

# Comparison of Clinical Outcomes of Different Connection Modes of Extracorporeal Membrane Oxygenation Combine with Continuous Renal Replacement Therapy

Miaomiao Liu, MD,<sup>1</sup> Yang Yan, MD,<sup>1</sup> Gang Li, MD,<sup>2</sup> Ying Zhang, MD,<sup>1</sup> Fengwei Guo, MD<sup>1</sup>

<sup>1</sup>Department of Cardiovascular Surgery, Xi'an Jiaotong University Medical College First Affiliated Hospital, China; <sup>2</sup>Hanzhong 3201 Hospital, China

## ABSTRACT

**Objective:** To evaluate the effect of different connection modes of ECMO and CRRT on patients with acute kidney injury (AKI).

**Methods:** Twenty-one patients received ECMO with AKI. These patients were admitted to our center from December 2018 to February 2021, selected, and treated with both ECMO and CRRT. They were divided into A connection mode (pre-membrane-pre-pump connection) and B connection mode (post-membrane-post-pump connection). We compared clinical indicators and outcomes between two connection modes.

**Results:** There were eight cases (38.91%) in A connection mode and 13 cases (61.09%) in B connection mode, with median durations of ECMO assistance of 5 days and 7 days, respectively. Median flow rates of ECMO of 3.0 L/min and 2.5 L/min, respectively; CRRT flow rates of 200 mL/min and 180 mL/min, respectively. CRRT filter lifetime was over 48h in both connection modes. Except for NT-pro BNP, no significant differences in clinical indicators were observed between the two groups before or after the treatment ( $P > .05$ ).

**Conclusion:** Both connection modes could achieve the therapeutic purpose and need no higher level of anticoagulation for patients simultaneously treated with ECMO and CRRT. Two modes had no impact on treatment effect and clinical indicators in patients. It had no effect on length of ICU stay and prognostic.

## INTRODUCTION

In the last decade, extracorporeal membrane oxygenation (ECMO) technology has developed rapidly in the world and has been widely used in circulatory failure and/or respiratory failure [Hou 2020; Li 2019]. In adults undergoing ECMO,

the mortalities of acute kidney injury (AKI) are 78% and non-AKI patients only 20% [Lin 2006]. Continuous renal replacement therapy (CRRT) is used in combination with ECMO for fluid management and simultaneously eliminated inflammatory substances and metabolites. To date, the method of CRRT and ECMO simultaneous application has been approved by most ECMO centers [Askenazi 2012]. However, the safest and most effective approach for connecting ECMO and CRRT has not been determined. When the CRRT circuit is connected to ECMO, its circuit pressure is non-physiological under the high flow of ECMO. Thus, the inlet and outlet pressures of CRRT often deviate from the safe range, causing pressure alarms in CRRT and affecting the treatment effect [Askenazi 2012; Chen 2014]. Nevertheless, studies have reported different connection modes, using different standards and resulting in different conclusions [Seczyka 2014; Ricci 2010].

This study objective was to evaluate whether different connection modes of ECMO and CRRT have the impact on treatment effect or clinical indicators, such as blood routine examination, kidney functions and liver functions, and explore approaches to safely and effectively connect ECMO and CRRT equipment.

## MATERIALS AND METHODS

### Connection methods

There are many modalities to combine ECMO and CRRT, such as the separate vascular access of ECMO and CRRT, in-line connection of the hemodiafilter to the ECMO circuit, and connecting CRRT to ECMO in parallel circuit [Marlies 2018]. Among these, connecting ECMO and CRRT in parallel is the most common in clinical treatment. However, the use of different parallel modes of ECMO and CRRT may cause different problems. Further exploration of their impacts on treatment effect is necessary.

### Classification and discharge criteria

A total of 21 patients received ECMO with AKI who all had been treated with ECMO and CRRT and who were admitted to our center from December 2018 to February 2021. The appropriate type of ECMO cannula was determined, according to each patient's condition. ECMO machine, tubes, and

Received October 7, 2021; accepted October 14, 2021.

Correspondence: Yang Yan, MD, Department of Cardiovascular Surgery, Xi'an Jiaotong University Medical College First Affiliated Hospital, 277 West Yanta Road, Xi'an, Shaanxi, P.R.China; +86(029)85323869 (e-mail: [yanyang001001@163.com](mailto:yanyang001001@163.com)).

Table 1. General information on 21 patients with ECMO and CRRT

No.	Age (y)	Sex	Primary disease	ECMO mode	ECMO duration (d)	Connection mode with CRRT	Connection duration with CRRT (d)	Outcome	Cause of death
1	59	M	AMI	VAV	23	A	23	Death	Sepsis
2	70	M	AMI	VA	7	A	7	Death	Circulator v failure
3	47	M	AMI	VA	3	A	3	Death	Circulator v failure
4	66	M	Severe pneumonia	VV	44	A	2	Improved	
5	66	M	Fulminant myocarditis	VA	3	A	3	Death	Circulator v failure
6	36	M	AMI	VA	10	A	10	Improved	
7	52	M	heart failure	VA	2	A	2	Death	Circulator v failure
8	74	M	AMI	VA	2	A	2	Death	Circulator v failure
9	71	F	AMI	VA	6	B	6	Death	Circulator v respirator v failure
10	66	M	AMI	VA	7	B	7	Improved	
11	65	M	AMI	VA	3	B	3	Death	Circulator v failure
12	35	M	respiratory failure	VV	4	B	4	Improved	
13	37	F	Fulminant myocarditis	VA	2	B	0.3	Death	Circulator v failure
14	57	M	Severe pneumonia	VAV	8	B	8	Death	Circulator v respirator v failure
15	37	M	heart failure	VA	14	B	10	Improved	
16	40	M	respiratory failure	VV	9	B	9	Improved	
17	71	F	AMI	VA	7	B	7	Death	Circulator v failure
18	63	M	AMI	VA	4	B	4	Death	Malignant arrhythmia
19	63	F	AMI	VA	12	B	13	Death	Hematencephalon
20	40	M	Fulminant myocarditis	VA	7	B	7	Improved	
21	29	F	Fulminant myocarditis	VA	7	B	7	Improved	

M, male; F, female; AMI, acute myocardial infarction; VA, veno-arterial mode; VV, veno-veno mode; VAV, veno-arterial-veno mode

membrane oxygenators were purchased from Maquet GmbH (Rastatt, Germany). CRRT machines were purchased from Baxter International (Deerfield, IL, USA) with ST-100 hemo-filter and tubing. For each patient, we assembled the tube branches of these two machines into one of two parallel connection modes: pre-membrane oxygenator–pre-centrifugal pump or post-membrane oxygenator–post centrifugal pump. The 21 patients were divided into A connection mode (pre-membrane–pre-pump connection) and B connection mode (post-membrane–post-pump connection).

#### **The diagnostic criteria for AKI were in accordance with the Kidney Disease**

Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [Kellum 2013]. This means the patient's serum creatinine level had increased  $\geq 26.5 \mu\text{mol/L}$  within 48 hours, and it had been confirmed or inferred that the creatinine value increased to  $\geq 1.5$  times the baseline value within the past 7 days, or the patient's urine output was  $< 0.5 \text{ ml/kg/h}$  for 6 consecutive hours.

#### **Data collection**

This was a retrospective study. We collected patient demographic information, the ECMO and CRRT parameters, results from blood routine examination, kidney functions, liver functions, and biological indicators for infection. In addition, the ECMO assistance parameters, CRRT conditions parameters, total fluid balance, homeostasis times, infection conditions, length of ICU stay, and outcomes of the two groups of patients were compared to analyze the possible impact of the two modes on the patients.

#### **Statistical analysis**

In this study, variables distributed normally were presented as mean  $\pm$  standard deviation, and the difference between groups were compared with T test. Variables distributed non-normally were presented as median (interquartile range, IQR), and Wilcoxon rank-sum test was used to analyze the differences between the groups. Categorical variables were summarized by frequency and proportion and tested by Fisher's exact test.  $P < .05$  was considered statistically significant in this study.

Table 2. Compare of the two connection modes on clinical data

Data	A	B	t/Z	P/P of Fisher's exact test
Sex	M	8 (100)	8 (66.67)	.1107
	F	0 (0)	5 (33.33)	
Age ( $\chi \pm s$ )	58.75 $\pm$ 12.90	53.25 $\pm$ 15.38	0.83	.4158
ECMO assistance (d) (M (IQR))	5 (14)	7 (4)	-0.2559	.7980
ECMO flow (L/min) (M (IQR))	3.0 (0.75)	2.5 (0.80)	1.2520	.2106
ECMO+CRRT time (d) (M (IQR))	5 (33)	7 (3)	-0.5472	.5838
CRRT flow (mL/min) (M (IQR))	200 (35)	180 (50)	0.7961	.4260
CRRT filter lifetime	55 (42)	58 (48)	0.0755	.9398
Total fluid balance	Positive	5 (62.50)	5 (33.33)	.3870
	Negative	3 (37.50)	8 (66.67)	
Homeostasis time (h) ( $\chi \pm s$ )	46.286 $\pm$ 28.082	49.667 $\pm$ 25.036	0.28	.7833
Length of ICU stay (d) (M (IQR))	8 (13.5)	12 (9)	-0.6192	.5358
Prognosis	Improvement	2	6	.3999
	Death	6	7	

## RESULTS

### General information

Among the 21 patients treated with ECMO and CRRT in our center, there were 16 males (76.19%) and five females (23.81%), age 29–74 years old, with primary diseases of acute myocardial infarction (11 cases, 52.38%) and fulminant myocarditis (four cases, 19.05%), including eight cases (38.91%) with CRRT connected through pre-membrane–pre-pump connection in A connection mode and 13 cases (61.09%) with CRRT connected through post-membrane–post-pump connection in B connection mode (Table 1).

### Comparison of the connection parameters

The median duration of ECMO assistance in A connection mode and B connection mode was 5 days and 7 days, respectively. The CRRT flow rates of A connection mode and B connection mode were 200 mL/min and 180 mL/min, respectively. The connection mode in A connection mode was prone to extremely negative CRRT pressure alarms, and the connection mode in B connection mode was prone to extremely positive CRRT pressure alarms. The median length of ICU stay for A connection mode and B connection mode was eight and 12 days, respectively. There were no significant differences found between the collected clinical data of the two groups, despite differences in the parameters of the two connection modes ( $P > .05$ ) (Table 2).

### Comparison of clinical test indices of different connection modes

By comparing the changes in related indicators before and after treatment between the two groups of patients, we observed a significant difference in the changes in N-terminal NT-pro BNP levels before and after treatment. The change

in A connection mode was  $6553.57 \pm 10779.62$  ng/L, and the change in B connection mode was  $-7168.96 \pm 14611.01$  ng/L ( $t = 2.13$ ,  $P = .0487$ ). However, no significant differences in other indicators were found between the two connection modes before and after treatment ( $P > .05$ ) (Table 3).

## DISCUSSION

ECMO-assisted patients often suffer from acute and critical illness, with an extremely high incidence of AKI that often requires concomitant CRRT. While ECMO assists circulatory and respiratory, CRRT performs fluid management, eliminates inflammatory mediators and metabolites, corrects internal environmental disorders [Fleming 2012], and possibly improves patient prognosis [Shum 2014]. The combination of ECMO and CRRT has been approved by various ECMO centers [Cao 2017].

Multiple connection methods are available for the combined use of ECMO and CRRT. Each can be used separately, but ECMO often requires systemic heparinization and prolonged clotting time to prevent thrombosis in the circuit. Under this circumstance, the invasive surgery for CRRT circuit placement may increase the risk of bleeding and infection and increase cost [Rubin 2010]. Further, the additional placement of CRRT circuit may also require deeper sedation or protective restraints on patients due to the reduction of CRRT alarms and the maintenance of longer filter usage, which may increase patient discomfort and complications [Seczyka 2014]. Therefore, most centers use CRRT in parallel with ECMO to achieve simultaneous application. This study showed that CRRT can safely and effectively be connected to the ECMO circuit in our two modes. Thirteen of the 20 patients achieved total fluid balance

Table 3. Comparison of the two connection modes on clinical data ( $x \pm s$ )

Data	A	B	t/Z	P/P Fisher's exact test
Cr $\chi \pm s$	21.875 $\pm$ 51.842	3.462 $\pm$ 90.781	0.52	.6086
BUN (M (IQR))	0.63 (6.52)	2.49 (8.86)	-0.3259	.7445
GFR $\pm s$	-4.45 $\pm$ 12.410	4.527 $\pm$ 34.242	-0.80	.4376
NT-pro BNP ( $\chi \pm s$ )	6553.57 $\pm$ 10779.62	-7168.96 $\pm$ 14611.01	2.13	.0487
Hb (M (IQR))	-11.0 (57.5)	3.0 (22.0)	-1.0511	.2932
PLT ( $\chi \pm s$ )	-71.0 $\pm$ 63.0465	-79.7692 $\pm$ 120.8795	0.19	.8523
WBC (M (IQR))	4.21 (11.54)	-6.285 (22.990)	1.4466	.1480
CRP (M (IQR))	39.70 (153.40)	-17.20 (113.80)	0.000	1
PCT (M (IQR))	0.37 (14.117)	-2.12 (12.057)	1.5045	.1325
Infection	Positive	2 (25.00)	4 (30.77)	1
	Negative	6 (75.00)	9 (69.23)	
PO <sub>2</sub> /FiO <sub>2</sub> ( $\chi \pm s$ )	-22.3362 $\pm$ 144.2038	41.6583 $\pm$ 148.3209	-0.96	.3520
Lactic ( $\chi \pm s$ )	-2.125 $\pm$ 1.8373	-2.55 $\pm$ 1.1150	0.40	.7062
AST (M (IQR))	116.0 (3731.0)	-147.0 (686.0)	1.7743	.0760
ALT (M (IQR))	10.5 (2152.0)	-28.0 (801.0)	0.9777	.3282
TBIL (M (IQR))	31.40 (60.30)	3.50 (45.5)	1.8467	.0648
Albumin ( $\chi \pm s$ )	2.3625 $\pm$ 7.0795	7.1923 $\pm$ 9.6456	-1.22	.2363

Normal ranges: Cr, 41-73  $\mu$ mol/L; BUN, 2.6-7.5 mmol/L; GFR, >90 mL/min; NT pro-BNP, 1-125 ng/L; ALT, 9-50 U/L; AST, 15-40 U/L; TBIL, 3.4-17.1  $\mu$ mol/L; PO<sub>2</sub>/FiO<sub>2</sub>, 400-500 mmHg; Lactic, 0.5-2.0 mmol/L; Hb, 130-175 g/L; WBC, 3.5-9.5  $\times 10^9$ /L; PLT, 125-350  $\times 10^9$ /L; CRP, 0-10 mg/L; PCT,  $\leq 0.5$  ng/mL; Albumin, 40-55 g/L

or even negative balance with the aid of CRRT, resulting in the elimination of inflammatory metabolites and correction of the internal environment disorders. However, seven patients were critically ill with underlying diseases causing severely unstable circulation and respiratory conditions, which affected their treatment effect.

The various ECMO-CRRT connection methods have their advantages and disadvantages currently in use. In this study, we know that the A connection mode was prone to extreme negative pressure CRRT alarms, while the B connection mode was prone to extremely positive pressure CRRT alarms may cause of the direction of blood flow. When CRRT connect in ECMO circuit, the usage flow rate for ECMO is 2-5 L/min, which is 10 times than the usual blood flow rate for CRRT (commonly 0.15-0.2 L/min). Causing pressure alarms CRRT circuit to bear a larger pressure to cause the machine to stop and frequent stops reduced the treatment effectiveness and required circuit replacement due to blood clotting. The reduction of CRRT alarms and prevention of blood clotting in the filter is a particular challenge. By contrast, there was no significant differences in ECMO duration or flow, CRRT duration or flow and CRRT filter lifetime were found between the two connections. Both A and B connection could get the suggestion of KDIGO to keep the filtration fraction nearly 25% and the flow 35 ml/kg/h [Jörres 2013]. CRRT filter lifetime was over 48h in the two

connection modes that systemic anticoagulation by heparin with ECMO met requirement of CRRT without adding more anticoagulants. The combination of ECMO and CRRT do not need a higher level of anticoagulation.

There have been many debates on the application timing and effects of ECMO combined with CRRT. Research has shown that CRRT effectively eliminates inflammatory mediators and metabolites and maintains the homeostasis of the internal environment with ECMO, providing circulatory and respiratory support [Cao 2017]. All 21 patients in this study reached homeostasis and improvement in liver functions, kidney functions, routine bloodwork, and infectious indicators, but there was no statistical difference. Thus, the connection modes had no alteration in treatment effect. Most reached a state of total fluid balance or even a negative balance, but their length of ICU stay was largely the same, showing no significant difference and prognostic alteration between the connection modes. It is consistent with the research by Antonucci [Antonucci 2013]. In addition, the two modes showed statistically significant differences in NT-pro BNP. It may be that the post-membrane-post-pump connection mode allows blood to pass through the membrane oxygenator of ECMO twice, which increases the elimination. Whether this finding is clinically meaningful requires further study.

This study showed that the connection modes of CRRT and ECMO in patients had no statistical difference in

clinical data, but both modes could achieve the therapeutic purpose and did not need a higher level of anticoagulation. The connection modes had no effect on length of ICU stay and prognostic.

However, a limitation of this study is that the sample size may cause degrees of bias for further exploration of relevant research directions.

## REFERENCES

- Antonucci E, Lamanna I, Fagnoul D, Vincent JL, Backer DD, and Taccone FS. 2013. The impact of renal failure and renal replacement therapy on outcome during extracorporeal membrane oxygenation therapy. *J. Artif Organs* 40, 746-754.
- Askenazi DJ, Selewski DT, Paden ML, Cooper DS, Bridges BC, Zappitelli M, and Fleming GM. 2012. Renal replacement therapy in critically ill patients receiving extracorporeal membrane oxygenation. *J. Clin J Am Soc Nephrol* 7, 1328-1336.
- Cao Y, Chai YF, Chen YG, and Emergency Clinical Application of Blood Purification Guideline Work Group. 2017. Expert consensus on clinical application of blood purification in China. *J. Chinese Journal of Emergency Medicine* 26, 24-36.
- Chen H, Yu RG, Yin NN, and Zhou JX. 2014. Combination of extracorporeal membrane oxygenation and continuous renal replacement therapy in critically ill patients: a systematic review. *J. Crit Care* 18, 675.
- Fleming GM, Askenazi DJ, Bridges BC, Cooper DS, Paden ML, Selewski DT, and Zappitelli M. 2012. A multicenter international survey of renal supportive therapy during ECMO: The Kidney Intervention During Extracorporeal Membrane Oxygenation (KIDMO) Group. *J. ASAIO J* 58, 407-414.
- Hou XT. 2020. No ruly practice, no satisfied outcomes: final countdown for launching standardization of extracorporeal membrane oxygenation in China. *J. Natl Med J China* 25, 481-483.
- Li CL, Hou XT, Hei FL, Qiu HB, Li A, Tong ZH, Li YM, Sun RQ, Liu B, and Jiang Y. 2019. China statistics of extracorporeal life support in 2018. *J. National Medical Journal of China* 99, 1911-1915.
- Lin CY, Chen YC, Tsai FC, Tian YC, Jenq CC, Fang JT, and Yang CW. 2006. RIFLE classification is predictive of short-term prognosis in critically ill patients with acute renal failure supported by extracorporeal membrane oxygenation. *J. Nephrol Dial Transplant* 21, 2867-2873.
- Jörres A, John S, Lewington A, Wee PM, Vanholder R, Biesen WV, Tattersall J, and ad-hoc working group of ERBP. 2013. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines on Acute Kidney Injury: part 2: renal replacement therapy. *J. Nephrol Dial Transplant* 28, 2940-2945.
- Kellum JA, Lameire N, and KDIGO AKI Guideline Work Group. 2013. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *J. Crit Care* 17, 204.
- Marlies O, Michael CJ, and Kianoush K. 2018. Continuous renal replacement therapy during extracorporeal membrane oxygenation: why, when and how? *J. Curr Opin Crit Care* 24, 493-503.
- Ricci Z, Ronco C, and Picardo S. 2010. CRRT in series with extracorporeal membrane oxygenation in pediatric patients. *J. Kidney Int* 77, 469-470.
- Rubin S, Poncet A, Wynckel A, and Baehrel B. 2010. How to perform a haemodialysis using the arterial and venous lines of an extracorporeal life support. *J. Eur J Cardiothorac Surg* 37, 967-968.
- Seczyka B, Krikowski W, Nowak I, Jankowski M, Szułdrzyński K, and Szczeklik W. 2014. Continuous renal replacement therapy during extracorporeal membrane oxygenation in patients treated in medical intensive care unit: technical considerations. *J. The Apher Dial* 18, 523-534.
- Shum H, Kwan AM, Chan KC, and Yan WW. 2014. The use of regional citrate anticoagulation continuous venous hemofiltration in extracorporeal membrane oxygenation. *J. ASAIO J* 60, 413-418.