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Left Ventricular Unloading is Associated with Lower Mortality in Cardiogenic Shock Patients Treated with Veno-Arterial Extracorporeal Membrane Oxygenation:

Results From An International, Multicenter Cohort Study

Running Title: *Schrage et al.; LV Unloading in CS Patients on VA-ECMO*

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Abstract

Background: Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly used to treat cardiogenic shock. However, VA-ECMO might hamper myocardial recovery. The Impella unloads the left ventricle. The aim of this study was to evaluate if left ventricular unloading in cardiogenic shock patients treated with VA-ECMO was associated with lower mortality.

Methods: Data from 686 consecutive patients with cardiogenic shock treated with VA-ECMO with or without left ventricular unloading (using an Impella) at 16 tertiary-care centers in 4 countries were collected. The association between left ventricular unloading and 30-day mortality was assessed by Cox regression models in a 1:1 propensity-score-matched cohort.

Results: Left ventricular unloading was used in 337 of the 686 patients (49%). After matching, 255 patients with left ventricular unloading were compared with 255 patients without left ventricular unloading. In the matched cohort, left ventricular unloading was associated with lower 30-day mortality (hazard ratio 0.79, 95% confidence interval 0.63-0.98, p=0.03) without differences in various subgroups. Complications occurred more frequently in patients with left ventricular unloading; e.g. severe bleeding in 98 (38.4%) vs. 45 (17.9%), access-site related ischemia in 55 (21.6%) vs. 31 (12.3%), abdominal compartment in 23 (9.4%) vs. 9 (3.7%) and renal replacement therapy in 148 (58.5%) vs. 99 (39.1%).

Conclusions: In this international, multicenter cohort study, left ventricular unloading was associated with lower mortality in cardiogenic shock patients treated with VA-ECMO, despite higher complication rates. These findings support use of left ventricular unloading in cardiogenic shock patients treated with VA-ECMO and call for further validation, ideally in a randomized, controlled trial.

Key Words: VA-ECMO; Impella; cardiogenic shock; unloading; ECMELLA

Non-standard Abbreviations and Acronyms

CI	Confidence interval
ECMELLA	Addition of an Impella on top of veno-arterial extracorporeal membrane oxygenation
VA-ECMO	Veno-arterial extracorporeal membrane oxygenation
eCPR	VA-ECMO-assisted cardiopulmonary resuscitation
HR	Hazard ratio
IQR	Interquartile range
LV	Left ventricular

Clinical Perspective

What is new?

- In this international, multicenter cohort study of 686 cardiogenic shock patients treated with veno-arterial extracorporeal membrane oxygenation, use of left ventricular unloading was associated with lower mortality.
- However, use of left ventricular unloading in these patients was also associated with higher risk of complications, such as severe bleedings or interventions due to access-site related ischemia.

What are the clinical implications?

- Our study supports use of left ventricular unloading in cardiogenic shock patients treated with veno-arterial extracorporeal membrane oxygenation.
- These findings furthermore call for an evaluation of this treatment strategy in a randomized, controlled trial.

Introduction

Cardiogenic shock is associated with a high mortality rate of up to 50%.[1, 2] Over the past decades, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has been increasingly used to treat cardiogenic shock,[2, 3] however, the effect of VA-ECMO on mortality is still discussed.[2, 4] VA-ECMO increases left ventricular (LV) pressure due to retrograde aortic perfusion. This could slow myocardial recovery or even damage the myocardium and negatively impact survival.[5]

LV unloading using percutaneous assist devices has been suggested as an approach to address the increased afterload present in patients supported with VA-ECMO.[6] By decreasing LV pressure (e.g. unloading the LV), these assist devices might facilitate myocardial recovery, increase the probability of successful VA-ECMO weaning and ultimately could lead to improved survival in cardiogenic shock.[6]

The micro-axial flow pump Impella (Abiomed, Danvers, MA, USA) is a catheter-based LV assist device which is inserted into the LV cavity via arterial access (predominantly femoral access in cardiogenic shock). From that position, it actively drains blood from the LV and propels it into the proximal ascending aorta, thereby decreasing LV preload and increasing cardiac output.[5] It has been suggested that addition of an Impella to VA-ECMO (ECMELLA) might be feasible to treat patients with cardiogenic shock, and could even improve outcome.[7, 8] Although this approach holds promise based on pathophysiology, the published evidence comparing VA-ECMO alone to an ECMELLA strategy is limited to case reports and smaller studies.[6, 9, 10]

The primary aim of this study was to evaluate outcome in an international, multicenter registry of cardiogenic shock patients treated with VA-ECMO with or without LV unloading using an Impella. Secondary aims were to examine prespecified subgroups as well as the overall complication rate with both approaches.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Setting

Consecutive patients with cardiogenic shock treated with either VA-ECMO alone or ECMELLA between 2005 and 2019 from 16 centers in 4 countries, were retrospectively enrolled (NCT03313687). All participating hospitals are large centers experienced in the treatment of cardiogenic shock in general and in the use of mechanical circulatory support devices in particular. Cardiogenic shock was defined at the discretion of the local investigator. Post-cardiotomy cardiogenic shock and age below 18 years were the only exclusion criteria for this registry. Patients were treated at discretion of the local investigators and per local guidelines. Baseline was defined as implantation of first device and variables were recorded in a dedicated database.

The study was conducted in accordance with the Declaration of Helsinki and was approved by local ethics committees and institutional review committees. The need for informed consent was waived by the main ethics committee as this was a retrospective analysis and only completely anonymized data was collected and analyzed.

This study was designed by the authors, who also gathered and analyzed the data, vouch for this study, wrote the paper, and ultimately decided to publish. No company was involved in any part of this process.

Endpoints

The primary endpoint of this study was 30-day all-cause mortality (e.g. events which occurred after 30 days were censored).

Safety endpoints were chosen to assess bleeding complications (severe/moderate bleeding defined by GUSTO criteria; intracerebral bleeding or hemorrhagic stroke on computed tomography; intervention due to bleeding; hemolysis, defined as lactate dehydrogenase ≥1000U/l and haptoglobin <0.3g/l in two consecutive samples within 24 hours), ischemic complications (ischemic stroke on computer tomography; intervention due to access-site related ischemia; laparotomy due to abdominal compartment or bowl ischemia) and other complications (hypoxic brain damage on computed tomography; renal replacement therapy; sepsis, defined as systemic inflammatory response syndrome criteria and ≥2 positive blood cultures).

Statistical analyses

Missing data were handled by multiple imputations with chained equations (R-package mice; 10 imputed data sets; variables used for the multiple imputation are shown in *Table 1*).[11] In the imputed datasets, propensity scores for ECMELLA were calculated by a logistic regression model and then averaged. The following variables were used for the calculation of the propensity score: Age (categorized), sex, cause of cardiogenic shock, prior cardiac arrest, VA-ECMO-assisted cardiopulmonary resuscitation (eCPR), mean blood pressure (categorized), heart rate (categorized), lactate (categorized) and pH (categorized). Based on these propensity scores, patients treated with ECMELLA were matched 1:1 to patients treated with VA-ECMO only by

using the nearest neighbor method with a caliper of 0.05 and no replacement. After propensity score matching, the balancing of baseline characteristics between both groups was assessed by absolute standard differences (defined as the difference in means, proportions or ranks divided by the mutual standard deviation), with a value below 0.1 considered as not significant.

Categorical variables are shown as counts (frequencies) and compared by the c^2 test. Continuous variables are shown as mean (±standard deviation) and compared by t-test when normally distributed; and shown as median (interquartile range) and compared by Man-Whitney U test when non-normally distributed.

The Kaplan-Meier method was used in the unmatched as well as in the matched study cohort to obtain crude 30-day mortality risk and confidence intervals in patients treated with ECMELLA vs. VA-ECMO and a Cox regression model was fitted to evaluate the association of ECMELLA use with 30-day mortality. Proportional hazards assumption for ECMELLA use was assessed based on Schoenfeld residuals and met.

To evaluate the association between ECMELLA use and mortality risk in prespecified subgroups of interest, Cox regression models including the interaction between ECMELLA use and the variable representing the subgroup were fitted in the matched study cohort.

To evaluate the association between ECMELLA use and selected safety endpoints (severe bleeding and intervention due to access-site related ischemia), logistic regression models were fitted in the overall matched study cohort as well as in prespecified subgroups of interest (by including the interaction term between ECMELLA use and the variable representing the subgroup). Additionally, logistic regression models were fit to evaluate the association between severe bleeding and access-site related ischemia or ischemic stroke; to evaluate the association between use of antegrade perfusion and intervention due to access-site related ischemia; and a

Cox regression model was fit to evaluate the association between use of antegrade perfusion and 30-day mortality.

To evaluate the impact of timing of LV unloading in patients treated with VA-ECMO on outcomes, two additional matched cohorts were fitted: First, only ECMELLA patients in whom the Impella was implanted before or within 2 hours after the VA-ECMO implantation were considered for the matching; e.g. matching patients with early LV unloading vs. patients treated with VA-ECMO only. Second, only ECMELLA patients in whom the Impella was implanted more than two hours after the VA-ECMO implantation were considered; e.g. matching patients with delayed LV unloading vs. patients treated with VA-ECMO only. The two-hour blending period was chosen to reflect time delay in clinical routine; e.g. transportation to the catheterization laboratory. In these two additional matched cohorts, outcomes were then assessed using the same methods as described above.

All statistical analyses were performed using R 3.5.3.[12] A p-value <0.05 was considered as statistically significant.

Results

Study cohort (Table 1)

A total of 686 patients with cardiogenic shock were enrolled in the registry and included into the analysis, of whom 349 (51%) were treated with VA-ECMO only (procedures performed between 07/2005 and 12/2019) and 337 (49%) were treated with ECMELLA (procedures performed between 09/2013 and 11/2019). In both groups, a femoro-femoral access via a percutaneous approach was primarily used for VA-ECMO implantation. After matching, the cohort was

restricted to 510 patients with cardiogenic shock, 255 treated with ECMELLA vs. 255 treated with VA-ECMO.

In the unmatched cohort, mean age was 56.6±13.2 years and 22.3% of the patients were female. Cardiogenic shock was caused by acute myocardial infarction in 64.3% of the patients and 98.3% of these patients were successfully revascularized, 67.1% had prior cardiac arrest; baseline lactate was 8.9±5.8 mmol/l and baseline pH was 7.18±0.21. Although distribution of most baseline characteristics was comparable between groups, non-ischemic cardiogenic shock and eCPR were more frequent in ECMELLA patients. In the unmatched ECMELLA group, VA-ECMO was implanted as first device in 149 (44%) patients, and Impella was implanted first in 188 (56%) patients. Median interval from Impella to VA-ECMO insertion was 0.0 [interquartile range (IQR)-2.0,3.0] hours, with negative hours indicating VA-ECMO implantation before Impella implantation. An Impella 2.5 was used in 73 (21.7%) of the cases, an Impella CP in 234 (69.4%) of the cases and an Impella 5.0 in 16 (4.7%) of the cases [missing data on type of Impella used in 13 (4.2%) of the cases]. Median duration of VA-ECMO use was 5.0 (IQR 3.0,8.0) days in the ECMELLA vs. 4.0 (IQR 2.0,7.0) days in the VA-ECMO only group; median duration of LV unloading in the ECMELLA group was 6.0 (IQR 2.0,10.0) days. Of these patients, 18 patients treated with VA-ECMO (5.4%) and 44 patients treated with ECMELLA (13.6%) were implanted with a durable left ventricular assist device ($p<0.01$).

After matching, baseline characteristics considered for calculation of the propensity score were well balanced between patients. In the matched ECMELLA group, VA-ECMO was implanted as first device in 111 (44%) patients, and Impella was implanted first in 144 (56%) patients; median interval from implantation of Impella to VA-ECMO was 0.0(IQR -2.0,3.0) hours (negative hours indicate VA-ECMO implantation before Impella). An Impella 2.5 was

used in 57 (22.3%) of the cases, an Impella CP in 171 (67.1%) of the cases and an Impella 5.0 in 14 (5.5%) of the cases [missing data on type of Impella used in 14 (5.1%) of the cases]. Median duration of VA-ECMO use was 5.0 (IQR 3.0,8.0) days in the ECMELLA vs. 4.0 (IQR 2.0, 7.9) days in the VA-ECMO group; median duration of LV unloading in the ECMELLA group was 6.0(IQR 2.0, 10.0) days. Of these patients, 16 patients treated with VA-ECMO (6.5%) and 30 patients treated with ECMELLA (12.4%) were implanted with a durable left ventricular assist device (p=0.20).

Outcome analysis

In the unmatched cohort, 421 (61.4%) patients died during a median follow-up of 13 (IQR 3,30) days [16 (IQR 4,30) days in patients treated with ECMELLA vs. 10 (IQR 3,30) days in patients treated with VA-ECMO]. Crude 30-day mortality risk in patients treated with ECMELLA vs. VA-ECMO was 60.2% [95% confidence interval (CI) 54.5-65.3%] vs. 66.2% (95% CI 60.6-70.9%). Corresponding unadjusted hazard ratio (HR) for ECMELLA use was 0.82 (95% CI 0.68-1.00, p=0.05, *Figure 1*).

In the matched cohort, 307 (60.2%) patients died during a median follow-up of 14 (IQR 4,30) days [17 (IQR 5,30) days in patients treated with ECMELLA vs. 10 (IQR 3,30) days in patients treated with VA-ECMO]. Crude 30-day mortality risk in patients treated with ECMELLA vs. VA-ECMO was 58.3% (95% CI 51.6-64.1%) vs. 65.7% (95% CI 59.2-71.2), with an HR for ECMELLA use of 0.79 (95% CI 0.63-0.98, p=0.03, *Figure 2*).

Associations between ECMELLA use and mortality in the prespecified subgroups are reported in *Figure 3*. There were no significant interactions between ECMELLA use and the variables which defined the subgroups (e.g. older vs. younger patients, females vs. males, patients with vs. without cardiogenic shock due to acute myocardial infarction, patients with vs.

without prior cardiac arrest, patients with vs. without eCPR and patients with higher vs. lower lactate).

Safety analysis in the matched study cohort (Table 2)

In the matched cohort, bleeding complications and hemolysis occurred more frequently in patients treated with ECMELLA vs. patients treated with VA-ECMO; e.g. severe bleeding was observed in 38.4% of the ECMELLA vs. 17.9% in the VA-ECMO patients and hemolysis was observed 33.6% of the ECMELLA vs. 22.4% of the VA-ECMO patients. The rate of interventions due to bleeding was comparable between both groups. In the logistic regression model, the association between ECMELLA use and higher risk of severe bleeding was consistent in all evaluated subgroups (*Figure 4*). There was an association between severe bleeding and a higher risk of interventions due to access-site related ischemia (OR 2.24, 95% CI 1.38-3.62, p<0.01), but not with ischemic stroke (OR 1.12, 95% CI 0.52-2.27, p=0.77).

There was no significant difference in the rate of ischemic strokes or laparotomies due to bowel ischemia between patients treated with ECMELLA vs. VA-ECMO. Interventions due to access-site related ischemia (21.6% of ECMELLA vs. 12.3% of VA-ECMO patients) and laparotomies due to abdominal compartment syndrome (9.4% of ECMELLA and 3.7% of VA-ECMO patients) occurred more frequently in patients treated with ECMELLA. In the logistic regression model, the association between ECMELLA use and a higher likelihood of interventions due to access-site related ischemia was consistent through all evaluated subgroups (*Figure 5*). Furthermore, there was no significant association between use of antegrade perfusion and 30-day mortality (HR 0.75, 95% CI 0.46-1.23, p=0.25) or intervention due to access-site related ischemia (OR 1.24, 95% CI 0.73-2.16, p=0.44).

Renal replacement therapy was more frequently used in ECMELLA patients (58.5% vs. 39.1%), but there was no difference in the rate of sepsis or hypoxic brain damage.

Timing of Impella and VA-ECMO implantation

For this analysis, 222 patients with early LV unloading (e.g. Impella implantation before or shortly after VA-ECMO implantation) were matched to 222 patients who were treated with VA-ECMO only; and 76 patients with delayed LV unloading (e.g. Impella implantation >2 hours after VA-ECMO implantation) were matched to 76 patients who were treated with VA-ECMO only (*Tables I-IV in the Supplement*).

In this subanalysis, as compared with VA-ECMO without unloading early LV unloading was associated with lower 30-day mortality (HR 0.76, 95% CI 0.60-0.97, p=0.03, *Figure 6*), whereas delayed LV unloading was not (HR 0.77, 95% CI 0.51-1.16, p=0.22, *Figure 6*).

A similar trend towards higher incidence of bleeding/ischemic complications with ECMELLA use was seen in both matched cohorts, e.g. patients with early LV unloading as well as patients with delayed LV unloading.

Discussion

In this large, international, multicenter cohort study of patients with cardiogenic shock, LV unloading with an Impella on top of VA-ECMO was associated with a 21% lower 30-day mortality compared with VA-ECMO alone. The association with a lower mortality risk was consistent through all tested subgroups, including older vs. younger patients, female vs. male patients, patients with vs. without cardiogenic shock due to acute myocardial infarction, patients with vs. without prior cardiac arrest, patients with vs. without eCPR as well as patients with

higher vs. lower lactate. However, complications, including bleeding, hemolysis, and limb ischemia, were more frequently observed in the ECMELLA group.

Contemporary use of VA-ECMO in cardiogenic shock

VA-ECMO use addresses the central problem of severely reduced cardiac output in cardiogenic shock by providing adequate tissue perfusion.[3] However, increased afterload due to retrograde aortic perfusion interferes with myocardial recovery and could negatively impact outcome.[13] This adverse hemodynamic influence of VA-ECMO might partially explain the observation that mortality rates in cardiogenic shock have remained at a high-level despite increasing use of VA-ECMO.[2]

This study enrolled patients with severe cardiogenic shock, e.g. patients presented with high lactate, low pH and about a third as eCPR. The observed mortality rate in the overall study cohort was 61%, which is consistent with reports from other studies[3], and all patients presented with cardiogenic shock Society for Cardiovascular Angiography & Intervention class D or E[14]. Interestingly, LV unloading (in the unmatched study cohort) was more frequently used in eCPR cases and in patients with non-ischemic cardiogenic shock. This indicates that physicians prefer this approach in sicker patients, e.g. SCAI class E patients, and as a bail out therapy, as there is no evidence-based treatment for patients with non-ischemic cardiogenic shock.[1, 3, 9, 14]

Compared with VA-ECMO, ECMELLA use was associated with lower risk of 30-day mortality in the unmatched as well as in the matched study cohort. This association might be explained by the potentially beneficial effect of LV unloading in cardiogenic shock patients treated with VA-ECMO. Previous studies have indicated that early LV unloading improves myocardial recovery via reduction in preload, which might be linked to better outcomes.[10, 13, 15] Both devices were implanted in quick succession in the ECMELLA group, indicating that early

initiation of LV unloading might explain the lower observed mortality. Furthermore, addition of an LV unloading mechanism might improve chances of successful VA-ECMO weaning by providing partial cardiac output support.[16]

The finding of a lower mortality risk with ECMELLA was consistent through all tested subgroups. This included patients with vs. without cardiogenic shock due to acute myocardial infarction as well as patients with vs. without prior cardiac arrest or eCPR. It is increasingly recognized that various diseases can cause cardiogenic shock and that the majority of cases are not caused by acute myocardial infarction.[17, 18] As the only evidence-based treatment is early revascularization of the culprit lesion in cardiogenic shock caused by acute myocardial infarction, it is important to identify other treatments which cover the whole spectrum of cardiogenic shock.[19, 20]

Aside from LV unloading during VA-ECMO with an Impella, other mechanical circulatory support devices which might provide LV unloading are the intra-aortic balloon counter-pulsation pump and transseptal left atrial cannulation devices/strategies. Although the intra-aortic balloon counter-pulsation pump failed to show a benefit in a randomized cardiogenic shock trial as a stand-alone therapy, its passive counter-pulsation-mechanism could alleviate the increase in LV afterload if combined with VA-ECMO.[21] A recent meta-analysis of observational studies indicated that LV unloading irrespective of the used device/strategy was associated with lower mortality, but did provide a comparison of various unloading strategies.[6] Although some aspects might favor Impella over intra-aortic balloon counter-pulsation pump for LV unloading in cardiogenic shock patients treated with VA-ECMO (e.g. active vs. passive mechanism, preload vs. afterload reduction), the Impella also requires a larger vascular access which might mitigate its benefits.[22] Ultimately, randomized trials are needed to confirm the mortality

reduction observed with LV unloading and to determine which unloading strategy is optimal for patients with cardiogenic shock.

Safety outcomes associated with ECMELLA use

In this study, bleeding complications, ischemic complications and renal replacement therapy occurred more frequently in the ECMELLA vs. the VA-ECMO group; and the association between ECMELLA use and bleeding/ischemic complications was consistent in several evaluated subgroups. This contrasts earlier studies, which reported comparable complication rates between VA-ECMO and ECMELLA treated patients with cardiogenic shock.[7, 8] However, these studies had a small sample size and were most likely underpowered to demonstrate a difference. Additionally, several mechanisms support the observation of a higher complication rate with ECMELLA use. First, it has been shown that VA-ECMO use alone is associated with an increase in complications.[23] The addition of a second device, including the need for a second arterial access, increases the likelihood of bleeding/ischemic complications; especially as ultrasound-guided vascular access, which could reduce such complications, is not always feasible in cardiogenic shock.[24] Second, previous studies have shown that use of Impella alone is associated with bleeding/ischemic complications, which might be explained by the relatively large vascular access required (12/14 French for the Impella 2.5/CP).[25-27] Additionally, the underlying mechanism of the Impella (forcing blood through a small inlet and outlet) causes a high shear stress on blood elements and is associated with increased hemolysis.[28] Third, higher complication rates, especially higher need for renal replacement therapy, bleeding and access-site related ischemia, might to a certain degree be explained by survivorship-bias. As ECMELLA patients had a better survival and therefore a longer follow-up, they were also more exposed to the risk of complications (e.g. surviving long enough to develop complications).

Several techniques have been suggested to reduce complications in patients on mechanical circulatory support; such as use of antegrade perfusion cannulas and dedicated protocols.[29, 30] Ultimately, the finding of lower mortality but more complications in this study highlights the need for appropriate patient selection to optimize the benefit/risk ratio. Future studies are needed to identify factors which increase/decrease the risk of complications in this setting and could thus be used to guide decision-making in regard to ECMELLA use.

Timing of Impella and VA-ECMO implantation

In a subanalysis, early LV unloading followed by VA-ECMO (e.g. when the Impella was implanted before or shortly after the VA-ECMO) had a persistent association with a lower mortality risk. However, if the LV unloading was delayed (e.g. when the Impella was implanted >2 hours after the VA-ECMO), the association was not statistically significant anymore. Although early unloading might prevent severe LV distension additional research is needed to determine the optimal timing of unloading.

Limitations

The strengths of this study include the use of a large, international, multi-center cohort of cardiogenic shock patients with broad data available on several prognostic factors and characteristics. This allowed us to perform a propensity-score matching based on relevant confounders.

The main limitation of this study is its observational design, so that even after matching residual and unmeasured confounding cannot be ruled out. Data on relevant procedural characteristics, such as cannulation size or anticoagulation strategy, and data on baseline characteristics beyond those reported are missing, which might have impacted the results. Similarly, hemodynamic data from right heart catheterization or functional echocardiographic

data were not captured in this registry, hence we were not able to investigate differences in intracardiac pressures or LV distension between both groups.[31] Furthermore, data on additional outcomes of interest such as aortic root thrombosis and North-South syndrome was not available. Although the underlying registry covers several hospitals and nations, generalizability to hospitals without sufficient experience on the use of both devices might be limited. Lastly, the relatively small sample size of the matched cohort, especially in the cohorts which were matched to evaluate the impact of the timing of LV unloading, might have obscured significant differences in the subgroup analyses.

Conclusion

In this large, international, multicenter cohort study of cardiogenic shock patients treated with VA-ECMO, LV unloading with an Impella was associated with a lower mortality, but also with more bleeding and ischemic complications, compared with VA-ECMO alone. Although this study supports the use of an Impella for LV unloading in cardiogenic shock patients treated with VA-ECMO, it also calls for appropriate patient selection and very strict vascular access management to optimize the benefit/risk ratio. This study supports performance of randomized controlled trials evaluating LV unloading in cardiogenic shock patients supported with VA-ECMO.

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Supplemental Materials

Supplemental Tables I-IV

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Table 1. Baseline table

Variable	Unmatched study cohort				Matched study cohort		
	VA-ECMO, unmatched (N=349)	ECMELLA (N=337)	Missing data	P	VA-ECMO, matched (N=255)	ECMELLA (N=255)	SD
Age, years	57.50 (±13.37)	55.66 (±12.99)	0%	0.07	56.55 (±13.21)	56.39 (±12.72)	0.01
Age, categorized*				0.35			0.09
<52 years	106/349 (30.4%)	113/337 (33.5%)			80/255 (31.4%)	87/255 (34.1%)	
52-62 years	115/349 (33.0%)	118/337 (35.0%)			92/255 (36.1%)	81/255 (31.8%)	
>62 years	128/349 (36.7%)	106/337 (31.5%)			83/255 (32.5%)	87/255 (34.1%)	
Sex, male*	271/349 (77.7%)	262/337 (77.7%)	0%	0.99	195/255 (76.5%)	195/255 (76.5%)	<0.01
Cause of CS*			0%	<0.01			0.02
Acute myocardial infarction	242/349 (69.3%)	199/337 (59.1%)			162/255 (63.5%)	159/255 (62.4%)	
ST-elevation myocardial Infarction	183/242 (75.6%)	143/198 (72.2%)	<1%	0.48	124/162 (76.5%)	119/158 (75.3%)	0.02
Non-ST-elevation myocardial Infarction	38/242 (15.7%)	52/198 (26.3%)	1%	0.01	26/162 (16.0%)	38/158 (24.1%)	0.20
Revascularization	214/225 (95.1%)	165/185 (89.2%)	8%	0.04	145/152 (95.4%)	129/146 (88.4%)	0.26
Non-ischemic	107/349 (30.7%)	138/337 (40.9%)			93/255 (36.5%)	96/255 (37.6%)	
Prior cardiac arrest*	231/349 (66.2%)	229/337 (68.0%)	0%	0.68	171/255 (67.1%)	170/255 (66.7%)	<0.01
eCPR*	94/349 (26.9%)	133/337 (39.5%)	0%	<0.01	88/255 (34.5%)	84/255 (32.9%)	0.03
Mean blood pressure, mmHg	50.70 (±30.20)	60.02 (±21.72)	9%	<0.01	56.48 (±30.51)	58.39 (±22.12)	0.07
Mean blood pressure, categorized*				<0.01			0.06
<49 mmHg	83/322 (25.8%)	44/302 (14.6%)			41/237 (17.3%)	43/226 (19.0%)	
49-62 mmHg	82/322 (25.5%)	55/302 (18.2%)			53/237 (22.4%)	46/226 (20.4%)	
>62 mmHg	63/322 (19.6%)	70/302 (23.2%)			55/237 (23.2%)	53/226 (23.5%)	
eCPR	94/322 (29.2%)	133/302 (44.0%)			88/237 (37.1%)	84/226 (37.2%)	
Heart rate, bpm	101 (80,133)	108 (87,128)	9%	0.97	104 (86,130)	103 (85,126)	0.03
Heart rate, categorized*				<0.01			0.03
<90 bpm	74/318 (23.3%)	47/305 (15.4%)			41/234 (17.5%)	43/229 (18.8%)	
90-120 bpm	80/318 (25.2%)	69/305 (22.6%)			60/234 (25.6%)	58/229 (25.3%)	
>120 bpm	70/318 (22.0%)	56/305 (18.4%)			45/234 (19.2%)	44/229 (19.2%)	
eCPR	94/318 (29.6%)	133/305 (43.6%)			88/234 (37.6%)	84/229 (36.7%)	
Lactate, mmol/l	9.07 (±5.82)	8.74 (±5.87)	13%	0.48	8.55 (±5.69)	8.58 (±5.67)	<0.01

Lactate, categorized*				0.62			0.04
<5 mmol/l	97/318 (30.5%)	96/281 (34.2%)			80/236 (33.9%)	70/211 (33.2%)	
5-10.8 mmol/l	110/318 (34.6%)	94/281 (33.5%)			82/236 (34.7%)	77/211 (36.5%)	
>10.8 mmol/l	111/318 (34.9%)	91/281 (32.4%)			74/236 (31.4%)	64/211 (30.3%)	
pH	7.18 (±0.20)	7.18 (±0.21)	13%	0.77	7.20 (±0.20)	7.18 (±0.20)	0.06
pH, categorized*				0.09			0.03
<7.12	102/311 (32.8%)	97/283 (34.3%)			72/227 (31.7%)	70/212 (33.0%)	
7.12-7.29	114/311 (36.7%)	81/283 (28.6%)			77/227 (33.9%)	69/212 (32.5%)	
>7.29	95/311 (30.5%)	105/283 (37.1%)			78/227 (34.4%)	73/212 (34.4%)	
Creatinine clearance, ml/min	47 (32, 60)	50 (32,66)	19%	0.46	48 (32,61)	48 (31,63)	0.02
SAVE score, points	-7.53 (±6.41)	-8.64 (±6.86)	25%	0.06	-7.67 (±6.13)	-8.68 (±6.91)	0.15
SAPS II, points	63.35 (±20.27)	62.63 (±21.85)	18%	0.69	62.22 (±20.62)	63.42 (±22.10)	0.06
Time to VA-ECMO implantation, hours	4.0 (2.0,14.0)	5.0 (1.5,13.3)	6%	0.81	4.0 (2.0,12.4)	5.0 (2.0,12.7)	0.04
Antegrade perfusion cannula for the arterial VA-ECMO access site	234/319 (73.4%)	190/290 (65.5%)	11%	0.04	167/233 (71.7%)	140/217 (64.5%)	0.15

Categorical variables are shown as counts (frequencies) and compared by the c^2 test. Continuous variables are shown as mean (±standard deviation) and compared by t-test when normally distributed; and shown as median (interquartile range) and compared by Man-Whitney U test when non-normally distributed. Variables marked with * were included in the multiple imputation model (together with ECMELLA use and the primary outcome) and were used for the calculation of the propensity-scores. Continuous variables were categorized based on tertiles. VA-ECMO: veno-arterial extracorporeal membrane oxygenation therapy; ECMELLA: Impella+ECMO; SD: absolute standard difference; CS: cardiogenic shock; eCPR: VA-ECMO-assisted cardiopulmonary resuscitation; SAVE score: Survival after veno-arterial ECMO score; SAPS II: Simplified Acute Physiology Score II.

Table 2. Complications

Variable	Unmatched study cohort				Matched study cohort		
	VA-ECMO, unmatched (N=349)	ECMELLA (N=337)	Missing	P	VA-ECMO, matched (N=255)	ECMELLA (N=255)	P
Bleeding complications							
Intracerebral bleeding	17/239 (7.1%)	20/288 (6.9%)	23%	0.99	16/182 (8.8%)	18/216 (8.3%)	0.99
Hemorrhagic stroke	10/237 (4.2%)	8/289 (2.8%)	23%	0.50	10/181 (5.5%)	7/216 (3.2%)	0.38
Severe bleeding	62/345 (18.0%)	129/336 (38.4%)	<1%	<0.01	45/252 (17.9%)	98/255 (38.4%)	<0.01
Moderate bleeding	103/256 (40.2%)	167/322 (51.9%)	16%	<0.01	74/192 (38.5%)	123/241 (51.0%)	0.01
Intervention due to bleeding	43/270 (15.9%)	61/332 (18.4%)	12%	0.50	33/201 (16.4%)	47/251 (18.7%)	0.61
Hemolysis	54/259 (20.8%)	111/315 (35.2%)	16%	<0.01	43/192 (22.4%)	79/235 (33.6%)	0.01
Ischemic complications							
Ischemic stroke	26/328 (7.9%)	25/304 (8.2%)	8%	0.99	22/242 (9.1%)	16/230 (7.0%)	0.50
Intervention due to access-site related ischemia	42/345 (12.2%)	73/336 (21.7%)	<1%	<0.01	31/252 (12.3%)	55/255 (21.6%)	<0.01
Laparotomy due to abdominal compartment	10/331 (3.0%)	33/326 (10.1%)	4%	<0.01	9/243 (3.7%)	23/245 (9.4%)	0.02
Laparotomy due to bowl ischemia	7/331 (2.1%)	13/326 (4.0%)	4%	0.24	7/243 (2.9%)	11/245 (4.5%)	0.48
Other complications							
Hypoxic brain damage	20/235 (8.5%)	44/290 (15.2%)	24%	0.03	19/179 (10.6%)	29/216 (13.4%)	0.49
Renal replacement therapy	135/347 (38.9%)	194/333 (58.3%)	1%	<0.01	99/253 (39.1%)	148/253 (58.5%)	<0.01
Sepsis	59/269 (21.9%)	95/332 (28.6%)	12%	0.08	44/200 (22.0%)	70/251 (27.9%)	0.19

Variables are shown as counts (frequencies) and compared by the c^2 test. VA-ECMO: veno-arterial extracorporeal membrane oxygenation therapy; ECMELLA: Impella+VA-ECMO

Figure Legends

Figure 1. Kaplan-Meier curve of the unmatched study cohort

VA-ECMO: veno-arterial extracorporeal membrane oxygenation therapy; ECMELLA: Impella+VA-ECMO; HR: hazard ratio; CI: confidence interval.

Figure 2. Kaplan-Meier curve of the matched study cohort

VA-ECMO: veno-arterial extracorporeal membrane oxygenation therapy; ECMELLA: Impella+VA-ECMO; HR: hazard ratio; CI: confidence interval.

Figure 3. Association between ECMELLA use and 30-day all-cause mortality in prespecified subgroups

P-interaction for age <52 years vs. age 52-62 years is 0.79, 0.95 for age <52 years vs. >62 years and 0.82 for age 52-62 years vs. >62 years. P-interaction for lactate <5 mmol/l vs. 5-10.8 mmol/l is 0.23, 0.20 for <5 mmol/l vs. >10.8 mmol/l and 0.90 for 5-10.8 mmol/l vs. >10.8 mmol/l. P-interaction for SAVE score >-6 vs. -6- -11 is 0.55, 0.99 for >-6 vs. <-11 and 0.52 for -6- -11 vs. <-11. P-interaction for SAPS II <52 vs. -52-76 is 0.16, 0.21 for <52 vs. >76 and 0.86 for 52-76 vs. >76. VA-ECMO: veno-arterial extracorporeal membrane oxygenation therapy; ECMELLA: Impella+VA-ECMO; HR: hazard ratio; CI: confidence interval; NS: non-significant; SAVE score: Survival after veno-arterial ECMO score; SAPS II: Simplified Acute Physiology Score II.

Figure 4. Association between ECMELLA use and severe bleeding in prespecified subgroups

P-interaction for age <52 years vs. age 52-62 years is 0.30, 0.11 for age <52 years vs. >62 years and 0.50 for age 52-62 years vs. >62 years. P-interaction for lactate <5 mmol/l vs. 5-10.8 mmol/l is 0.21, 0.77 for <5 mmol/l vs. >10.8 mmol/l and 0.32 for 5-10.8 mmol/l vs. >10.8 mmol/l. P-interaction for SAVE score >-6 vs. -6- -11 is 0.74, 0.72 for >-6 vs. <-11 and 0.97 for -6- -11 vs. <-11. P-interaction for SAPS II <52 vs. -52-76 is 0.70, 0.67 for <52 vs. >76 and 0.41 for 52-76 vs. >76. VA-ECMO: veno-arterial extracorporeal membrane oxygenation therapy; ECMELLA: Impella+VA-ECMO; OR: odds ratio; CI: confidence interval; NS: non-significant; SAVE score: Survival after veno-arterial ECMO score; SAPS II score: Simplified Acute Physiology Score II.

Figure 5. Association between ECMELLA use and intervention due to access-site related ischemia in prespecified subgroups

P-interaction for age <52 years vs. age 52-62 years is 0.75, 0.95 for age <52 years vs. >62 years and 0.82 for age 52-62 years vs. >62 years. P-interaction for lactate <5 mmol/l vs. 5-10.8 mmol/l is 0.62, 0.52 for <5 mmol/l vs. >10.8 mmol/l and 0.23 for 5-10.8 mmol/l vs. >10.8 mmol/l. P-interaction for SAVE score >-6 vs. -6- -11 is 0.58, 0.51 for >-6 vs. <-11 and 0.23 for -6- -11 vs. <-11. P-interaction for SAPS II <52 vs. -52-76 is 0.65, 0.64 for <52 vs. >76 and 0.31 for 52-76 vs. >76. VA-ECMO: veno-arterial extracorporeal membrane oxygenation therapy; ECMELLA: Impella+VA-ECMO; OR: odds ratio; CI: confidence interval; NS: non-significant; SAVE score: Survival after veno-arterial ECMO score; SAPS II score: Simplified Acute Physiology Score II.

Figure 6. Kaplan-Meier curves for all-cause mortality in ECMELLA patients treated with early left ventricular unloading (A) and delayed left ventricular unloading (B) vs. matched patients treated with VA-ECMO only.

In panel A, only ECMELLA patients in whom the Impella was implanted before or within 2 hours after the VA-ECMO implantation were considered for the matching; e.g. matching patients with early LV unloading vs. patients treated with VA-ECMO only. In panel B, only ECMELLA patients in whom the Impella was implanted more than two hours after the VA-ECMO implantation were considered; e.g. matching patients with delayed LV unloading vs. patients treated with VA-ECMO only. VA-ECMO: veno-arterial extracorporeal membrane oxygenation therapy; ECMELLA: Impella+VA-ECMO; LV: left ventricular; HR: hazard ratio; CI: confidence interval.