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Original Article

The correlation between early net fluid balance and the clinical outcomes of patients receiving extracorporeal cardiopulmonary resuscitation

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Abstract: Objective: To investigate correlation between early net fluid balance and the clinical outcomes of patients receiving extracorporeal cardiopulmonary resuscitation (ECPR). Methods: Adult patients on ECPR admitted to the Department of Emergency in the First Affiliated Hospital of Nanjing Medical University from May 2015 to December 2020 were included. Net fluid balance for consecutive 4 days after ECPR was recorded. The primary outcome was survival to intensive care unit (ICU) discharge. We used multivariable logistic regression to assess the association between fluid status and clinical outcomes. Results: A total of 72 patients were enrolled and divided into two groups: the survivor group and the non-survivor group. The overall rate of survival to ICU discharge was 44.4%. Daily fluid balance (DFB) in the survivor group was lower than that in the non-survivor group at day 4 (-11.47 (-19.74, 8.7) vs. -5.08 (-12.94, 13.9) mL/kg, P=0.046), as was cumulative fluid balance (CFB) over the first 4 days (-36.03 (-51.45, 19.03) vs. -7.22 (-32.79, 21.02) mL/kg, P=0.009). Both continuous renal replacement therapy (CRRT) and CFB from days 1-4 were significantly correlated with survival to ICU discharge (OR=14.617, 95% CI: 1.344, 48.847, P=0.028; OR=1.261, 95% CI: 1.091, 1.375, P=0.003, respectively). CFB from days 1-4 was determined to have a roughly linear association with the log odds of survival to ICU discharge. Conclusion: Early negative fluid balance maybe associated with survival to ICU discharge in patients receiving ECPR.

Keywords: Fluid balance, extracorporeal cardiopulmonary resuscitation, cardiac arrest, critical care

Introduction

The standard therapy for cardiac arrest (CA) is cardiopulmonary resuscitation (CPR). Recent studies have reported 20% survival after hospital discharge in patients with in-hospital CA (IHCA) and 10% in patients with out-hospital CA (OHCA) [1, 2]. To improve the neurological outcome and survival rate in patients with CA, extracorporeal cardiopulmonary resuscitation (ECPR) has been proposed in some selected cases of refractory CA [3-5]. Once ECPR has been initiated, frequent blood and fluid transfusion may be required to maintain the targeted mean arterial pressure (MAP) and blood flow of extracorporeal membrane oxygenation (ECMO). Excessive positive fluid administration may, in turn, result in cardiogenic/non-cardiogenic pulmonary edema, acute kidney injury (AKI), systemic capillary leakage and so on [6, 7]. In light of this, the restrictive fluid balance strategy has been advocated in patients with septic shock, acute respiratory distress syndrome (ARDS) and AKI [8-10]. In terms of fluid management in patients receiving ECMO treatment, there are few studies reporting the association between fluid balance and clinical outcomes. Schmidt et al. retrospectively analyzed the data of 115 refractory heart failure patients and 57 refractory respiratory failure patients, who were treated by ECMO, and the results showed that positive fluid balance at ECMO day 3 was an independent predictor of 90-day mortality [11]. Staudacher et al. retrospectively investigated data of 195 cases who received VA-ECMO implantation and reported that higher fluid balance was correlated with poor survival; however, whether lower fluid balance might improve outcomes or represents a prognostic marker is still unclear [12]. Therefore, more evidence is urgently needed to reveal the relationship between fluid management in patients receiving ECMO treatment and their outcomes.

To date, no consensus on fluid administration strategies has been achieved in patients on ECPR. Given the high incidence of positive fluid administration and potential adverse effects caused by inappropriate fluid management, it is important to understand the association of fluid balance status with clinical outcomes.

Our objective was to determine the prevalence of positive fluid balance in patients receiving ECPR and to evaluate the association between fluid balance status and survival after intensive care unit (ICU) discharge.

Materials and methods

Case selection and ethic approval

This retrospective study collected data from a 17-bed ICU in *The First Affiliated Hospital of Nanjing Medical University*, which is a university-affiliated teaching hospital. All cases received ECPR from May 2015 to December 2020. The Ethics Committee of the First Affiliated Hospital of Nanjing Medical University approved this study and the need for written consent was waived because of the retrospective design of the study.

A patient's eligibility for ECPR was assessed by the physician on duty who was leading the ECMO team, and this eligibility was based on the following factors: age <70 years, witnessed CA, shockable rhythm, <5 min of estimated no-flow time, <30 min of low-flow time, and no malignant tumor.

The inclusion criteria: adult patients on ECPR, duration of ECMO ≥96 hours with complete clinical data. The exclusion criteria: under 18 years of age, pregnancy, duration of ECMO <96 hours, ECMO modality switching and intracranial hemorrhage.

Data collection and outcomes measures

The patients' demographic and laboratory data were retrieved from electronic medical records. The data included age, sex, weight, comorbidities, location of CA, ECMO parameter settings, continuous renal replacement therapy (CRRT) and intra-aortic balloon pump (IABP) initiation, duration of mechanical ventilation (MV), ICU stay, and vasoactive inotropic score (VIS). VIS was calculated as (epinephrine + noepinephrine) μg/kg/min × 100 + (dobutamine + dopamine) μg/kg/min × 100 + milrinone μg/kg/min × 15 + vasopressin IU/kg/min × 10000 [13]. The amounts of input fluid and output fluid were continuously recorded within 4 days of ECMO initiation. The daily fluid balance (DFB) was calculated by the difference between fluid inputs and outputs and was divided by the patient's actual body weight. Weight was measured daily at 8 am using the automated-weighing bed system upon admission. The cumulative fluid balance (CFB) was defined as the cumulative total input fluid minus the cumulative total output fluid and obtained by the addition of each daily fluid balance from ECMO commencing until the day of evaluation. Survival was observed at ICU discharge, and patients were classified into the survivor group or non-survivor group according to their clinical outcome. The primary outcomes were DFB and statistical analyses for factors associated with survival to ICU discharge.

Statistical analysis

Continuous variables not normally distributed were expressed as median and inter quartile range (IQR) and compared with Mann-Whitney U test. Normally distributed continuous variables were expressed as mean ± standard deviation (SD) and compared with Student's t-test. Categorical variables were expressed as percentages and compared with the chi-square test. Kendall's tau-b correlation was used to quantify the relationship between continuous variables and categorical variables. Univariate and multivariate analyses were performed to identify factors associated with survival to ICU discharge. Associations between clinical outcomes and net fluid balance were evaluated with the Cochran-Armitage trend test for binary variables. Statistical significance was set at a two-sided P value of less than 0.05. All data were analyzed using GraphPad Prism v8.0 and SPSS software v24.0.

Results

Characteristics of study subjects

A total of 84 patients admitted to the ICU for ECPR between May 2015 and December 2020 were enrolled. Eight patients were excluded

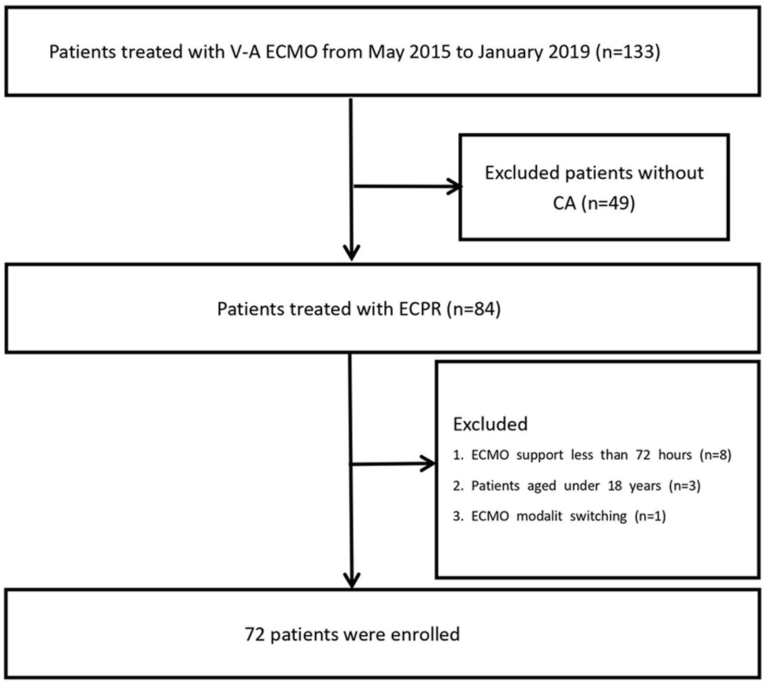

Figure 1. Flowchart of participant enrollment. CA: cardiac arrest; ECPR: extracorporeal cardiopulmonary resuscitation; V-A ECMO: venous-arterial extracorporeal membrane oxygenation.

due to a duration of ECMO support less than 96 hours, three patients were excluded because of ages under 18 years, and one patient was excluded due to ECMO modality switching. Finally, 72 patients were eligible for further analysis (**Figure 1**).

The baseline characteristics of the patients are presented in **Table 1**. The mean age was 42.6±16.3 years, and 66.67% (48/72) were males. The average time on VA-ECMO was 164.8 (98.1, 212.3) hours in all patients, while the duration of MV was 173.5 (93, 233) hours. To investigate the factors associated with survival to ICU discharge, we categorized the enrolled patients into survivor and non-survivor groups according to clinical outcome at ICU discharge. Compared with the non-survivor group, those in the survivor group were more likely to have a lower APACHE II score (25, 95% CI: 17-45 vs. 39, 95% CI: 24-64, P=0.033) and to be predisposed to receive CRRT (37.5% versus 90%, P=0.001, 95% CI: 1.3%-39.4%), respectively. In addition, the duration of MV was significantly shorter in the survivor group (100.5, 95% CI: 57.4-196.1 vs. 200, 95% CI: 165.3-308.1, P=0.003). In contrast, the survivor group had a longer ICU stay (17.5, 95% CI: 16.3-26.1 vs. 9, 95% CI: 8.1-15.2, P=0.001). All other patient characteristics, including age, gender, body weight, location of CA, preexisting cardiovascular disease, ECMO therapy duration and VIS, were not different between the two groups (all P>0.05).

Daily and cumulative fluid status

Table 2 shows the details of DFB and CFB during the first 4 days of ECMO commencement. A positive DFB was only noted in the non-survivor group at day 1 (0.15, IQR: -2.68-11.75). At all other investigated time points, a negative DFB was achieved. DFB at day 4 was significantly higher in non-survivors compared with the survivals (-5.08, 95% CI: -8.5 to 11.6 vs. -11.47, 95% CI: -18.4 to -7.9, P= 0.046). No difference was observed between the two groups from day 1 to day 3. CFB increased progressively over time. Further analysis demonstrated a significant difference in days 1-4 CFB between the two groups (-36.03, 95% CI: -51.2 to -3.9 vs. -7.22, 95% CI: -18.1 to 28.1, P=0.009).

Relationships between fluid status and ICU survival

The overall rate of ICU survival was 44.4%. Univariate logistic regression analysis showed a significant association between survival to ICU discharge and APACHE II on admission, ICU stay, CRRT, duration of MV, DFB at day 4 and CFB from days 1-4. Multivariate logistic regression analysis identified that both CRRT and CFB from days 1-4 were significantly correlated with survival to ICU discharge (OR: 14.617, 95% CI: 1.344 to 48.847, P=0.028; OR: 1.261, 95% CI: 1.091 to 1.375, P=0.003; **Table 3**).

The unadjusted association of CFB from days 1-4 with survival to ICU discharge was assessed using univariate logistic regression and natural cubic splines. CFB from days 1-4 was determined to have a roughly linear association with

Table 1. Baseline data analysis: univariate comparisons of demographic factors and outcomes

Variables	Survivor (n=32)	Non-survivor (n=40)	*P* value
Age (years)	41.2±16.3	43.7±16.7	0.646
Male (%)	18/32 (56.3%)	30/40 (75%)	0.236
IHCA (%)	22/32 (68.8%)	16/40 (40%)	0.086
Causes of CA (%)			0.642
Coronary heart disease	26/32 (81.2%)	33/30 (82.5%)	
Myocardial disease	4/32 (12.5%)	7/40 (17.5%)	
Non-cardiac cause	2/32 (6.3%)	1/40 (2.5%)	
CPR (hours), median (IQR)	85 (58-156)	88 (55-172)	0.965
Time from CA to CPR initiation (Scends), median (IQR)	67 (38-167)	63 (44-171)	0.093
APACHE II on admission (scores), median (IQR)	25 (18-38)	39 (29-55)	0.033
ICU stay (days), median (IQR)	17.5 (13-44)	9 (4-27)	0.001
CRRT (%)	12/32 (37.5%)	36/40 (90%)	0.001
IABP (%)	8/32 (25%)	6/40 (15%)	0.451
Duration of MV (hours), median (IQR)	100.5 (17-174)	200 (168.8-263)	0.003
Time from CA to ECMO initiation (Minutes), median (IQR)	41 (31-54)	39 (29-51)	0.561
Duration of ECMO (hours), median (IQR)	144.4 (100.5-173.9)	176.6 (98-227.5)	0.126
Blood flow of ECMO (lpm)	3.8±0.3	4.1±0.6	0.37
VIS score at day 1, median (IQR)	17.2 (6.3-39.4)	31.5 (0-92.8)	0.421
VIS score at day 2, median (IQR)	8.8 (0-12.9)	16 (0-77.8)	0.113
VIS score at day 3, median (IQR)	2.5 (0-6.7)	9.6 (0-75)	0.128
VIS score at day 4, median (IQR)	1.6 (0-24.1)	10.7 (0-33.8)	0.24

Note: Continuous variables are presented as means ± SD or median (quartile 1-quartile 3). IHCA: in-hospital cardiac arrest; CA: cardiac arrest; CPR: cardiopulmonary resuscitation; CVD: cardiovascular disease; ICU: intensive care unit; IQR: inter quartile range; CRRT: continuous renal replacement therapy; IABP: intra-aortic balloon pump; MV: mechanical ventilation; ECMO: extracorporeal membrane oxygenation; VIS: vasoactive inotropic score; lpm: liter per minute; SD: standard deviation.

Table 2. Details of daily and cumulative fluid balance

Variables	Survivor (n=32)	Non-survivor (n=40)	*P* value (95% CI)
DFB (mL/kg)			
Day 1	-0.99 (-7.24, 6.22)	0.15 (-2.68, 11.75)	0.352 (0.341, 0.360)
Day 2	-7.67 (-16.66, 5.36)	-5.89 (-8.63, 8.12)	0.262 (0.251, 0.268)
Day 3	-10.69 (-13.21, -4.28)	-5.93 (-12.43, 9.47)	0.095 (0.088, 0.099)
Day 4	-11.47 (-19.74, -8.7)	-5.08 (-12.94, 13.92)	0.046 (0.040, 0.048)
CFB (mL/kg)			
Days 1-2	-13.98 (-20.22, 1.38)	-6.12 (-15.72, 15.07)	0.168 (0.157, 0.171)
Days 1-3	-25.02 (-35.54, -6.51)	-8.35 (-21.61, 19.3)	0.053 (0.047, 0.056)
Days 1-4	-36.03 (-51.45, -19.03)	-7.22 (-32.79, 21.02)	0.009 (0.001, 0.04)

Note: Continuous variables are expressed as median (quartile 1, quartile 3). DFB: daily fluid balance; CFB: cumulative fluid balance; CI: confidence interval.

the log odds of survival to ICU discharge (**Figure 2**).

Discussion

There is robust evidence in literature that discourages excessive fluid accumulation in critically ill patients with sepsis/septic shock [9, 14-16]. Similar results were also reported in patients on V-VECMO or V-AECMO [11, 12, 17, 18]. However, it is unclear whether patients on ECPR should also receive restrictive fluid administration. Patients receiving ECPR often require large-volume fluid infusion during and after ECPR initiation to guarantee appropriate ECMO blood flow and perfusion pressure, and

Table 3. Univariate and multivariate logistic regression analysis for ICU survival

Variables	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
APACHE II on admission	1.466 (0.517, 4.355)	0.033		
ICU stay	0.858 (0.764, 0.963)	0.001		
CRRT	15 (2.537, 88.701)	0.003	14.617 (1.344, 48.847)	0.028
Duration of MV	1.018 (1, 1.116)	0.003		
DFB at day 4	1.071 (1.004, 1.142)	0.046		
CFB from days 1-4	1.018 (1.007, 1.037)	0.009	1.261 (1.091, 1.375)	0.003

Note: Continuous variables are expressed as median (quartile 1-quartile 3). ICU: intensive care unit; CRRT: continuous renal replacement therapy; MV: mechanical ventilation; DFB: daily fluid balance; CFB: cumulative fluid balance; CI: confidence interval; OR: odds ratio.

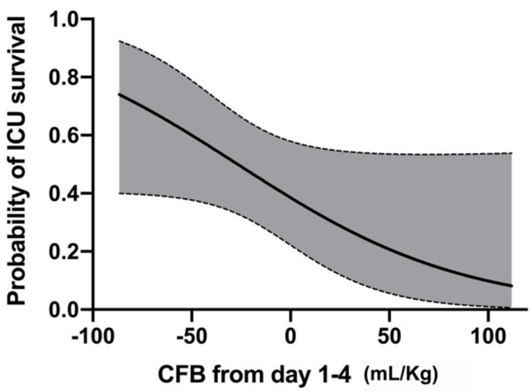

Figure 2. Cubic spline curve for the association between CFB and survival to ICU discharge. CFB: cumulative fluid balance; ICU: intensive care unit.

positive fluid balance or excessive fluid accumulation is sometimes inevitable [19, 20]. To date, there are scarce data that investigate the relationship between early net fluid balance status and clinical outcomes in patients on ECPR.

In clinical practice, fluid resuscitation is often the cornerstone of early management to stabilize hemodynamics in critically ill patients. Vincent has proposed four distinct phases of fluid resuscitation in patients with sepsis: rescue, optimization, stabilization and de-escalation [21]. Strategies of fluid management emphasizes not only fluid resuscitation but also "reversed fluid resuscitation", which equals de-escalation. Undoubtedly, intensivists around the world have attached great importance to the first two phases when critically ill patients manifest macrocirculation and/or microcirculation dysfunction. However, the last phase is not always given priority to by physicians after patients achieve hemodynamic improvement. Therefore, a positive fluid balance commonly occurs in patients, especially during the early phase. Brotfain reported that patients with sepsis/septic shock who experienced less positive cumulative fluid balance had lower ICU and in-hospital mortality (P<0.001 for both ICU and in-hospital mortality, OR: 1.04 (95% CI: 1.02 to 10.6); OR: 1.06 (95% CI: 1.03 to 1.08)) [10]. Chao also found that a positive CFB from days 1-4 was independently associated with a higher 30-day mortality in critically ill patients with influenza (HR: 1.088, 95% CI: 1.007 to 1.074) [22].

Similar conclusions have been drawn by several authors regarding V-AECMO patients with refractory cardiac shock. In a retrospective analysis, Besnier et al. demonstrated that patients with more positive fluid balance at day 1 had higher mortality (OR: 14.34, 95% CI: 1.58 to 129.79). A threshold of 38.8 mL/kg fluid balance predicted mortality with a sensitivity of 60% and a specificity of 83% [19]. Another retrospective multicenter study enrolling 723 patients on V-AECMO revealed a significantly increased risk of 90-day mortality in patients with higher CFB during the first 3 days after ECMO initiation (HR: 1.76, 95% CI: 1.37 to 2.27, P<0.001). Further analysis found that the relative hazard ratio (HR) of mortality started to increase significantly when CFB exceeded 82.3 mL/kg [23]. Therefore, higher fluid balance was consistently linked to poor outcomes.

Similarly, CA is frequently considered as a sepsis-like syndrome [24]. Patients with CA typically encounter circulatory collapse and subsequently undergo a systemic inflammatory response, including pathologic vasodilation, increased capillary leakage, and low albumin levels. Large-volume fluid and other drugs are often administered to maintain intravascular volume and improve cardiac output, especially at the early stage during and after ECPR [25, 26]. As mentioned above, liberal fluid resuscitation is actually not recommended in critically ill patients with sepsis. Thus, it is still unknown which fluid administration strategy is preferred in patients receiving ECPR.

In this study, excessive CFB from days 1-4 was found to be independently associated with ICU survival. To date, few studies have evaluated the impact of fluid balance in patients receiving ECPR. A study conducted by Staudacher admitted 195 patients on V-AECMO due to refractory cardiogenic shock and found no evidence to support a liberal fluid strategy [12]. Of note, 149 of recruited patients developed IHCA or OHCA, which implied that the study might have comprised several patients receiving ECPR. However, further subgroup analysis was not available.

In our center, as long as macrocirculation and microcirculation got improvement, "reversed fluid resuscitation" was always put on the agenda during the ECMO course. Therefore, except for the daily fluid balance of non-survivors at day 1, a negative net fluid balance was acquired at all other investigated points within 4 days of ECMO commencement. Moreover, the difference in CFB between the two groups became more statistically significant over time. In addition, the application of CRRT was more common in the non-survivor group, which we thought accounted for more fluid administration in the non-survivor group. Strict fluid control has several advantages, including effective preload reduction, decreased cardiac-wall stress, avoidance of fluid congestion and high hydrostatic pressure, tissue edema alleviation, and so on. Actually, the conception of "less is more" should be recommended by intensivists during the management of critically ill patients [27-29]. The core value of the conception is that physiological indexes and medical interventions matching the patient's current pathophysiological state are strongly suggested. In other words, overtreatment should be avoided. Taking fluid resuscitation for instance, as long as both macrocirculation and microcirculation perfusion are sufficient, restrictive fluid management should be considered. Furthermore, if permitted, "reversed fluid resuscitation" should also be taken into consideration, which implies that it is strongly recommended to initiate the phases of stabilization and de-escalation as early as possible [19, 30].

Limitations

Our study had some limitations. First, the definition of fluid inputs only included intravenous fluids, and enteral-nutritional-solution intake was not taken into account. On the other hand, fluid outputs included urine, adding the net fluid balance via CRRT. Drainage of serosal effusions was ignored. Second, all patients in our study had colloid fluid administration in conjunction with crystalloid fluid. Given the different effects of volume expansion between colloid and crystalloid fluids [31, 32], the same amount of fluid inputs with different crystal-colloid ratios may finally lead to different volume changes. Third, this was a single-center retrospective observational trial. In addition, we found that receiving CRRT were significantly correlated with increased survival to ICU discharge, but the 95% CIs for CRRT is large (OR: 14.617, 95% CI: 1.344 to 48.847, P=0.028). We think this may be related to the limited sample size in this study. Therefore, our findings cannot indicate causality. Further studies are warranted to confirm these findings.

Conclusion

We found a significant association between CFB during the first 4 days after ECMO treatment and survival to ICU discharge in this observational cohort study. Restrictive fluid administration may be an appropriate alternative for guiding the management of patients on ECPR.

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Disclosure of conflict of interest

None.

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