Prompt Extracorporeal Cardiopulmonary Resuscitation with Left Ventricular Unloading by IMPELLA Improves Outcome of Patients with Refractory Cardiac Arrest: A Single-Site Retrospective Cohort Study

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Research

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Abstract

Background: Extracorporeal cardiopulmonary resuscitation (E-CPR) using venoarterial extracorporeal membrane oxygenation (VA-ECMO) is a novel lifesaving method for refractory cardiac arrest (CA). However, VA-ECMO increases damaged left ventricular (LV) afterload. The percutaneous microaxial pump, Impella, can reduce LV preload with simultaneous circulatory support, which may have significant effect on clinical outcome by concomitant use of VA-ECMO and IMPELLA (ECPELLA). In the current retrospective cohort study, we assessed factors affecting outcome of CA patients who underwent E-CPR.

Method: We retrospectively reviewed 149 consecutive CA patients with E-CPR from January 2012 through December 2020 in our institute. Patients were divided into three groups, ECEPLLA (n=29), IABP + VA-ECMO (n=78), and single VA-ECMO (n=42). We assessed 30-day survival and neurological outcome using the Cerebral Performance Categories (CPC).

Results: There were no significant differences in age, gender, out of hospital CA, acute coronary syndrome among groups. The ECPELLA showed the highest cumulative 30-day survival (ECPELLA: 55%, IABP + VA-ECMO: 23%, VA-ECMO: 9.5; p=0.001) and the rates of CPC score 1 or 2 (ECPELLA: 31%, IABP + VA-ECMO: 13%, VA-ECMO: 7%; p=0.02). Multivariate analysis revealed that age (hazard ratio [HR], 1.30, 95% confidence interval [CI], 1.13-1.52, P=0.005) and Time from CA to ECMO support (HR, 1.22, 95%CI, 1.13-1.31, P<0.0001) and ECPELLA (HR, 0.46, 95%CI, 0.24-0.88, P=0.02) were significantly associated with the clinical outcome.

Conclusion: Earlier initiation of E-CPR is critical to improve patient survival and neurological outcome. Additional Impella support, ECPELLA, appears to significantly improve the clinical outcome.

Background

Management of patients with refractory cardiac arrest (CA) who do not respond to conventional cardiopulmonary resuscitation is controversial. Outcome of such patients remains to be improved despite of recent advancement in use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) during the cardiopulmonary resuscitation (E-CPR) by which oxygenized blood is supplied via the femoral artery. [1] [2] Although, VA-ECMO can preserve end-organ perfusion with oxygenized blood, the arterial blood perfusion by ECMO increases damaged left ventricular (LV) afterload resulting in increased myocardial wall stress by LV chamber distension that may lead further myocardial damage. [2] [3] [4]

Intra-aortic balloon pumping (IABP) has been used for treatment of such patients often combined with VA-ECMO as the additive mechanical circulatory support (MCS). [5] While IABP can reduce LV afterload at certain levels, the damaged LV still needs to eject blood into the systemic arterial tree to maintain end-organ perfusion. When IABP is combined with VA-ECMO, the reduction of LV afterload appears to be quite limited due to significantly increased LV afterload by VA-ECMO,[4] and IABP can also interfere the oxygenized blood supply from the arterial cannula placed at the distal side of the balloon during the

diastolic phase. A recent study also reported that the combined use of IABP and VA-ECMO treatment for patients with cardiogenic shock did not improve the outcome compared to VA-ECMO alone.[6]

There are several studies showing that combined mechanical circulatory support using a microaxial Impella pump (Impella, Abiomed Inc. Danvers, MA) and VA-ECMO for patients with refractory cardiogenic shock (CS) could improve short-term survival.[7] [8] [9] The Impella pump can directly pump out the blood from the LV cavity and anterogradely eject into ascending aorta, which can achieve simultaneous circulatory support and the LV preload reduction.[10] When it is combined with VA-ECMO, Impella does not only contribute the circulatory support, but also significantly reduce LV preload. Thus, the combination of Impella and VA-ECMO, called ECPELLA, may have superior clinical outcome compared to IABP + VA-ECMO treatment considering the different hemodynamic effects.

In our institute, we have been applying VA-ECMO as the first choice for treatment of patients with refractory CA requiring extracorporeal CPR (E-CPR). Since Impella pump was available in 2018 in our institute, we have been using IABP or Impella as the adjunct MCS on VA-ECMO support following the E-CPR. However, it remains unclear whether ECPELLA has better clinical outcome compared to the conventional IABP + VA-ECMO for treatment of patients requiring E-CPR.

Thus, in the present study, we retrospectively reviewed and compared cumulative 30-day survival and neurological outcome among ECPELLA, IABP + VA-ECMO, and single VA-ECMO groups in refractory CA patients whom E-CPR was required. Our results suggest that ECPELLA showed superior 30-day survival and neurological outcome compared to conventional IABP + VA-ECMO or single VA-ECMO support.

Method And Results

The current single-center observational study was approved by the local Institutional Ethics Committee (Saiseikai Kumamoto Hospital, Approval: No. 875) and the study follows the Declaration of Helsinki.

Patients. We retrospectively reviewed 203 consecutive patients on their individual patient records, who underwent VA-ECMO for various disease conditions from January 2012 to December 2020. We excluded 54 patients whom VA-ECMO was not applied for E-CPR. There were 149 patients who underwent E-CPR due to refractory cardiac arrest despite of standard cardiopulmonary resuscitation procedure. The E-CPR was carried out according to our institutional criteria [11] [12]; 1) collapse witnessed by a bystander or reliable report of estimated collapse time; 2) assuming cardiac origin events; 3) refractory ventricular arrhythmias or pulseless electric activity with short duration of CA that cannot be recovered by conventional CPR. The exclusion criteria were; 1) apparent aortic dissection prior to the E-CRP; 2) non-cardiac origins including severe trauma and/or stroke; and 3) known poor prognosis or terminal malignancies. Twenty-nine patients with ECPELLA (ECPELLA group), 78 patients with IABP + VA-ECMO (IABP-ECMO group), and 42 patients with single VA-ECMO support (VA-ECMO group) were included in the current study (Fig. 1). Either Impella or IABP was added when LV distension due to increased LV afterload by VA-ECMO became significant.

Mechanical Circulatory Support Devices. In our institute, Terumo VA-ECMO system (CAPIOX, Terumo, Tokyo, Japan), and the Getinge IABP system (Datascope CS100/CS300 or Cardiosave IABP Hybrid, Getinge Japan, Tokyo, Japan) were used. The Impella 2.5 (until July 2019) or CP pump (after August 2019) was used for ECPELLA.

Endpoints. The primary endpoint was cumulative 30-day survival after the initiation of VA-ECMO support. The secondary endpoints included success rate of VA-ECMO weaning, and rates of Cerebral Performance Category (CPC) 1 or 2. We also assessed factors that affected the outcome, such as age, gender, presence of initial shockable rhythms, acute coronary syndrome, or time to VA-ECMO support. Other data analyses include changes in MCS flows, arterial, pulmonary artery and central venous pressures (days 1 to 3), serum lactate levels (at VA-ECMO initiation (E-CPR), days 1 to 3), and vasoactive inotrope scores (VISs) (days 1 to 3) under MCS.

Statistical analysis. Statistical analyses were conducted by JMP version 15.2.0 (SAS institute inc.). Kaplan-Meier survival curve analysis was conducted with log-rank test. Comparison of patient characteristics, serum lactate levels and VISs among ECPELLA, IABP + VA-ECMO, and single VA-ECMO groups was carried out by extended Fisher's exact test. Continuous variables including hemodynamic parameters were assessed by 2-way ANOVA. Baseline patient characteristics were assessed as predictors for 30-day mortality in multivariate regression analyses. Those variables identified as significant predictors in their respective multivariate models were reported. Statistical significance was defined as the p-value less than 0.05 in all statistical analyses.

Results

Background characteristics of the patients.

Table 1 summarizes clinical characteristics of the patients. Male patient ratios of ECPELLA (76%) and IABP + VA-ECMO (74%) groups were higher than VA-ECMO group (50%, p = 0.02). Bystander-CPR rate in VA-ECMO was higher than other groups (83% in ECPELLA, 85% in IABP + VA-ECMO, and 98% in VA-ECMO, respectively, p = 0.03). While shockable rhythms were seen in both ECPELLA (48%) and IABP + VA-ECMO (47%) groups, no cases were seen in VA-ECMO group (0%, p < 0.001). Pulseless electric activity in VA-ECMO was higher than other groups (41% in ECPELLA, 47% in IABP + VA-ECMO, and 88% in VA-ECMO, respectively p < 0.001). Rates of out of hospital cardiac arrest (OHCA) were higher in ECPELLA (41%) and IABP + VA-ECMO (42%) compared to VA-ECMO (19%, p = 0.02). Higher rates of acute coronary syndrome were seen in ECPELLA (66%) and IABP + VA-ECMO (56%) compared to VA-ECMO (24%, p = 0.0003). Both Door to ECMO time (23 min in ECPELLA, 36 min in IABP + VA-ECMO, and 39 min in VA-ECMO, $p = 0.005$) and Collapse to ECMO time (27 min in ECPELLA, 49 min in IABP + VA-ECMO, 36 min in VA-ECMO, p = 0.004) were shorter in ECPELLA group.

Changes in hemodynamic parameters, serum lactate, and Vasoactive Inotrope Score.

Figure 2A shows changes in MCS flows from support day 1 to day 3. The ECPELLA group was significantly higher MCS flow than other groups on days 1 and 2 ($P < 0.05$). While mean arterial pressure (Fig. 2B) was similar among treatment groups, VA-ECMO group showed significantly higher mean main pulmonary artery pressure (mPAP, Fig. 2C) and the central venous pressure (CVP) on day 1 compared to other groups ($P < 0.05$, Fig. 2D).

While rates of serum lactate levels more than 4mmol/L (Lact-4) were decreased from E-CPR to support day 3 in all groups, VA-ECMO group was higher than other groups at E-CPR. On support day 1, IABP + VA-ECMO group showed the highest rates of Lact-4 among groups. On days 2 and 3, the rates of Lact-4 in VA-ECMO group were higher than other groups and ECPELLA group showed the lowest Lact-4 rates among groups (Fig. 3 left panel).

The Vasoactive Inotrope Score was calculated as dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min) + 10000 × vasopressin dose (unit/kg/min) + 100 × norepinephrine dose (μg/kg/min). While the rate of VIS more than 10 (VIS-10) of IABP + VA-ECMO group was lower than other groups on day 1, both IABP + VA-ECMO and ECPELLA showed lower VIS-10 rates on days 2 and 3 compared to VA-ECMO group suggesting VA-ECMO group required more vasoactive inotropes from MSC support days 1 to 3 ($P < 0.05$, Fig. 3).

VA-ECMO weaning and rate of Cerebral Performance Category Score 1 or 2.

The VA-ECMO weaning rates were 62% in ECPELLA, 44% in IABP + VA-ECMO, and 17% in VA-ECMO, respectively. The VA-ECMO weaning rate in ECPELLA group was significantly higher than other groups ($P = 0.0002$). Rates of Cerebral Performance Category 1 or 2 in ECPELLA, IABP + VA-ECMO, and VA-ECMO groups were respectively 31%, 13%, and 7% indicating that ECPELLA group had better neurological outcome compared to other groups ($P = 0.02$) (Table 2).

Cumulative 30-day survival rates and factors affecting survival.

The Kaplan-Meier survival analysis revealed that cumulative 30-day survival rates were 55% in ECPELLA, 23% in IABP + VA-ECMO, and 9.5% in VA-ECMO, respectively ($P < 0.001$, Fig. 4). Multivariate Cox regression analysis for 30-day survival revealed that older age (per 10 years-old increment, HR: 1.30, 95% confidential interval (95%CI): 1.13–1.52, $p = 0.005$) and longer Collapse to VA-ECMO Time (per 10-minute increment, HR: 1.22, 95%CI: 1.13–1.31, $p < 0.0001$) increased the risk of survival. Among treatment modalities, ECPELLA significantly reduced the risk of 30-day survival compared to IABP + VA-ECMO (HR: 0.46, 95%CI: 0.24–0.88, $P = 0.02$, Table 3), whereas single VA-ECMO significantly increased the risk compared to IABP + VA-ECMO treatment (HR: 1.86, 95%CI: 1.16–2.99, $P = 0.01$, Table 3).

Discussion

Current study revealed that earlier initiation of E-CPR (VA-ECMO) is important for survival and combined therapy with the Impella pump, called ECPELLA, was significantly improved the success rate of VA-ECMO weaning. The 30-day cumulative survival of ECPELLA were also significantly higher than IABP + VA-ECMO and single VA-ECMO. Of note, ECPELLA also showed the best neurological outcome among 3 treatment modalities.

Previous studies showed that VA-ECMO is a powerful life-support tool for patients with CA, which can oxygenize the arterial blood and supply the oxygenized blood into the systemic circulation to maintain end-organ perfusion. [2] [13] Recently published data of ELSO Registry study showed that early VA-ECMO support in patients with cardiogenic shock is important to improve the clinical outcome. The survivals at 30 days from VA-ECMO support was 38.1% in acute myocardial infarction complicated by cardiogenic shock (AMICS) and 42.1% in non-AMICS. [3] For AMICS patients required E-CPR, the survival to discharge was reported 29.2%, which was higher than the both IABP + VA-ECMO and single VA-ECMO support groups of the current study (23% and 9.5%, respectively). Mean ages of the patients in the current study were, respectively, 65 years old and 68 years old (vs. 54 years old in ELSO Registry), and relatively higher rate of AMICS (56%: IABP + VA-ECMO, 24%: Single VA-ECMO vs, 11.9%: ELSO Registry) (Table 1). [3] Although AMICS and older age (the similar findings in the current study) are the risk causing poor survival, there should be multiple factors that have to be considered for the different survival rates between ELSO Registry and current study. In contract, both VA-ECMO weaning rate and 30-day survival of ECPELLA group were higher than the ELSO Registry results (62% vs. 52% and 55% vs. 29.2%, respectively) despite of older mean age (64 years old) and higher AMICS rate (66%) suggesting that ECPELLA appears to be superior effects on short-term survival in CA patients with E-CPR.

In the current study Collapse to ECMO time was the shortest in ECPELLA group (23 minutes) followed by single VA-ECMO (36 minutes) and IABP + VA-ECMO (49 minutes) with statistical significance. While the results clearly indicate that earliest circulatory support for patients with CA is the most important to improve the survival, it is interesting that 30-day survival of IABP + VA-ECMO group was better than single VA-ECMO group despite IABP + VA-ECMO group had longer Collapse to ECMO time compared to the single VA-ECMO group. In addition, ECPELLA significantly improved the 30-day survival ($p < 0.001$, Fig. 1). Changes in hemodynamic parameters for the first 3 days showed ECPELLA had significantly larger circulatory support compared to other 2 groups from day 1 to day 3, and single VA-ECMO was significantly higher mean pulmonary pressure and CVP compared to IABP + VA-ECMO and ECPELLA. It is noted that mean arterial pressure levels were similar among groups. Changes in serum lactate levels for the first 3 days showed that although serum lactate levels were decreased in all groups, ECPELLA groups showed the least lactate levels at day 3 with statistical significance. It is interesting that VIS on day 1 of IABP + VA-ECMO was significantly lower than single VA-ECMO, whereas ECPELLA did not show the statistical significance to single VA-ECMO group implying that IABP could contribute to reduce vasoactive inotrope use on day 1. However, on day 3 VIS in ECPELLA was significantly lower than VA-ECMO group, and no difference was found between single VA-ECMO and IABP + VA-ECMO (Fig. 2). These results

suggest that while sufficient circulatory support is the most important for the patient survival, larger effect of the LV unloading rather than the arterial pressure also plays an important role in early survival that may also ameliorate the LV myocardial damage with reduced overloading condition to the right heart and the pulmonary circulation. [14] It is noted that VA-ECMO should have effect on the right ventricular preload reduction in all groups.

It is well-known that VA-ECMO can directly supply oxygenized blood to the entire system circulation during E-CPR. Previous studies showed that E-CPR has significant beneficial effect on both early patient survival and favorable neurological outcome,[15] [16] Murakami et al. recently reported that 30-day neurological outcome can be predicted by the interval from collapse to start of CPR better than the interval from collapse to start E-CPR time. [11] In the current study, we did not investigate the interval from collapse to CPR and the interval from collapse to E-CPR appeared to be shorter (< 36 minutes) than their report in all treatment groups (favorable and unfavorable neurological groups were, 50.1 and 55.1 minutes, respectively [11]). In their study, rates of CPC 1 or 2 of total collapse duration between 0 to 45 minutes were 19.2% and that of ECPELLA in the current study was 31%, whereas IABP + VA-ECMO and VA-ECMO were 13% and 7%, respectively. Although direct comparisons between current study and their study cannot be performed, earlier ECPELLA support appeared to have superior effect on the favorable neurological outcome. It is noted that total MCS in ECPELLA was higher than other groups for the first 3 days of support without changes in MAP (Figs. 2 and 3). These results suggest that ECPELLA has larger systemic circulatory support without increase in arterial blood pressure and additional vasoactive inotropes (lower vascular resistance), which could also reduce the risk of cerebral vascular events, such as hemorrhage and/or tissue injury [17]. Further studies are necessary whether ECPELLA effects on the favorable neurological outcome.

Several limitations in the current study must be discussed. First, this is a single center retrospective study in which historical clinical experience in the institute must be considered when comparing the treatment groups since Impella pump was available from 2018 and IABP and VA-ECMO had been used for E-CPR at that time already. We are confident that use of VA-ECMO should be consistent through the entire study period, however, indication of VA-ECMO and IABP for patients with CA might be changed over time. Since Impella were available in our institute and ECPELLA support was merging as the treatment option for patients with CA, the clinical experience using ECPELLA was the least among treatment options. Despite this situation, the 30-day survival and neurological outcome are statistically superior in ECPELLA group by which we may be able to consider this therapeutic modality is superior to previous therapeutic options in this patient population. Second, it remains unknown mechanistic explanations why ECPELLA showed better 30-day survival and neurological outcome. We speculate that ECPELLA achieved higher total mechanical circulatory support compared to single VA-ECMO or IABP + VA-ECMO during the most critical lifesaving treatment period. In addition, Impella does not only provide the systemic circulatory support, but also decreases LV loading condition by VA-ECMO resulting in reduction of the damaged myocardial oxygen consumption.[10] Finally, a prospective randomized study is considered the best to evaluate ECEPELLA effects compared to conventional E-CPR options. However, the randomized study with enough case numbers is difficult to conduct in this patient population due to both ethical and practical reasons.

Although the current study has these major limitations, it is a real-world retrospective study and consecutive patients were enrolled, which has less biased during the patient enrollment group allocation. It is obvious that further studies including multicenter observational studies are necessary to determine whether ECPELLA can be the first-choice therapeutic option for patients with CA.

Conclusions

Earlier initiation of E-CPR is critical to improve patient survival and neurological outcome. Additional Impella support appears to be critical for further improvement of clinical outcome.

Abbreviations

ANOVA
analysis of variance
CA
cardiac arrest
CPC
Cerebral Performance Categories
CS
cardiogenic shock
CVP
central venous pressure
ECPELLA
Combination of VA-ECMO and IMPELLA microaxial heart pump support
E-CPR
Extracorporeal cardiopulmonary resuscitation
HR
Hazard ratio
IABP
intra-aortic balloon pumping
LV
left ventricle
MCS
mechanical circulatory support
mPAP
mean pulmonary arterial pressure
VA-ECMO
venoarterial extracorporeal membrane oxygenation
VIS
vasoactive inotrope score

Declarations

Ethics approval and consent to participate: This study was approved by the Institutional Ethics Committee described in the text (Saiseikai Kumamoto Hospital, Institutional Ethics Committee Approval: No. 875).

Consent for publication: Consent for publication was included in the individual consent form for the treatment that was approved by the Institutional Ethics Committee described in the text.

Availability of data and materials: The datasets generated and/or analyzed during the current study are not publicly available due to our Institutional policy. However, they are available from the corresponding author on reasonable request.

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TU is a corresponding author who is responsible all aspects of the current manuscript, who conducted and executed research design, data collection, data analyses and interpretation, and manuscript drafting and substantially revised it.

UT, HS, and TS contributed the research design, and data collection (patient care/treatment).

MH contributed data collection (patient care/treatment) according to the research design.

MY. ET contributed data collection, analyses, and drafted the manuscript and revised it.

KN contributed research design, data interpretation, manuscript drafting, and substantially revised it.

TS is a co-investigator of the study, who contributed research design, data analysis and interpretation, manuscript drafting, and substantially revised it.

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Tables

Table 1. Clinical characteristics of the patients

	ECPELLA	IABP + VA-ECMO	VA-ECMO	*p*-value
n	29	78	42	-
Age, y	64 ± 14	65 ± 16	68 ± 15	0.5
Male, n (%)	22 (76)	58 (74)	21 (50)	0.02
Witness, n (%)	27 (93)	71 (91)	40 (95)	0.7
Bystander-CPR, n (%)	24 (83)	66 (85)	41 (98)	0.03
Initial rhythm				
shockable, n (%)	14 (48)	37 (47)	0 (0)	<0.001
PEA, n (%)	12 (41)	37 (47)	37 (88)	<0.001
Asystole, n (%)	3 (10)	4 (5)	5 (12)	0.4
OHCA, n (%)	12 (41)	33 (42)	8 (19)	0.02
ACS, n (%)	19 (66)	44 (56)	10 (24)	0.0003
Door to ECMO time, min (OHCA)	23 [19-29]	36 [29-48]	39 [33-48]	0.005
Collapse to ECMO time, min	27 [14-44]	49 [28-75]	36 [23-53]	0.004

PEA, pulseless electric activity; OHAC, out of hospital cardiac arrest; ACS, acute coronary syndrome.

Table 2. ECMO weaning and outcome of cerebral performance category 1 or 2

	ECPELLA	ECMO with IABP	ECMO alone	*p*-value
ECMO weaning, *n (%)*	18 (62)	34 (44)	7 (17)	0.0002
Cerebral Performance Category 1 or 2 , *n (%)*	9 (31)	10 (13)	3 (7)	0.02

Table 3. Multivariate Cox regression analysis for cumulative 30-day survival

	HR	95% CI		P-value
Age (per 10 years increase)	1.30	1.13	1.52	0.005
Initial shockable rhythm	0.73	0.45	1.20	0.2
Collapse to ECMO time (per 10 min increase)	1.22	1.13	1.31	<0.0001
MCS				
IABP + VA-ECMO (references)	1.00	-	-	-
ECMO alone	1.86	1.16	2.99	0.01
ECPELLA	0.46	0.24	0.88	0.02

Figures

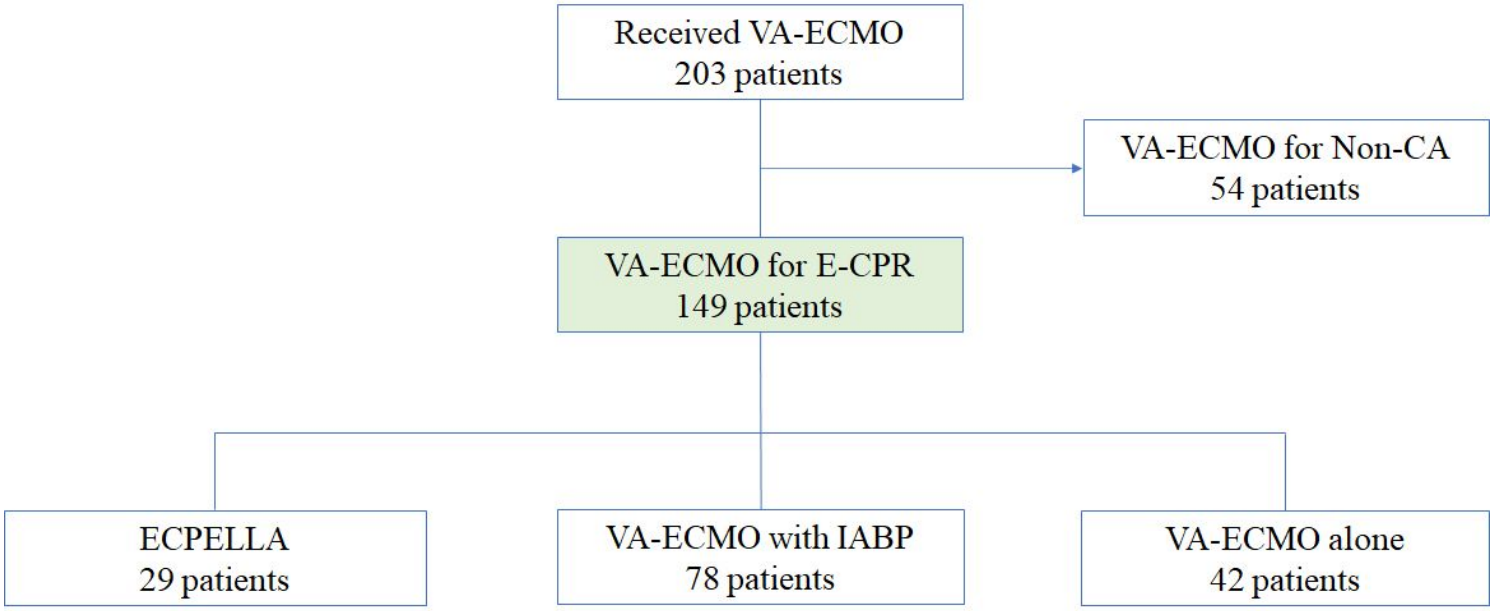


Figure 1

Study flow chart of patient enrollment and study group allocation CA, cardiac arrest; E-CPR, extracorporeal cardiopulmonary resuscitation, ECPELLA, Impella + VA-ECMO, IABP, intra-aortic balloon pumping; VA-ECMO, venoarterial extracorporeal membrane oxygenation

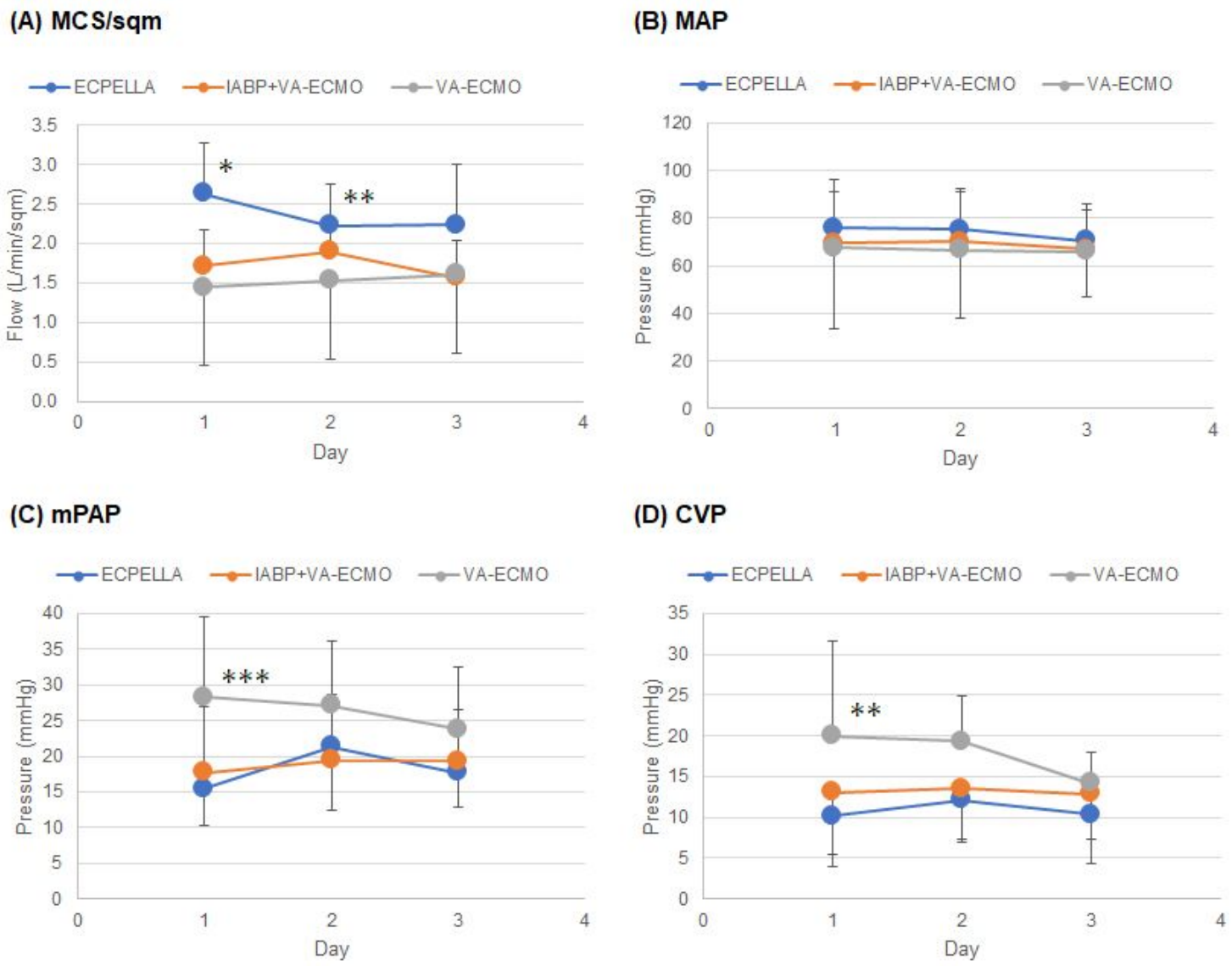


Figure 2

Major hemodynamic parameters for the first 3 days treatment period MCS, mechanical circulatory support (L/min/m2); MAP, mean arterial pressure (mmHg); mPAP, mean pulmonary arterial pressure (mmHg); CVP, central venous pressure (mmHg).

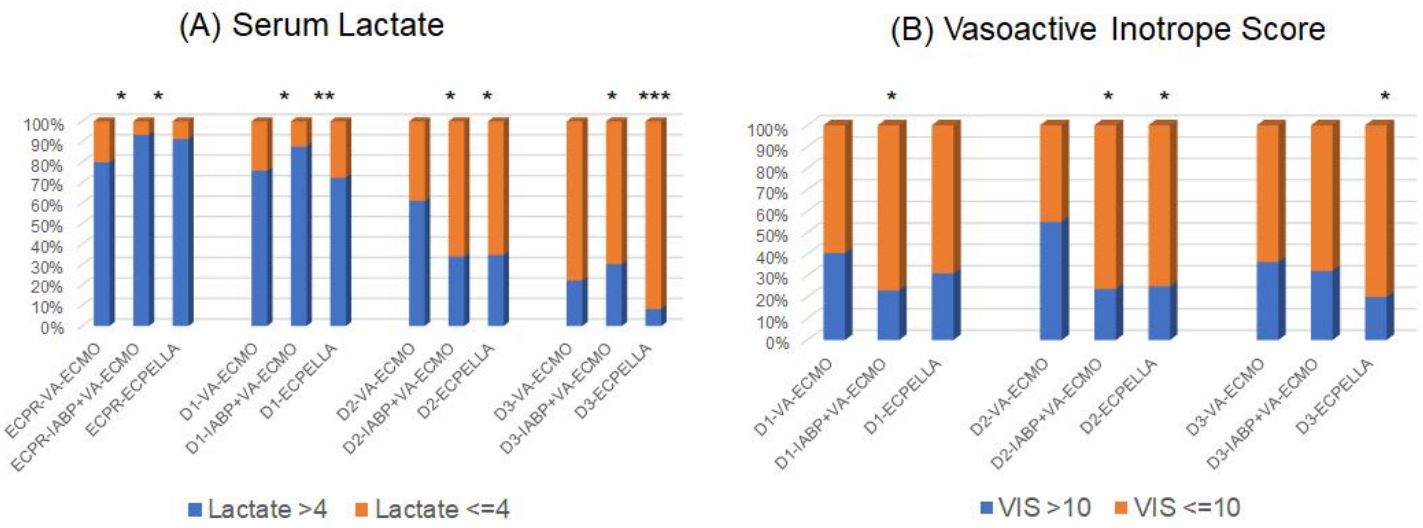
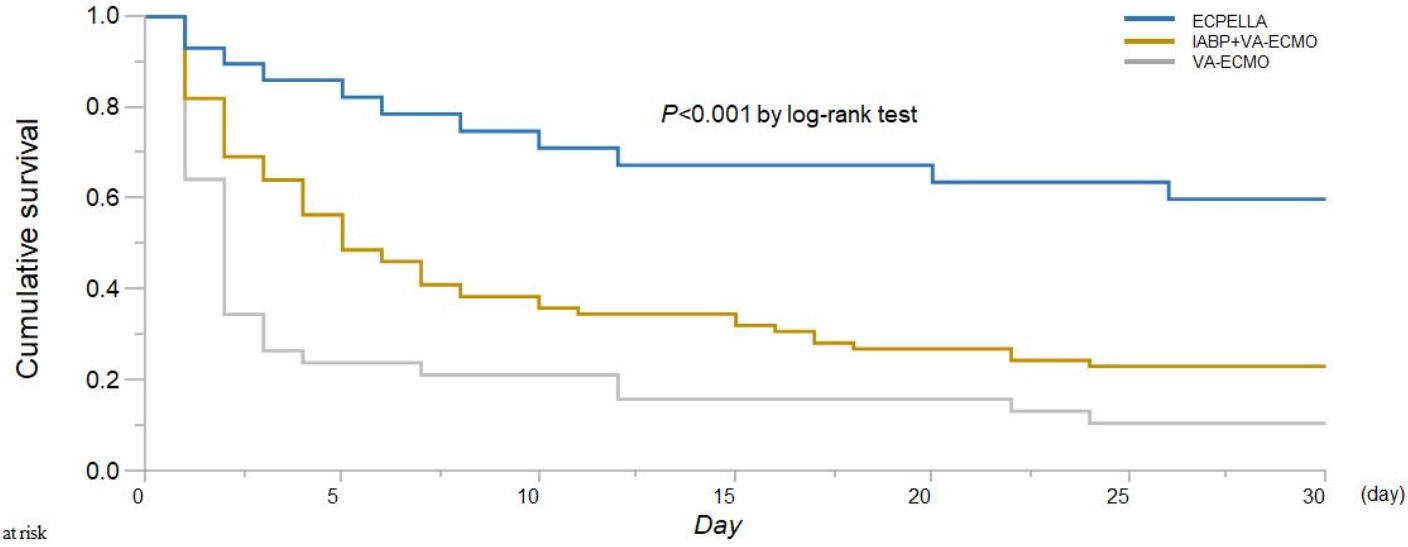


Figure 3

Changes in serum lactate levels and vasoactive inotrope scores for the first 3 days of treatment period Vasoactive Inotrope Score was calculated as dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min) + 10000 × vasopressin dose (unit/kg/min) + 100 × norepinephrine dose (μg/kg/min). *, P<0.05 vs. VA-ECMO; ** P<0.05 vs. IABP + VA-ECMO; *** P<0.05 vs. VA-ECMO and IABP + VA-ECMO



No. at risk							
ECPELLA	29	23	20	19	18	18	16
IABP+VA-ECMO	78	45	31	28	23	22	18
VA-ECMO	42	10	9	8	8	6	4

Figure 4

Cumulative 30-day survival curves (Kaplan-Meier analysis) Cumulative 30-day survival rates were respectively, 55% in ECPELLA, 23% in IABP + VA-ECMO, and 9.5% in VA-ECMO (P<0.001).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- floatimage1.jpeg