

Prompt extracorporeal cardiopulmonary resuscitation with left ventricular unloading by IMPELLA improves the outcome of patients with refractory cardiac arrest: A single-site retrospective cohort study

Takashi Unoki (✉ tunoki@hotmail.co.jp)

1) Department of Cardiology and Intensive Care Medicine, Saiseikai Kumamoto Hospital

Yudai Tamura

Department of Cardiology and Intensive Care Medicine, Saiseikai Kumamoto Hospital

Motoko Hirai

Department of Cardiology and Intensive Care Medicine, Saiseikai Kumamoto Hospital

Hiroto Suzuyama

Department of Cardiology and Intensive Care Medicine, Saiseikai Kumamoto Hospital

Masayuki Inoue

Department of Cardiology and Intensive Care Medicine, Saiseikai Kumamoto Hospital

Megumi Yamamuro

Department of Cardiology and Intensive Care Medicine, Saiseikai Kumamoto Hospital

Eiji Taguchi

Department of Cardiology and Intensive Care Medicine, Saiseikai Kumamoto Hospital

Tadashi Sawamura

Department of Cardiology and Intensive Care Medicine, Saiseikai Kumamoto Hospital

Koichi Nakao

Department of Cardiology and Intensive Care Medicine, Saiseikai Kumamoto Hospital

Tomohiro Sakamoto

Department of Cardiology and Intensive Care Medicine, Saiseikai Kumamoto Hospital

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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 a significant effect on clinical outcome by concomitant use of VA-ECMO and IMPELLA (ECPELLA). In the current retrospective cohort study, we assessed factors affecting the 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: ECPELLA (n=29), IABP + VA-ECMO (n=78), and single VA-ECMO (n=42). We assessed 30-day survival and neurological outcome using cerebral performance categories (CPCs).

Results: There were no significant differences in age, sex, out-of-hospital CA, or acute coronary syndrome among the groups. 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

The management of patients with refractory cardiac arrest (CA) who do not respond to conventional cardiopulmonary resuscitation is controversial. The outcome of such patients remains to be improved despite recent advancements in the use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) during 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, arterial blood perfusion by ECMO increases damaged left ventricular (LV) afterload, resulting in increased myocardial wall stress by LV chamber distension that may lead to further myocardial damage. [2] [3] [4]

Intra-aortic balloon pumping (IABP) has been used for the treatment of such patients, often combined with VA-ECMO as 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 in LV afterload appears to be quite

limited due to significantly increased LV afterload by VA-ECMO,[4] and IABP can also interfere with 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 it into the ascending aorta, which can achieve simultaneous circulatory support and LV preload reduction.[10] When it is combined with VA-ECMO, Impella not only contributes circulatory support but also significantly reduces LV preload. Thus, the combination of Impella and VA-ECMO, called ECPELLA, may have superior clinical outcomes 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 the treatment of patients with refractory CA requiring extracorporeal CPR (E-CPR). Since the 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 E-CPR. However, it remains unclear whether ECPELLA has a better clinical outcome than conventional IABP + VA-ECMO for the treatment of patients requiring E-CPR.

Thus, in the present study, we retrospectively reviewed and compared cumulative 30-day survival and neurological outcomes among the ECPELLA, IABP + VA-ECMO, and single VA-ECMO groups in refractory CA patients who required E-CPR. Our results suggest that ECPELLA showed superior 30-day survival and neurological outcomes 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 followed the Declaration of Helsinki.

Patients. We retrospectively reviewed 203 consecutive patients in their individual patient records who underwent VA-ECMO for various disease conditions from January 2012 to December 2020. We excluded 54 patients for whom VA-ECMO was not applied for E-CPR. There were 149 patients who underwent E-CPR due to refractory cardiac arrest despite the standard cardiopulmonary resuscitation procedure. 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; and 3) refractory ventricular arrhythmias or pulseless electric activity with short duration of CA that cannot be recovered by conventional CPR. The exclusion criteria were as follows: 1) apparent aortic dissection prior to E-CPR; 2) noncardiac 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 (Figure 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, a Terumo VA-ECMO system (CAPIOX, Terumo, Tokyo, Japan) and a 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 the 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, sex, 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 the log-rank test. Comparison of patient characteristics, serum lactate levels and VISs among the 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 a p-value less than 0.05 in all statistical analyses.

Results

Background characteristics of the patients.

Table 1 summarizes the clinical characteristics of the patients. The male patient ratios of the ECPELLA (76%) and IABP+VA-ECMO (74%) groups were higher than those of the VA-ECMO group (50%, $p=0.02$). The bystander-CPR rate in VA-ECMO was higher than that in the other groups (83% in ECPELLA, 85% in IABP+VA-ECMO, and 98% in VA-ECMO, $p=0.03$). While shockable rhythms were seen in both the ECPELLA (48%) and IABP + VA-ECMO (47%) groups, no cases were seen in the VA-ECMO group (0%, $p<0.001$). Pulseless electric activity in VA-ECMO was higher than that in the other groups (41% in ECPELLA, 47% in IABP + VA-ECMO, and 88% in VA-ECMO, $p<0.001$). Rates of out-of-hospital cardiac arrest (OHCA) were higher in ECPELLA (41%) and IABP + VA-ECMO (42%) than in VA-ECMO (19%, $p=0.02$). Higher rates of acute coronary syndrome were seen in ECPELLA (66%) and IABP+VA-ECMO (56%) than in 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 the 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 had a significantly higher MCS flow than the other groups on days 1 and 2 ($P<0.05$). While the mean arterial pressure (Figure 2B) was similar among the treatment groups, the VA-ECMO group showed significantly higher mean main pulmonary artery pressure (mPAP, Figure 2C) and central venous pressure (CVP) on day 1 than the other groups ($P<0.05$, Figure 2D).

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

The vasoactive inotrope score was calculated as dopamine dose ($\mu\text{g}/\text{kg}/\text{min}$) + dobutamine dose ($\mu\text{g}/\text{kg}/\text{min}$) + $100 \times$ epinephrine dose ($\mu\text{g}/\text{kg}/\text{min}$) + $10 \times$ milrinone dose ($\mu\text{g}/\text{kg}/\text{min}$) + $10000 \times$ vasopressin dose (unit/kg/min) + $100 \times$ norepinephrine dose ($\mu\text{g}/\text{kg}/\text{min}$). 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 ($P<0.05$, Figure 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. The VA-ECMO weaning rate in the ECPELLA group was significantly higher than that in the other groups ($P=0.0002$). The rates of cerebral performance category 1 or 2 in the ECPELLA, IABP + VA-ECMO, and VA-ECMO groups were 31%, 13%, and 7%, respectively, indicating that the ECPELLA group had better neurological outcomes than the 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 ($P<0.001$, Figure 4). Multivariate Cox regression analysis for 30-day survival revealed that older age (per 10-year 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

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

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

In the current study, collapse to ECMO time was the shortest in the 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 30-day survival ($p < 0.001$, Figure 1). Changes in hemodynamic parameters for the first 3 days showed that ECPELLA had significantly larger circulatory support than the other 2 groups from day 1 to day 3, and single VA-ECMO was significantly higher in mean pulmonary pressure and CVP than IABP + VA-ECMO and ECPELLA. The mean arterial pressure levels were similar among the groups. Changes in serum lactate levels for the first 3 days showed that although serum lactate levels were decreased in all groups, the ECPELLA groups showed the lowest 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 statistical significance to the single VA-ECMO group, implying that IABP could contribute to reducing vasoactive inotrope use on day 1. However, on day 3, VIS in the ECPELLA group was significantly lower than that in the VA-ECMO group, and no difference was found between VA-ECMO alone and IABP+VA-ECMO (Figure 2). These results suggest that while sufficient circulatory support is the most important for patient

survival, a larger effect of LV unloading rather than arterial pressure also plays an important role in early survival and may also ameliorate LV myocardial damage with reduced overloading conditions to the right heart and pulmonary circulation. [14] VA-ECMO should have an effect on right ventricular preload reduction in all groups.

VA-ECMO can directly supply oxygenized blood to the entire system circulation during E-CPR. Previous studies showed that E-CPR has a 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, the rates of CPC 1 or 2 of total collapse duration between 0 and 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 the current study and their study cannot be performed, earlier ECPELLA support appeared to have a superior effect on favorable neurological outcomes. The total MCS in ECPELLA was higher than that in the other groups for the first 3 days of support without changes in MAP (Figures 2 and 3). These results suggest that ECPELLA has larger systemic circulatory support without an 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 to determine whether ECPELLA affects favorable neurological outcomes.

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 the Impella pump was available in 2018 and IABP and VA-ECMO had already been used for E-CPR. We are confident that the use of VA-ECMO should be consistent throughout the entire study period; however, the indications for VA-ECMO and IABP for patients with CA might change 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 were statistically superior in the ECPELLA group, and we may be able to consider this therapeutic modality to be superior to previous therapeutic options in this patient population. Second, it remains unknown mechanistic explanations why ECPELLA showed better 30-day survival and neurological outcomes. We speculate that ECPELLA achieved higher total mechanical circulatory support than VA-ECMO or IABP+VA-ECMO alone during the most critical lifesaving treatment period. In addition, Impella not only provides systemic circulatory support but also decreases LV loading conditions by VA-ECMO, resulting in a reduction in damaged myocardial oxygen consumption.[10] Finally, a prospective randomized study is considered the best to evaluate ECPELLA effects compared to conventional E-CPR options. However, a 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 was 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.

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 upon reasonable request.

Competing Interests: No competing Interests

Funding: No funding support

Authors' contributions: All authors agreed to the contents of the manuscript and approved the submitted version. The following are details of each author's contribution to the current manuscript.

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

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

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

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

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

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

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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

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Tables

Tables 1-3 are available as a download in the Supplementary Files section.

Figures

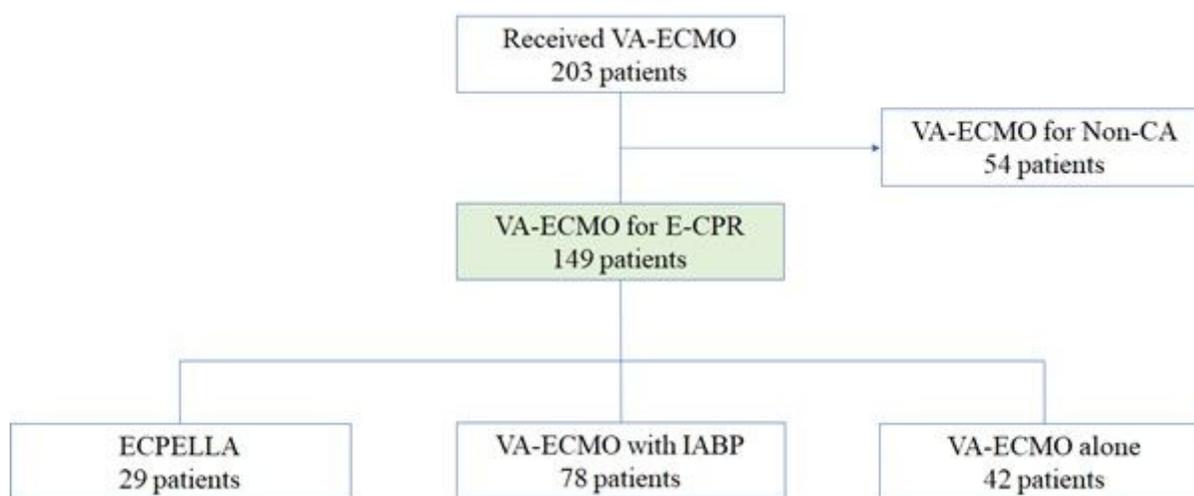
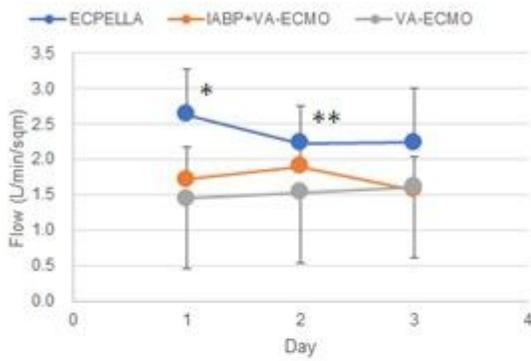


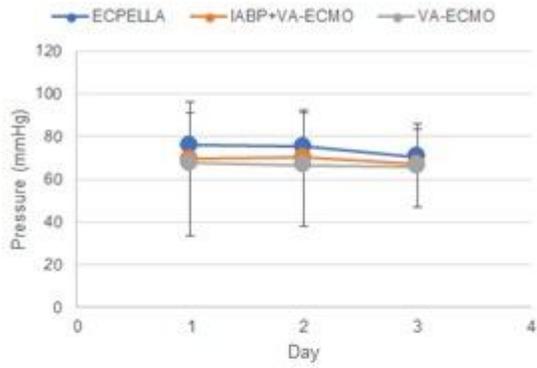
Figure 1

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

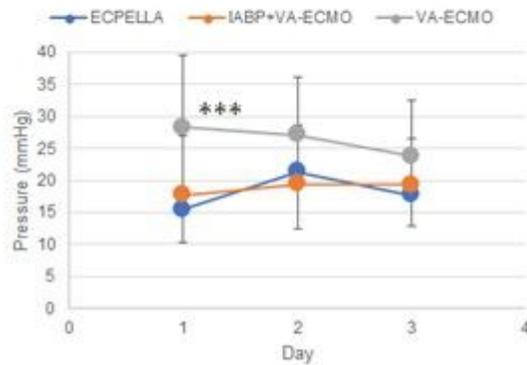
(A) MCS/sqm



(B) MAP



(C) mPAP



(D) CVP

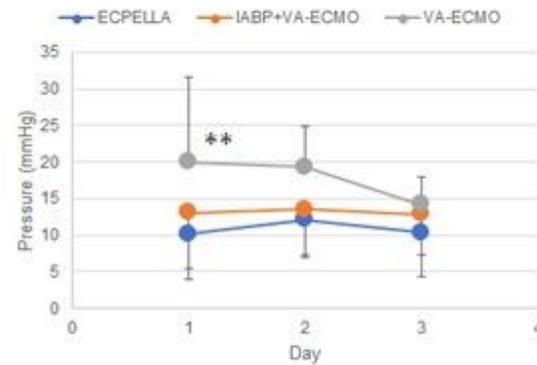
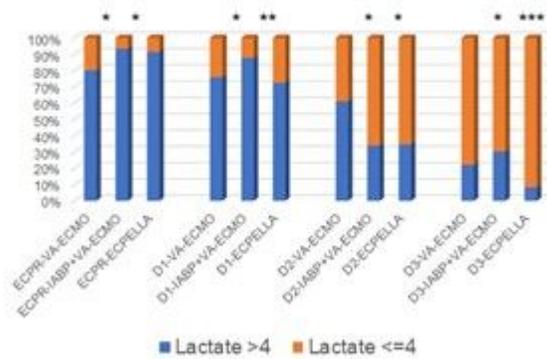


Figure 2

Major hemodynamic parameters for the first 3 days of the 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).

(A) Serum Lactate



(B) Vasoactive Inotrope Score

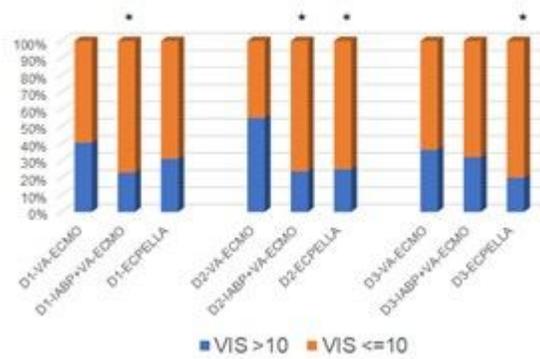


Figure 3

Changes in serum lactate levels and vasoactive inotrope scores for the first 3 days of the treatment period 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). *, P<0.05 vs. VA-ECMO; ** P<0.05 vs. IABP + VA-ECMO; *** P<0.05 vs. VA-ECMO and IABP + VA-ECMO

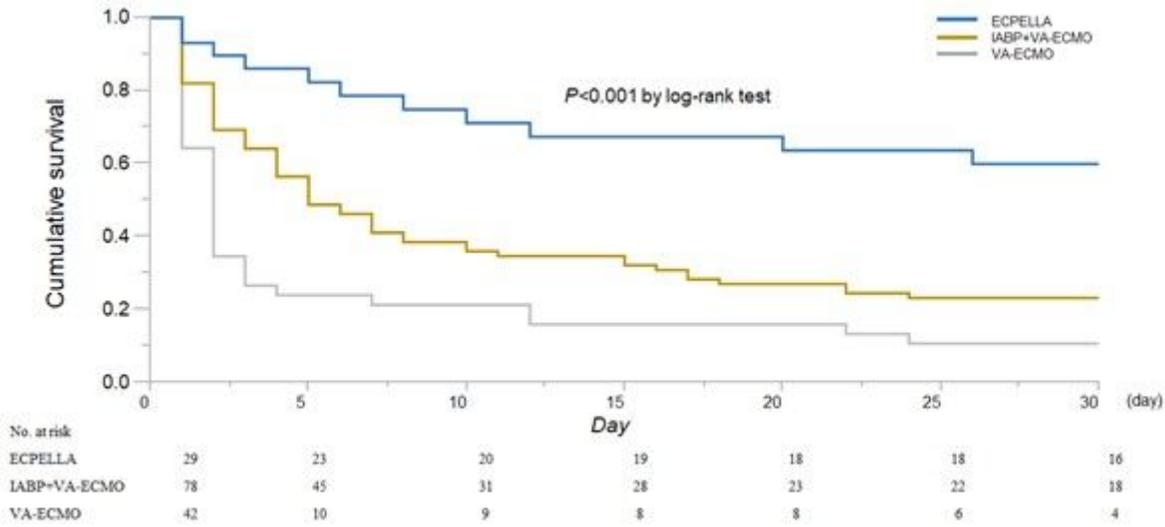


Figure 4

Cumulative 30-day survival curves (Kaplan-Meier analysis) Cumulative 30-day survival rates were 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.

- [graphicalabstract.png](#)
- [Tables.docx](#)