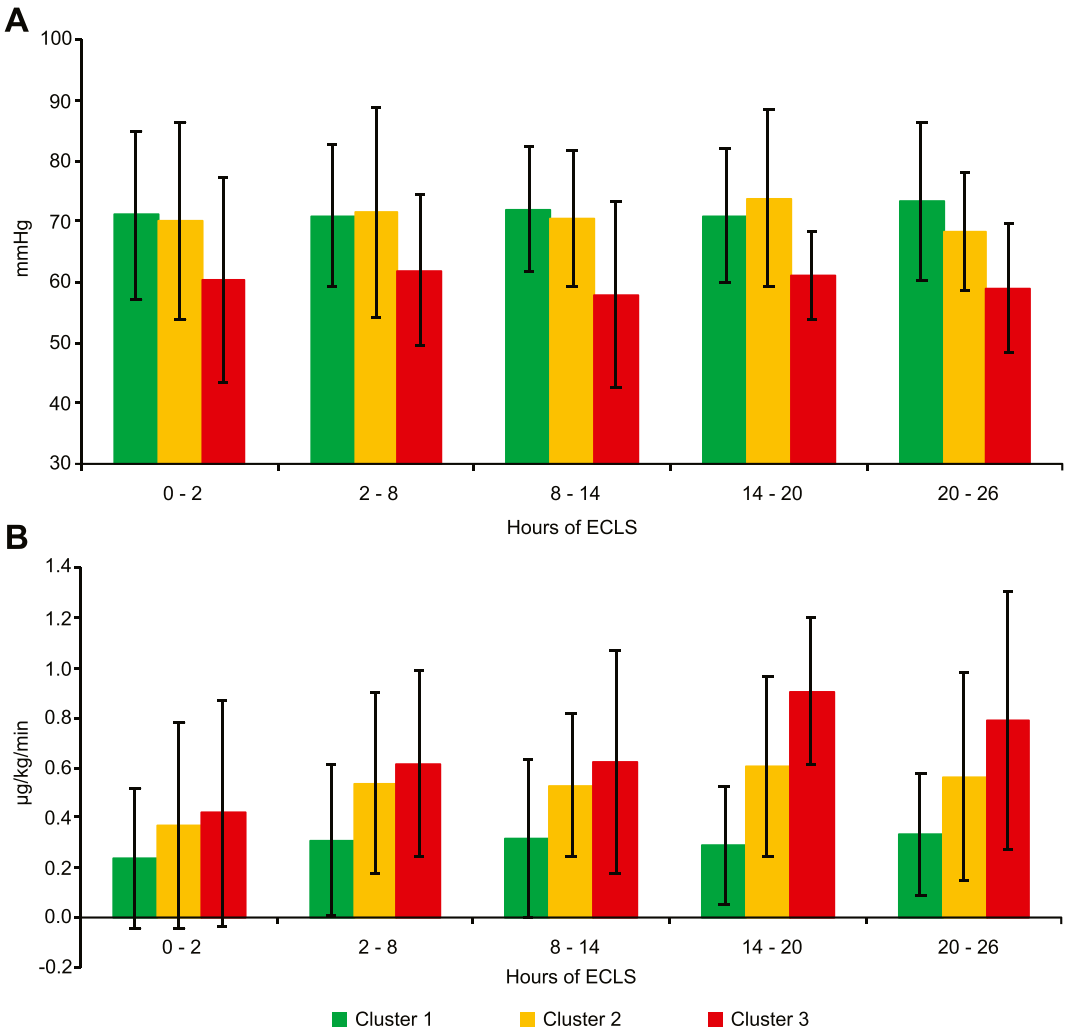

Fig. 6. a) Mean arterial pressure for different clusters and time periods. The mean arterial pressure significantly differed between the clusters at timepoints T2 (2–8 h: $F(2,118) = 3.31$, $p = 0.04$; T3 (8–14 h: $F(2,112) = 8,89$, $p < 0.0001$; and T4 (14–20 h: $F(2,97) = 3.85$, $p = 0.025$), representing the period of ECLS; b) norepinephrine infusion rate for different clusters and time periods. The infusion rate significantly differed between the clusters at timepoints T2 (2–8 h: $F(2,109) = 7.68$, $p = 0.001$); T4 (14–20 h: $F(2,93) = 10.29$, $p < 0.0001$); and T5 (20–26 h: $F(1,87) = 13.05$, $p < 0.0001$).

There are several ways to bypass this limitation that should be further investigated. Decreasing the metabolic rate by permissive hypothermia, used with success in trauma patients [45], could create a necessary excess (relative) oxygen delivery. Another possible way is to limit the duration of exposure to the products of anaerobic metabolism and the concomitant inflammatory response reaction of high-volume hemofiltration, which is widely used in critically ill patients [46,47] or zero-balanced ultrafiltration [48].

The retrospective single-center design has inherent limitations, including missing data and ascertainment bias. The absence of information about preserved myocardial contractility and cardiac output in patients sustained by ECLS did not allow us to estimate the actual oxygen delivery required for the effective repayment of accumulated oxygen debt. Additionally, patients with irreversible myocardium damage, patients who died from postoperative complications other than cardiogenic shock, or complications of ECLS were intentionally not excluded from the analysis and might have affected the reported mortality rate. Concomitant SIRS reactions as well as its effects on multiple organ failure in patients with cardiogenic shock are beyond the scope of our investigation.

The application of oxygen debt theory to cardiogenic shock patients sustained by v-a ECLS combined with cluster analysis uncovered three patterns of oxygen debt repayment. The patterns were associated with six-month mortality. Understanding the pathophysiology of oxygen debt accumulation and repayment as a basic pathophysiological process independent of the causes of the primary insult may offer new insights for a more rational, goal-directed treatment of this highly morbid condition with cardiogenic shock.

Ethics approval and consent to participate

The study was approved by the medical-ethical approval commission of Maastricht University Medical Centre (METC 2020–1448, 18-06-2020). No written consent was required.

Consent for publication

Not applicable.

Availability of data and materials

Available on request.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

YG: Conceptualization, Methodology, Writing – original draft;
EK: Data curation, Writing – original draft;
IW: Supervision, Writing – review & editing;
SK: Methodology, Formal Analysis;
PW: Writing – review & editing;
RL: Supervision, Writing – review & editing;
JM: Project administration, Supervision, Writing – review & editing.
All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

References

[1] Berg DD, Bohula EA, van Diepen S, et al. Epidemiology of shock in contemporary cardiac intensive care units. Circ Cardiovasc Qual Outcomes. 2019;12(3):e005618.
[2] Bjerkvig CK, Strandenes G, Eliassen HS, et al. "Blood failure" time to view blood as an organ: how oxygen debt contributes to blood failure and its implications for remote damage control resuscitation. Transfusion. 2016;56(Suppl. 2):S182–9.
[3] Ronco JJ, Fenwick JC, Tweeddale MG, et al. Identification of the critical oxygen delivery for anaerobic metabolism in critically Ill septic and nonseptic humans. JAMA. 1993;270(14):1724–30.
[4] Lazzeri C, Valente S, Chiostri M, Gensini GF. Clinical significance of lactate in acute cardiac patients. World J Cardiol. 2015;7(8):483–9.
[5] Bakker J, Postelnicu R, Mukherjee V. Lactate: where are we now? Crit Care Clin. 2020;36(1):115–24.
[6] Garcia-Alvarez M, Marik P, Bellomo R. Stress hyperlactataemia: present understanding and controversy. Lancet Diabetes Endocrinol. 2014;2(4):339–47.
[7] van Diepen S, Katz JN, Albert NM, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. Circulation. 2017;136(16):e232–68.
[8] Rixen D, Siegel JH. Metabolic correlates of oxygen debt predict posttrauma early acute respiratory distress syndrome and the related cytokine response. J Trauma. 2000;49(3):392–403.
[9] Lindholm MG, Hongisto M, Lassus J, et al. Serum lactate and A relative change in lactate as predictors of mortality in patients with cardiogenic shock - results from the cardshock study. Shock. 2020;53(1):43–9.
[10] Hayiroglu MI, Keskin M, Uzun AO, et al. Predictors of in-hospital mortality in patients with ST-segment elevation myocardial infarction complicated with cardiogenic shock. Heart Lung Circ. 2019;28(2):237–44.
[11] Gjesdal G, Braun OO, Smith JG, Schersten F, Tyden P. Blood lactate is a predictor of short-term mortality in patients with myocardial infarction complicated by heart failure but without cardiogenic shock. BMC Cardiovasc Disord. 2018;18(1):8.
[12] Pabst D, Foy AJ, Peterson B, Soleimani B, Brehm CE. Predicting survival in patients treated with extracorporeal membrane oxygenation after myocardial infarction. Crit Care Med. 2018;46(5):e359–63.
[13] Ro SK, Kim WK, Lim JY, Yoo JS, Hong SB, Kim JB. Extracorporeal life support for adults with refractory septic shock. J Thorac Cardiovasc Surg. 2018;156(3):1104–9.
[14] Davierwala PM, Leontyev S, Verevkin A, et al. Temporal trends in predictors of early and late mortality after emergency coronary artery bypass grafting for cardiogenic shock complicating acute myocardial infarction. Circulation. 2016;134(17):1224–37.
[15] Valente S, Lazzeri C, Vecchio S, et al. Predictors of in-hospital mortality after percutaneous coronary intervention for cardiogenic shock. Int J Cardiol. 2007;114(2):176–82.
[16] Hernandez G, Bellomo R, Bakker J. The ten pitfalls of lactate clearance in sepsis. Intensive Care Med. 2019;45(1):82–5.
[17] Barbee RW, Reynolds PS, Ward KR. Assessing shock resuscitation strategies by oxygen debt repayment. Shock. 2010;33(2):113–22.
[18] Rixen D, Siegel JH. Bench-to-bedside review: oxygen debt and its metabolic correlates as quantifiers of the severity of hemorrhagic and post-traumatic shock. Crit Care. 2005;9(5):441–53.
[19] Hill AV. The diffusion of oxygen and lactic acid through tissues. Proceed Royal Soc London Series B, Cont Papers Biol Char. 1928;104(728):39.
[20] Dunham CM, Siegel JH, Weireter L, et al. Oxygen debt and metabolic acidemia as quantitative predictors of mortality and the severity of the ischemic insult in hemorrhagic shock. Crit Care Med. 1991;19(2):231–43.
[21] Rixen D, Raum M, Holzgraefe B, et al. A pig hemorrhagic shock model: oxygen debt and metabolic acidemia as indicators of severity. Shock. 2001;16(3):239–44.
[22] Shoemaker WC, Appel PL, Kram HB. Tissue oxygen debt as a determinant of lethal and nonlethal postoperative organ failure. Crit Care Med. 1988;16(11):1117–20.
[23] Ganushchak YM, Fransen EJ, Visser C, De Jong DS, Maessen JG. Neurological complications after coronary artery bypass grafting related to the performance of cardiopulmonary bypass. Chest. 2004;125(6):2196–205.
[24] Jain AK. Data clustering: 50 years beyond K-means. Pattern Recogn Lett. 2010;31(8):651–66.
[25] van Giessen A, de Wit GA, Smit HA, et al. Patient selection for cardiac surgery: time to consider subgroups within risk categories? Int J Cardiol. 2016;203:1103–8.
[26] Castela Forte J, Perner A, van der Horst ICC. The use of clustering algorithms in critical care research to unravel patient heterogeneity. Intensive Care Med. 2019;45(7):1025–8.
[27] Han J, Kamber M, Pei J. Data mining: Concepts and techniques. 3d ed.. San Francisco, CA, USA: Morgan Kaufmann Publishers Inc.; 2011..
[28] den Uil CA, Maat AP, Lagrand WK, et al. Mechanical circulatory support devices improve tissue perfusion in patients with end-stage heart failure or cardiogenic shock. J Heart Lung Transplant. 2009;28(9):906–11.
[29] Werdan K, Gielen S, Ebelt H, Hochman JS. Mechanical circulatory support in cardiogenic shock. Eur Heart J. 2014;35(3):156–67.
[30] Mungan İ, Kazancı D, Bektaş Ş, Ademoglu D, Turan S. Does lactate clearance prognosticates outcomes in ECMO therapy: a retrospective observational study. BMC Anesthesiol. 2018;18(1):152.
[31] Jones TL, Nakamura K, McCabe JM. Cardiogenic shock: evolving definitions and future directions in management. Open Heart. 2019;6(1):e000960.
[32] Marin F, Pighi M, Pesarini G, Piccoli A, Ribichini F. Devices for mechanical circulatory support and strategies for their management in cardiogenic shock. Kardiol Pol. 2019;77(6):589–95.
[33] Berg DD, Barnett CF, Kenigsberg BB, et al. Clinical practice patterns in temporary mechanical circulatory support for shock in the critical care cardiology trials network (CCCTN) registry. Circ Heart Fail. 2019;12(11):e006635.
[34] den Uil CA, Lagrand WK, Valk SD, Spronk PE, Simoons ML. Management of cardiogenic shock: focus on tissue perfusion. Curr Probl Cardiol. 2009;34(8):330–49.
[35] Donnino MW, Miller J, Goyal N, et al. Effective lactate clearance is associated with improved outcome in post-cardiac arrest patients. Resuscitation. 2007;75(2):229–34.
[36] Jansen TC, van Bommel J, Schoonderbeek FJ, et al. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med. 2010;182(6):752–61.
[37] Vincent J-L, Quintairos Silva A, Couto L, Taccone FS. The value of blood lactate kinetics in critically ill patients: a systematic review. Crit Care. 2016;20(1):257.
[38] Hernandez G, Ospina-Tascon GA, Damiani LP, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK randomized clinical trial. JAMA. 2019;321(7):654–64.
[39] Siegel JH, Fabian M, Smith JA, et al. Oxygen debt criteria quantify the effectiveness of early partial resuscitation after hypovolemic hemorrhagic shock. J Trauma. 2003;54(5):862–80. [discussion 880].
[40] Staudacher D, Supady A, Biever P, et al. Comprehensive Analysis Of Absolute Lactate Levels and Lactate Clearance in VA-ECMO Patients – Impact on Survival. Resuscitation. 2019;142:e12.
[41] Baran DA, Grines CL, Bailey S, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock: this document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. Catheter Cardiovasc Interv. 2019;94(1):29–37.
[42] Jentzer JC, van Diepen S, Barsness GW, et al. Cardiogenic shock classification to predict mortality in the cardiac intensive care unit. J Am Coll Cardiol. 2019;74(17):2117–28.
[43] Ganushchak YM, Maessen JG, de Jong DS. The oxygen debt during routine cardiac surgery: illusion or reality? Perfusion. 2002;17(3):167–73.
[44] Ince C. Hemodynamic coherence and the rationale for monitoring the microcirculation. Crit Care. 2015;19(Suppl. 3):S8.
[45] Aggen D, Azeem M, Labana S, et al. How cold is cold enough? Retrospective review of therapeutic hypothermia outcomes and protocol revision in a community-based hospital. CHEST. 2015;148(4):241A.
[46] Junhai Z, Beibei C, Jing Y, Li L. Effect of high-volume hemofiltration in critically ill patients: A systematic review and meta-analysis. Med Sci Monit. 2019;25:3964–75.
[47] Luo Y, Sun G, Zheng C, et al. Effect of high-volume hemofiltration on mortality in critically ill patients: A PRISMA-compliant systematic review and meta-analysis. Medicine. 2018;97(38):e12406.
[48] Mick S, Hilberath JN, Davidson MJ, Fitzgerald D. Zero balance ultrafiltration for the correction of acute acidosis after a period of prolonged deep hypothermic circulatory arrest. Perfusion. 2012;27(1):9–11.