Weaning-Related Shock in Patients With ECMO: Incidence, Mortality, and Predisposing Factors

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Version of Record: https://www.sciencedirect.com/science/article/pii/S1053077020307424
Manuscript_984449cffe316ee1f1b67da99660d754

Original Article

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Declarations of interest

None.

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ABSTRACT

Objective: Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is commonly used to manage refractory cardiogenic shock after cardiac surgery, with 31 to 76% of patients successfully weaned off their ECMO. However, it is associated with high mortality rates and 20 to 65% of weaned patients do not survive to hospital discharge. This study aims to assess the incidence of ECMO weaning-related shock, their risk factors and prognosis in the Intensive Care Unit (ICU).

Design: Retrospective observational cohort study.

Setting: Surgical ICU of Cardiology Institute of Pitié-Salpêtrière University Hospital (Paris-France).

Participants: Patients who were assisted with a peripheral VA-ECMO from January 2015 to December 2017 were included. Patients with veno-venous, central or right ECMO were excluded.

Measurements: We collected data on patients' characteristics, during and after surgery. The indications for VA-ECMO implantation were ventricular dysfunction, primary graft dysfunction, and refractory cardiac arrest. Weaning-related shock was defined as the need to introduce or increase the dose of catecholamine at ECMO explantation or in the following week.

Results: After weaning off VA-ECMO, 56 out of 146 patients (38.4%) presented weaning-related shock: 55% were septic shocks, 12.5 % were caused by right ventricle failure and 7.1% by hemorrhage. ICU mortality was 42% versus 8% in patients who did not present shock. Multivariable analysis showed that patients with pulmonary hypertension and those with norepinephrine before weaning were more likely to develop shock.

Conclusion: ECMO weaning-related shock are frequent in patients with refractory cardiogenic shock after cardiac surgery. This was most commonly due to sepsis. These cause higher mortality rates, calling for further evaluation.

Keywords: Extracorporeal Life Support; Cardiac Surgical Procedure; Cardiopulmonary Bypass; Cardiogenic Shock

INTRODUCTION

The extracorporeal membrane oxygenation (ECMO) was first used nearly 50 years ago (1,2). It has been implemented as a treatment for pulmonary and cardiac failure (3), and is particularly used in patients with post-cardiotomy cardiogenic shock, a condition that can be fatal without mechanical circulatory support (4–7). Extracorporeal Life Support Organization (ELSO) database show the exponential increase in the use of venoarterial (VA)-ECMO in these cases (8). Nevertheless, morbidity rate in patients with ECMO is significant, often associated with prolonged hospital stays and poor quality of life for the survivors after hospital discharge (9–13). Moreover, in-hospital mortality is around 60% (14,15) and one-year survival is estimated to be 30% (15). Latest studies show that patients who have benefited from VA-ECMO for post-cardiotomy refractory cardiogenic shock can be weaned off in 48 to 60% of cases (14–17). Unfortunately, there is no consensus for the timing and weaning modalities of VA-ECMO, and so far, no explanation has been found regarding weaning failures or the causes of death in these patients.

The aim of this study is therefore to focus on the weaning of VA-ECMO, more particularly in patients who develop weaning-related shock after explantation, to analyze its consequences, and try to identify the predisposing factors for its occurrence.

METHODS

This study was approved by the ethics committee for research of the French Society of Anesthesia & Intensive Care Medicine (IRB 00010254-2019-103). Due to the retrospective design of the study, and in accordance with the decision of the ethics committee and French regulation and non-interventional studies, signed informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki principles.

Design and Setting

This observational single center retrospective study was conducted in the Surgical Intensive Care Unit (ICU) of the Cardiology Institute of La Pitié-Salpêtrière University Hospital (Paris, France). All patients admitted in our unit and assisted by VA-ECMO between January 2015 and December 2017 were screened. Patients with veno-venous ECMO, central ECMO or right VA-ECMO were excluded. We also excluded patients who died or were transferred to another unit before weaning off the VA-ECMO, and those whose VA-ECMO was bridged to cardiac transplantation or to Left Ventricular Assist Device. Patients were identified and data was collected using computerized medical records. Data collected was pseudonymized.

We collected socio-demographic and clinical characteristics of patients, intra operative data (such as type of intervention, antibioprophylaxis, duration of extracorporeal circulation, transfusion of blood products, administration of catecholamines or nitric oxide (NO), and the presence or absence of ECMO before or after surgery), and post-operative data (such as number of ECMO cannulations, dates and sites of cannula implantation and explantation, type of organ failure causing ECMO implementation, cardiac function before and after weaning, doses of catecholamines and / or NO before and after weaning, realization of a withdrawal test,

occurrence of weaning-related shock, occurrence of associated organ failure or death related shock, ECMO re-implantation, etiology attributed to the state shock, length of stay in ICU, duration of mechanical ventilation, occurrence of hemorrhagic, ischemic, or infectious complications, and the need for surgical revision).

Our protocol for ECMO weaning includes the following: a hemodynamically stable patient, with mean arterial pressure ≥ 65 mm Hg in the absence or at low doses of vasoactive agents, with a pulsatile arterial waveform, a left ventricular ejection fraction (LVEF) > 25-30%, a left ventricular outflow tract velocity time integral (VTI) > 12 cm, a partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) ratio > 200 with FiO2 delivered by the extracorporeal circuit ≤ 30% and that delivered by the ventilator circuit ≤ 60%.

Weaning-related shock was defined as the necessity to introduce catecholamine (to maintain a mean arterial blood pressure ≥ 65 mm Hg) or increase the dosage by at least 100% (in patients who already had catecholamine), occurring at the time of ECMO explantation or in the following week, accompanied by clinical organ failure (oliguria, confusion, clammy skin…) or biological organ failure (acute renal failure, hyperlactatemia, acute hepatic failure...) or the need of circulatory support. Catecholamine introduction or modification had to persist for more than 6 hours to be considered significant. This definition did not include hemodynamic failures due to vasoplegia when ECMO explantation occurred under general anesthesia. Right ventricular dysfunction was defined as tricuspid annular plane systolic excursion (TAPSE) ≤ 15 mm or tricuspid lateral annular systolic velocity (S') < 10 cm/s. Septic shock was considered only if it was documented by a positive blood, pulmonary, wound or urine culture.

Statistical analysis

Categorical variables were expressed as percentages. Continuous variables were expressed as median with its interquartile range (Q1 - Q3), or as mean +/- standard deviation. Statistical significance level is 0.05 and two-sided tests were used. For the univariable analysis of risk factors, continuous variables were compared with Student's test or the Wilcoxon signed-rank test, as appropriate. Categorical variables were compared using the Chi-2 tests or Fisher's exact test, as appropriate. Variables achieving p-value < 0.1 in univariable analysis were considered as candidates to enter in the multivariable models, except if they presented a rate of missing data larger than 40%. The final model was established using a backward step-by-step selection based on the likelihood ratio test. Logistic regressions were used to estimate corresponding odds ratio (OR) and 95% confidence interval (95% CI) relative to candidate factors in univariable models and final multivariate model. Statistical analyses were performed using R software (version 3.4.3, licenses GNU GPL, The R foundation for statistical computing, Vienna, Austria).

RESULTS

Study population

Between January 2015 and December 2017, 366 patients assisted with ECMO were hospitalized in our unit. The analysis included 146 patients (**Figure 1**, flowchart). Demographic and clinical characteristics of the population are described in **Table 1**.

Out of the 146 patients included in the study, 141 underwent surgery during their hospitalization, including 140 surgeries with cardiopulmonary bypass. The most frequent types of surgeries were the following: 57 heart transplantations (40.4%), 32 valve surgeries (22.7%), and 22 coronary artery bypass graft surgeries (15.6%).

VA-ECMO implantation and weaning

The indications for VA-ECMO implantation were biventricular dysfunction (40.4%), right ventricular dysfunction (24.7%), left ventricular dysfunction (21.9%), primary graft dysfunction (7.5%), or for refractory cardiac arrest (4.8%). Left ventricular venting (intra-aortic balloon pump or IMPELLA®) was employed in 44.5% of cases. The median LVEF at time of weaning was 40% [32.5-50]. ~~in patients who presented weaning-related shock versus 45% [38-50] in patients who did not develop weaning related shock.~~ Overall, 95.8% of patients had an LVEF ≥ 25%. The median left ventricular outflow tract VTI was 15cm [14-18]. Right ventricular function was normal at the time of weaning in 72% of cases and moderately altered in the remaining 28% of cases. The median duration before ECMO weaning was 7 days [5-11.75]. ~~in patients who presented weaning related shock versus 7 days [5-12] in the patients who did not develop weaning-related shock~~. Surviving patients were discharged from ICU 8 days [3.0-17.2] after VA-ECMO weaning.

Weaning-related shock

Of the 146 patients included, 56 presented weaning-related shock, out of which 41 recurrent shocks occurred on weaning day. The cumulative incidence of weaning-related shock in this population was 39.5%, 95% CI [30.8, 69.2]. No case of shock was observed after the 4th day of ECMO withdrawal (**Figure 2**). Concerning the causes of weaning-related shock, 53% have been attributed to septic shock documented by a positive blood, pulmonary, wound or urine culture, 11% were secondary to right ventricular dysfunction, 7% due to arrhythmias, 4% to hemorrhage, 9% miscellaneous, and 16% indeterminant. All the causes are summarized in **Table 2** with their corresponding percentages of hospital mortality. During their ICU stay, patients presented several complications summarized in **Supplemental Table 1**, according to whether they developed weaning-related shock.

The median LVEF at time of weaning was 40% [30-43.75] in patients who presented weaning-related shock versus 45% [38-50] in the patients who didn't develop weaning-related shock. The median duration before ECMO weaning was 8 days [6-11] in patients who presented weaning-related shock versus 7 days [5-12] in the patients who didn't develop weaning-related shock.

~~On the other hand, 22%~~ Twenty-two percent of patients who developed weaning-related shock, required ECMO re-implantation within a median delay of 2 days, versus only 2 patients (2.2%) among those who did not develop weaning-related shock.

Among patients who presented a state of shock, 42% died in the ICU and 67% of these deaths were attributed to weaning-related shock. Seven of the 90 patients (7.8%) who did not present weaning-related shock, died in the ICU, mainly secondary to neurological complications. The occurrence of weaning-related shock was associated with a 5.4 times higher mortality in ICU

(95% CI (Bootstrap) = [2.8-14.7]). Moreover, we noted a significant increase in length of stay in ICU (22.5 days [IQR 14-31.25] versus 16 days [IQR 10-26]) and duration of mechanical ventilation (16.5 days [IQR 5-29] versus 6 days [IQR 2-14]) in patients with weaning-related shock compared to those who did not present shock.

One patient was excluded from the univariable and multivariate analysis of risk factors for shock because of their early death, 3 days after weaning, among patients who did not present a state of shock. The six additional deaths in this group occurring after at least 11 days of ECMO withdrawal were kept in the analysis because we considered this delay to be sufficient to record a prior weaning-related shock. In univariable analysis, risk factors for developing weaning-related shock after VA-ECMO explantation were female sex, a Euroscore 2 > 10%, glomerular filtration rate < 50mL/min/1.73m² at ICU admission, history of hypertension or pulmonary hypertension, and an LVEF < 40% before explantation and the presence of norepinephrine prior to explantation. Heart transplantation was protective. Corresponding OR, estimated by logistic regression, are reported in **Table 3**. LVEF before weaning was not considered as a candidate factor to enter in the multivariate model because it was recorded in only 74 out of 145 patients. After a backward step-by-step selection based on the likelihood ratio test, the final multivariate model established is shown in **Table 3**. In our cohort, the final model computed in 99 patients. It included 2 factors: history of pulmonary hypertension and the presence of norepinephrine prior to explantation ~~allows~~ to predict the occurrence of a weaning-related shock after ECMO explantation. The area under the curve was 0.739; IC95% = [0.652-0.826] (Discrimination slope = 0.21, Mc Fadden pseudo-R2 = 0.17, Brier Score = 0.19, Hosmer Lemeshow test: p = 1).

DISCUSSION

In our study, 40% of patients weaned off their VA-ECMO presented weaning-related shock, which makes it a common complication. All shocks occurred within four days of explantation. To our knowledge, no studies so far investigated weaning-related shock, so it is not possible for us to compare our results with literature data.

Infection was the main cause of weaning-related shock with 53% of cases attributed to septic shock. These infections included, in order of frequency, pneumoniae, cannulation site infection, catheter-related infection, urinary infection and mediastinitis. Recent studies report a high rate of nosocomial infections in patients under ECMO (18,19). It is difficult to detect infection by conventional means in these patients, hence a high rate of daily blood cultures is performed as routine surveillance, and treatment failure of these infections is frequent (20). In their study, Abrams *et al.* (19) also describe that despite a lack of data demonstrating any benefit, antibiotic prophylaxis is commonly administered before implantation, which is usually the case in our unit when ECMO is implemented in the operating room. On the other hand, the benefit of selective digestive decontamination remains uncertain in patients under ECMO. Furthermore, we note that the main etiologies of weaning-related shock described in our study (infections, cardiac failure, arrhythmias and hemorrhage) seemed to correlate with the etiologies of in-hospital mortalities after ECMO withdrawal in patients with cardiogenic shock, as reported by Aso *et al* (21).

Right ventricular dysfunction was the second leading cause of weaning-related shock in our study. One hypothesis to explain this is pre-existing pulmonary hypertension in many of our patients; another hypothesis would be pulmonary embolism. In fact, cases of pulmonary embolism have been reported under ECMO (22) or following ECMO explantation (23). Their

diagnosis is not systematic because patients can be asymptomatic. Only one case of massive pulmonary embolism was reported among our patients.

The occurrence of weaning-related shock was accompanied by a 5.4 times higher mortality in ICU: 42% versus 8% in patients who did not present a state of shock. This can be related to a prolonged duration of low flow, which causes or aggravates organ failures in already weakened patients, also known as the "second hit" hypothesis (24). There was also a significant increase in length of stay in ICU and mechanical ventilation in patients with weaning-related shock compared to those who did not present shock. Even though no study analyzed weaning-related shock and the associated risk factors, Schmidt *et al.* (25) created the SAVE score to predict mortality in patients under VA-ECMO using a set of criteria. Among these criteria, our study also found a protective effect of cardiac transplantation, and an adverse effect of chronic renal failure in the occurrence of weaning-related shock, in the univariate analysis, which did not remain in the final model.

Moreover, all patients weaned off their ECMO had a pre-weaning LVEF ≥ 20%, which corresponds to the threshold advocated by Aissaoui *et al.* (26). In univariable analysis, it appeared that a low LVEF tends to favor the occurrence of weaning-related shock, but this parameter could not be included in the multivariable analysis because of the large number of missing data. Regarding pre-weaning echocardiographic criteria, Huang *et al.* described a correlation between a successful weaning off VA-ECMO and right ventricular ejection fraction (RVEF) > 24.6% (27). The right ventricle function did not appear to be a predictor of weaning failure in our study, but its evaluation was visual, therefore subject to greater inter-individual variability, and the evaluation of right ventricular function is much more complex and difficult than that of the left ventricle. Right ventricular dysfunction was, however, the second leading

cause of weaning-related shock, hence the right ventricle should be well explored before weaning.

The other risk factor reported in our study was the presence of norepinephrine at ECMO weaning. And results showed that more than half of weaning-related shock were septic, hence it is legitimate to think that the need for norepinephrine before weaning may reflect the beginning of a sepsis, unmasked by VA-ECMO withdrawal. Sepsis diagnosis, however, is not always easy in patients with ECMO, in whom the clinical signs can be discrete and fever absent. Diagnosing and treating early infections before ECMO withdrawal is a major challenge, taking into consideration the risk of prolonging the duration of ECMO, which increases the risk of iatrogenic complications including infections.

Limitations

This study is retrospective; hence its first limitation is the presence of missing data. Particularly, data loss concerned criteria used to decide weaning, performing or not an ECMO clamping test, as well as the results of pre- and post-weaning echocardiography including major factors such as LVEF and pulmonary hypertension. In addition, retrospective definition of exposure (weaning off ECMO) and outcome (shock) may have been a source of bias.

The heterogeneity of included patients (post-cardiotomy low cardiac output syndrome, primary graft dysfunction or refractory cardiac arrest) as well as the definition of weaning-related shock may limit the interpretability of the study. In addition, the study focused on ICU stay; therefore no data are available on overall in-hospital mortality. We can also note the lack of power of this study because of the small number of patients presenting weaning-related shock. Finally, the external reproducibility of our study is limited by being single centered.

Conclusions

VA-ECMO is commonly the mechanical circulatory assistance of choice for patients with refractory cardiogenic shock post-cardiotomy. It remains associated with high hospital mortality, even in patients who have been weaned off. Part of this mortality can be explained by the occurrence of a weaning-related shock after ECMO explantation, observed in 40% of our patients, and associated with a 5.4 times higher mortality. Weaning-related shock was attributed to septic shock in 53% of cases. History of pulmonary hypertension and the presence of norepinephrine prior to explantation were independent risk factors for weaning-related shock.

For a better evaluation of this issue, a prospective study is required, with a VA-ECMO weaning protocol, including systematic completion of a clamping test and systematic peri-test echocardiographic assessment that includes an advanced evaluation of the RV.

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FIGURE LEGENDS

Figure 1. Flowchart

Figure 2. Occurrence of shock according to the number of days after weaning

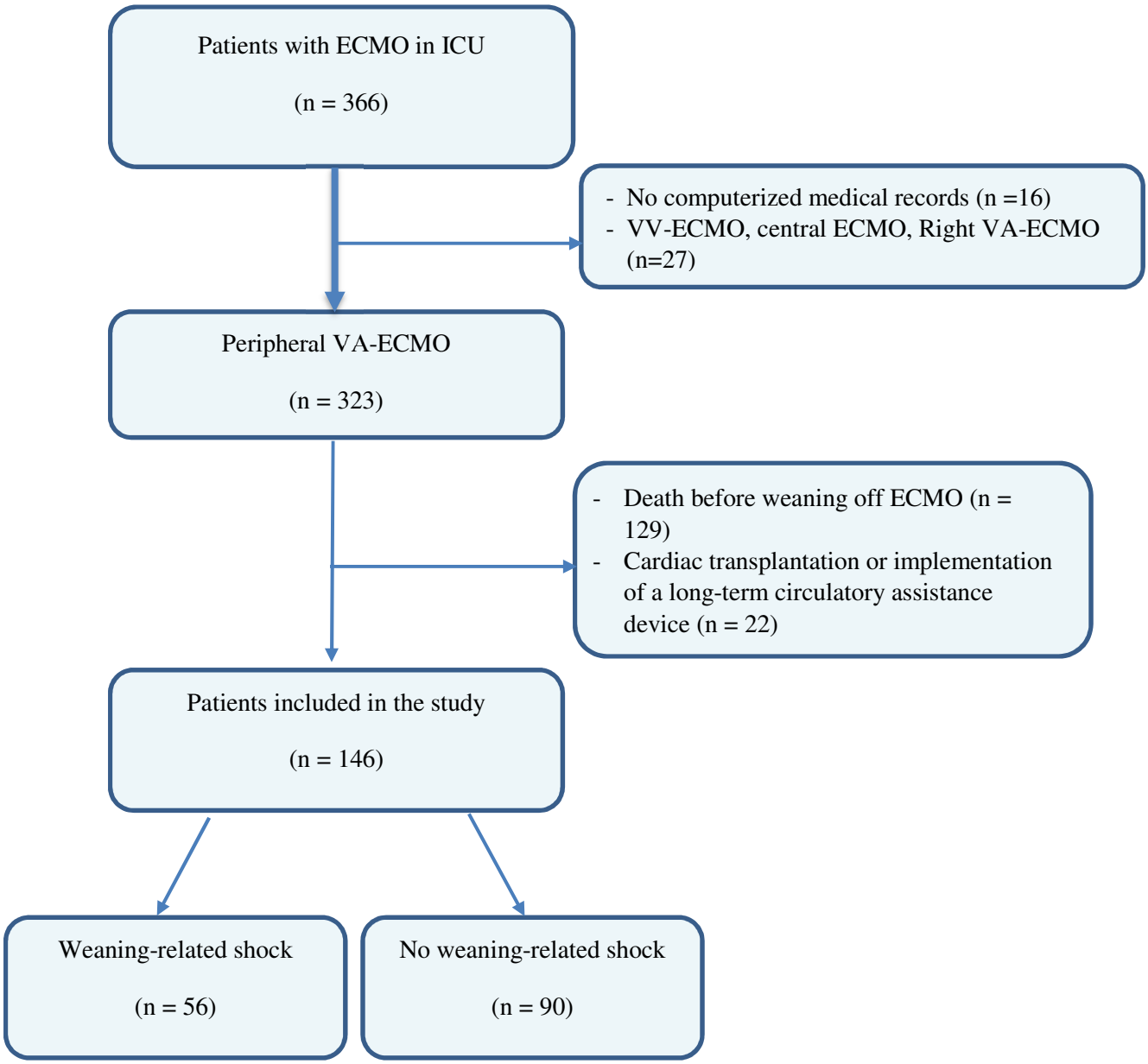

Figure 1. Flow chart

Abbreviations: ICU = intensive care unit, ECMO = extracorporeal membrane oxygenation, VA= veno-arterial, VV = veno-venous

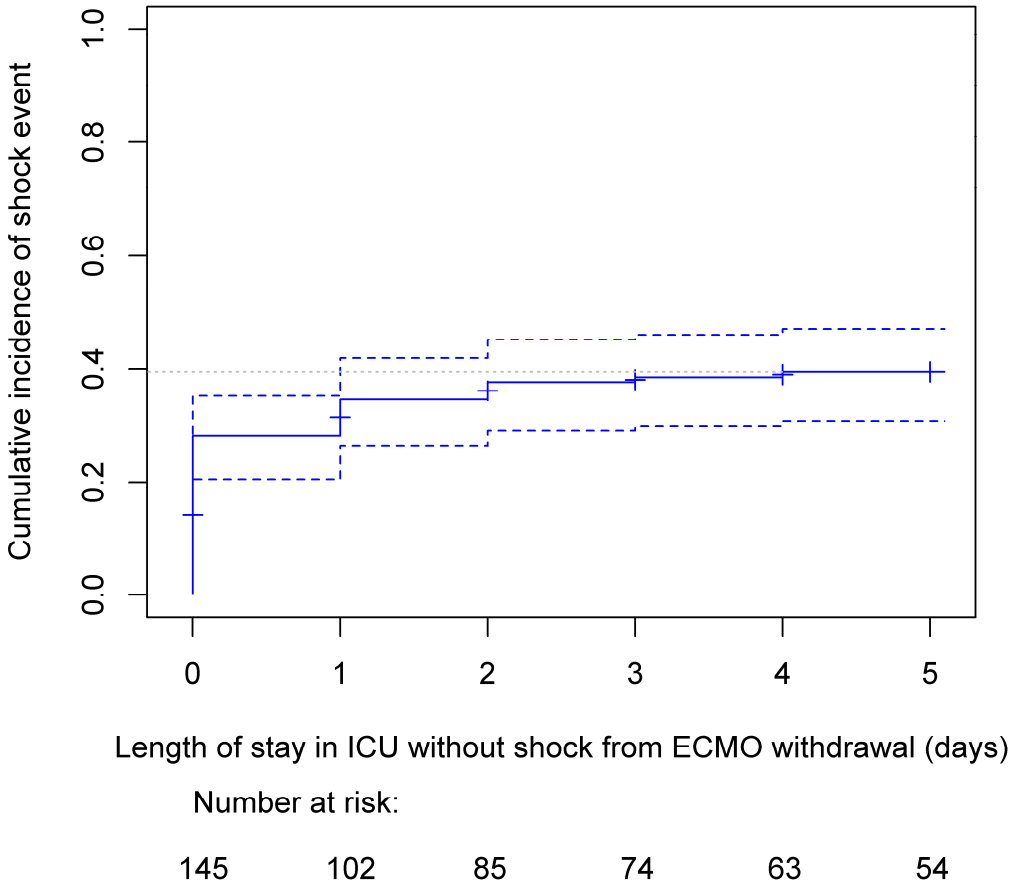

Figure 2. Occurrence of shock according to the number of days after weaning

Abbreviations: ICU = intensive care unit, ECMO = extracorporeal membrane oxygenation

Table 1. Patient characteristics and medical history

Age, median [IQR]	61 [52-69]
Sex, n (%)	
Male	107 (73,3%)
Female	39 (26,7%)
BMI, median [IQR]	25,2 [22,4-29,1]
ASA score, n (%)	
2	4 (2,8%)
3	44 (30,3%)
4	85 (58,6%)
5	12 (8,3%)
Euroscore 2, median [IQR]	15 [4,1-25]
SOFA score, median [IQR]	9 [7-10]
SAPS II score, median [IQR]	54,5 [46-65]
Glomerular Filtration Rate < 50ml/min, n (%)	33 (23,9%)
Dialysis prior to admission , n (%)	5 (3,4%)
COPD, n (%)	12 (8,2%)
Diabetes, n (%)	32 (21,9%)
Dyslipidemia, n (%)	66 (45,2%)
Hypertension, n (%)	66 (45,2%)
Peripheral artery disease, n (%)	11 (7,6%)
LVEF prior to admission, median [IQR]	35 [20-50]
Pulmonary hypertension, n (%)	65 (44,5%)

Abbreviations: IQR = interquartile range, BMI = body mass index, SOFA = sequential organ failure assessment, SAPS II = simplified acute physiology score II, COPD = chronic obstructive pulmonary disease, LVEF = left ventricular ejection fraction

Table 2. Etiologies of weaning-related shocks and their corresponding percentages of hospital mortality

	Variables	Total number of patients (%)	Number of deaths (%)	Number of surviving patients (%)
State of shock	No	90 (62%)	7 (23%)	83 (72%)
	Yes	55 (38%)	23 (77%)	32 (28%)
Etiologies of shock	Septic shock	29 (53%)	18 (78%)	11 (34%)
	Unknown etiology	9 (16%)	0 (0%)	9 (28%)
	Right ventricle dysfunction	6 (11%)	1 (4%)	5 (16%)
	Arrhythmia	4 (7%)	0 (0%)	4 (12%)
	Hemorrhagic shock	2 (4%)	1 (4%)	1 (3%)
	Septic and hemorrhagic shock	2 (4%)	1 (4%)	1 (3%)
	Left ventricle dysfunction	1 (2%)	0 (0%)	1 (3%)
	Mesentery ischemia	1 (2%)	1 (4%)	0 (0%)
	LVAD thrombosis	1 (2%)	1 (4%)	0 (0%)

Abbreviations: LVAD = left ventricular assistant device

Table 3. Risk factors for weaning-related shock

Factors	Univariable analysis			Multivariable analysis		
	N	*Odds Ratio [95%CI]*	*p-value*	*N*	*Odds Ratio [95%CI]*	*p-value*
Sex: Female	145	2.05 [0.97, 4.31]	0.06			
Renal failure	137	2.96 [1.4, 6.24]	0.003			
Pulmonary Hypertension	100	4.97 [1.9, 12.99]	<0.001	99	5.8 [2.0, 16.16]	≤ 0.001
Hypertension	145	1.78 [0.91, 3.5]	0.093			
Heart transplantation	140	0.53 [0.26, 1.08]	0.075			
Norepinephrine before weaning	144	3.32 [1.42, 7.72]	0.005	99	6.4 [1.848-21.8]	0.001
Euroscore 2 ≥ 10	122	0.51 [0.24, 1.07]	0.072			

Definitions:

- **Renal failure** (regardless of its cause) was defined by an estimated glomerular filtration rate below 60 mL / min / 1.73 m², for more than 3 months.
- **Pulmonary hypertension** was defined by a systolic pulmonary arterial pressure greater than 40 mmHg.
- **Norepinephrine before weaning** refers to the presence of Norepinephrine in the 24 hours before weaning regardless of its dose.