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Article

Veno-Arterial Extracorporeal Membrane Oxygenation for Postcardiotomy Refractory Hemorrhage in Children

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Abstract

Background: Refractory hemorrhage is generally considered a relative contraindication to the application of veno-arterial extracorporeal membrane oxygenation (VA-ECMO). Previous reports have presented the use of ECMO in the presence of various hemorrhages. **Methods**: Our clinical experience involves six pediatric patients supported with ECMO for postcardiotomy refractory hemorrhage. **Results**: All patients were weaned from ECMO successfully. Only one patient died of protein-losing enteropathy two months after ECMO weaning. The ECMO duration ranged from 32 to 134 hours. **Conclusion**: In our experience, ECMO could be used for postcardiotomy refractory hemorrhage. The timing of ECMO implantation, anticoagulation regimen and auxiliary measures are the keys to successful treatment.

Keywords

extracorporeal membrane oxygenation; refractory hemorrhage; postcardiotomy; pediatric

Introduction

Refractory hemorrhage is one of the most severe postcardiotomy complications in children with congenital heart disease (CHD), especially in redo-cardiac surgeries [1]. Conventional hemostasis measures cannot control refractory bleeding at surgical sites, with many blood products and fluids available to maintain circulatory stability. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is an effective device for circulatory and respiratory support in critically ill patients. The existence of refractory hemorrhage is generally considered a relative contraindication to ECMO [2]. ECMO requires anticoagulation to prevent thrombosis, but it can worsen bleeding. There have been encouraging reports of successful ECMO applied for intracranial hemorrhage, traumatic bleeding, and pulmonary hemorrhage [3–6].

We report on six pediatric patients who experienced refractory hemorrhage after cardiac surgery. We present the following article in accordance with the CARE checklist (**Supplementary material**). We used VA-ECMO as a rescue therapy for these patients and have summarized our experience.

Materials & Methods

This study presents six patients who were supported with VA-ECMO for postcardiotomy refractory surgical site hemorrhage from 2012 to 2022. Our institutional review board approved the study with a waiver of informed consent due to its retrospective nature.

Each ECMO system was implanted following failed attempts to wean the patient off cardiopulmonary bypass (CPB), as the surgical sites continued to bleed intractably after the surgical procedure was complete. Hemodynamics fluctuated obviously when trying to wean from CPB, even when we performed complete surgical hemostasis after satisfactory correction of cardiac malformation. Given that sufficient protamine was used to neutralize heparin, massive blood products were transfused, and hemostatic drugs were used in combination with other strategies. Finally, the gauze packing technique was utilized with delayed chest closure while the transition from CPB to VA-ECMO was performed in the operating room.

ECMO was performed according to the institutional protocol [7–9]. All patients were cannulated through the right atrium and ascending aorta at the original surgical incision. ECMO system selection was as follows: if the patient's weight was >30 kg, the Quadrox PLS® ECMO system was applied (MAQUET Cardiovascular, Hirrlingen, Germany; Sorin, Italy); if the patient's weight was <30 kg, a combination ECMO system was applied, which consisted of a centrifugal pump (Jostra; Maquet Inc., Rastatt, Germany), an oxygenator (Hilite 2400LTTM, Medos Medizintechnik AG, Stolberg, Germany) and a heparin coating circuit (Xijian Medical, Xi'an, China). The centrifugal pump flow was set appropriately to maintain hemodynamic stability. After ECMO implantation, the point-of-care (POC) activated clotting time (ACT) (Hemochron®, Barcelona,

Table 1. Demographic data, surgeries, complications and outcomes.

Patients #	Sex	Age (m)	Weight (kg)	Main diagnosis	Main procedure	Redo-cardiac surgery	CPB time (min)	Site of hemor-rhage	Clamp time (min)	ECMO duration (h)	Survival	Complication
1	Female	36.6	15.0	TGA	Arterial switch procedure	No	408	surgical sites	209	88	Yes	None
2	Male	1.7	3.4	CoA, HAA	Aortic arch repair	No	359	surgical sites	109	95	Yes	AKI, Circuit-related thrombosis
3	Male	110.2	24.0	AS, PS	Bentall + Konno procedure	Yes	450	surgical sites	180	107	Yes	Hemolysis, Hyperbiliru-binemia, AKI
4	Female	151.9	37.0	DORV, VSD	Rastelli procedure	Yes	471	surgical sites	195	134	No	Hemolysis, Hyperbiliru-binemia, AKI
5	Male	58.4	20.0	SV	Fonton procedure	Yes	901	surgical sites	234	128	Yes	AKI
6	Male	108.0	24.5	TGA, ASD, VSD, TCPC	Takedown procedure (DRT, SVC and IVC-RA, TVP, PVP)	Yes	682	surgical sites	386	32	Yes	Circuit-related thrombosis

Notes: CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; TGA, transposition of great arteries; CoA, aortic coarctation; HAA, hypoplastic aortic arch; AS, aortic stenosis; PS, pulmonary stenosis; DORV, double outlet right ventricle; VSD, ventricular septal defect; SV, single ventricle; AKI, acute kidney injury; DRT, double root transposition; SVC, superior vena cava; IVC, inferior vena cava; RA, right atrium; TVP, tricuspid valve plasty; PVP, pulmonary valvuloplasty; ASD, atrial septal defect; TCPC, total cavopulmonary connection.

Spain) and activated partial thromboplastin time (aPTT) were measured every 3 hours. The laboratory (LAB) aPTT, hemoglobin concentration, and platelet count were measured twice a day. Systemic heparinization was delayed appropriately according to lower coagulation parameters: an aPTT of 50–70 s and an ACT of 140–180 s. The dose of heparin was adjusted on the basis of the chest-tube drainage, ACT and aPTT values. Once the patient's condition had stabilized and chest-tube drainage had significantly reduced to below 2 mL/kg/h, a small dose of heparin (2–10 U/kg/h) was administered and the concentration was gradually increased.

In addition to a strict anticoagulation regimen, we also take various auxiliary measures to reduce hemorrhage and improve coagulation function: (1) filling the pericardial cavity with gauze for hemostasis by compression; (2) continuous bedside autologous blood reinfusion, which reduces allogeneic blood transfusion and prevents hemolysis; and (3) blood product transfusion for supplementing blood components was based on clinician bedside judgment without a protocolized approach; and (4) multiple hemostatics.

We paid attention to thrombosis in the ECMO system, recorded the pump flow and patient blood gas every 3 hours, checked the circuit and oxygenator every 12 hours, and measured transmembrane pressure and plasma-free hemoglobin daily.

Hemolysis, vasoactive-inotropic score (VIS), acute kidney injury (AKI) and hyperbilirubinemia were classified as previously described [7].

Results

The study includes 4 males and 2 females, aged 1.7 to 151.9 months (median age 83.2 months) and weighing 3.4 to 37.0 kg (median weight 22.0 kg) (Table 1). ECMO duration varied from 32 to 134 h (median duration 101 h). Patients #3 and #4 experienced hemolysis, hyperbilirubinemia, and AKI; patient #5 received peritoneal dialysis due to AKI. Circuit-related thrombosis was found in patients #2 and #6. All patients were successfully weaned from ECMO. We followed up all patients for six months. Patient #4 had preoperative losing enteropathy and died from it two months later, and the remaining 5 patients have survived without any late complications.

Patients' clinical characteristics at ECMO implantation are summerizd in Table 2. When ECMO was established, the left ventricular ejection fraction (LVEF) of all patients was greater than 20%, and two patients having LVEF of 60%; the mean arterial pressure (MAP) was within normal limits. Lactate levels were slightly elevated, with only two patients having lactate values above 7 mmol/L. VIS w-

Table 2. Patients' clinical characteristics at ECMO implantation.

Patients #	LVEF (%)	Lactate (mmol/L)	VIS	MAP	Hb (g/L)	PLT counts (×10^9/L)	RBC transfusion (U)	Plasma transfusion (mL)	PLT transfusion (U)	Hemostatics	
1	60	4.3	40	36	114	31	8	1000	1	Protamine, human fibrinogen, prothrombin complex	/
2	30	6.9	10	38	71	39	3	400	1		
3	60	8.9	45	47	111	69	12	1300	1		
4	26	2.8	42	52	75	110	9	1000	1		
5	45	6.9	22	38	72	33	4	1000	1		
6	45	10.9	25	44	116	56	11	900	2		rFVIIa

Notes: LVEF, left ventricular ejection fraction; VIS, vasoactive-inotropic score; MAP, mean arterial pressure; Hb, hemoglobin concentration; PLT, platelet; RBC, red blood cell; rFVIIa, recombinant human coagulation factor VIIa.

Table 3. Patients' clinical characteristics during ECMO.

Patients #	UFH Start (h)	UFH dose [U/(kg/h)]	POC ACT (s)	LAB aPTT (s)	Hb (g/L)	PLT counts (×10^9/L)	RBC trans-fusion (U)	Plasma transfu-sion (mL)	PLT trans-fusion (U)	Chest-tube (d)	Chest-tube drainage (mL/kg/d)	MAX pump speed (rpm)	MAX flow rate (mL/min)	MAX SCr (μmol/L)	MAX TBil (μmol/L)	MAX pFHb (mg/dL)
1	20	12 (0, 16)	166 (159, 181)	64.8 (61.4, 68.7)	99 (95, 111)	59 (31, 84)	9	500	2	4	121.0	2795	1250	58.4	28.0	20
2	15	4 (2, 10)	162 (156, 184)	58.9 (54.9, 63.4)	106 (79, 114)	45 (39, 92)	4.5	300	1	11	129.1	2560	400	46.6	23.2	30
3	11	10 (8, 16)	155 (141, 175)	60.4 (52.4, 69.4)	99 (92, 111)	61 (22, 78)	12	1800	1	11	128.7	2880	1270	113.9	65.5	50
4	28	7 (2, 16)	153 (163, 172)	57.0 (50.4, 65.8)	98 (90, 113)	96 (86, 109)	12	900	0	7	40.7	2965	2170	105.2	180.7	50
5	34	12 (4, 14)	158 (146, 178)	59.7 (55.0, 67.9)	95 (92, 110)	65 (33, 70)	14	2100	3	6	348.9	3600	1800	184.5	20.9	20
6	0	0	203 (170, 300)	64.3 (56.4, 88.5)	127 (122, 129)	59 (54, 88)	18	1200	3	6	88.8	2890	1400	52.5	25.6	30

Notes: Continuous data are presented as medians (interquartile ranges). UFH, unfractionated heparin; POC, point-of-care; ACT, activated clotting time; LAB, laboratory; aPTT, activated partial thromboplastin time; Hb, hemoglobin concentration; PLT, platelet; RBC, red blood cell; MAX, maximum; SCr, serum creatinine; TBil, total bilirubin; pFHb, plasma-free hemoglobin.

-as between 10 and 45 (median value 32.5). Even all patients had received a large amount of blood products and hemostatic drugs to maintain circulation and reduce bleeding, hemoglobin and platelet counts were significantly lower than normal levels. The parameters of anticoagulation regimens, coagulation, ECMO pump, and laboratory are presented in Table 3. Heparin was initially given 15–34 h (median time 28 h) after ECMO implantation. The ECMO system of patient #6 ran for 32 hours without anticoagulation.

Discussion

With the development of surgical techniques, patients with complex CHD could receive multiple-stage cardiac surgeries at a very young age. Postcardiotomy hemorrhage is common, but refractory hemorrhage is especially troublesome which affects circulatory stability. In cases where routine hemostasis is ineffective, the final method involves filling the pericardial cavity with a large amount of gauze to compress hemostasis; however, this could affect venous return and heart contraction. CPB cannot be weaned off, due to continuous massive bleeding from surgical wounds. Severe hemorrhage is generally considered a relative contraindication to ECMO. However, if life-threatening circulatory failure caused by postcardiotomy refractory hemorrhage does not respond to conventional treatments, ECMO support may be the only method for rescue. Timely initiation of ECMO is key to achieving good prognosis. All patients showed no significant decrease in cardiac function. The blood pressure maintained at normal levels without excessive vasoactive drug dosage and lactate levels did not meet the criteria for cardiogenic shock at ECMO implantation [2]. ECMO is a temporary mechanical circulatory support that provides patients with recovery time and ensures systemic perfusion and oxygenation for further treatment measures.

The severe surgical site hemorrhage in these 6 patients was caused mainly by the following issues. (1) Surgery-related factors. Patients #3, #4, #5 and #6 received ECMO support after their second cardiac surgery. Therefore, adhesion formation at the surgical site due to previous cardiac surgery made the procedure more difficult, and the wound surface increased. (2) Cardiopulmonary bypass (CPB)-related factors. Prolonged CPB time and hypothermia led to blood dilution, platelet rupture, coagulation factor production and fibrinogen consumption. All patients underwent a second bypass run due to severe hemorrhage and unstable hemodynamics. Patient #5 even underwent CPB 4 times, which further exacerbated coagulopathy and resulted in a vicious cycle. (3) Patient-related factors. CHD children have developmental hemostasis, which makes them more prone to bleeding [10].

The timing of anticoagulation is critical for patient prognosis. After ECMO implantation, the anticoagulation regimen needs to be carefully considered to reduce circuit-related thrombosis without increasing hemorrhage as much as possible. Because of the experience of long-term CPB, the coagulation function was too low to receive a heparin bolus during ECMO implantation. Therefore, we delayed the administration of heparin during initiation period. There is no consensus on the anticoagulation regimen of pediatric VA-ECMO [11]. Although we performed a successful case of ECMO without anticoagulation, it does not appear to serve as evidence for the efficacy of non-anticoagulation protocols. There have been successful case reports of the use of ECMO support for severe hemorrhage. Vobruba *et al*. [4] reported that a neonate received VA-ECMO support after pulmonary hemorrhage. Because of the severe coagulopathy (aPTT >160 s) in the child, heparin was not given before cannulation. Then, coagulopathy was partly corrected the next day, and heparin was given for systemic anticoagulation. Hu *et al*. [12] reported a patient who received intravenous anticoagulation during ECMO for refractory hypoxemic respiratory failure due to diffuse alveolar hemorrhage. Ultimately, the patient survived with the successful use of anticoagulation during ECMO. Fu *et al*. [3] reported that an infant received VA-ECMO in the presence of intracranial hemorrhage. Heparin was utilized for systemic anticoagulation throughout the ECMO period without additional hemorrhage. Wang *et al*. [13] performed a systematic review of trauma patients with ECMO; 55 patients did not receive anticoagulation, but the survival rate was lower than that of patients who received anticoagulation.

Repessé *et al*. [14] noted that recombinant human coagulation factor VIIa (rFVIIa) can effectively reduce hemorrhage during ECMO support, but there is a risk of thrombosis and embolism, which remains to be discussed. Two patients received rFVIIa after sufficient surgical hemostasis and the correction of other coagulation substance abnormalities. The hemorrhage was subsequently stopped.

Hemolysis, AKI, and hyperbilirubinemia are common complications during ECMO. They are interrelated and mutually reinforcing. All patients experienced prolonged CPB with severe blood damage, which is a risk factor for hemolysis and AKI. Previous studies have shown that thrombosis during ECMO is associated with hemolysis, AKI, and hyperbilirubinemia [7,15]. In the early non-anticoagulation stage, we appropriately increase pump flow, closely monitor coagulation indicators, and start anticoagulation in a timely manner. Two patients were found to have small thrombi at oxygenator and junction of the circuit, but none needed to replace the system, which might benefit from technological advancements in ECMO, including the use of heparin-bonded circuits and membrane oxygenators, centrifugal pumps, and miniaturization of circuits.

We reported the largest group of postcardiotomy refractory hemorrhage patients treated with VA-ECMO sup-

port. Only one patient died from preoperative protein-losing enteropathy, while the rest of the patients have survived to date. The survival rate is encouraging. This provides an option for current cardiac surgery practice. For patients undergoing prolonged CPB with severe postcardiotomy refractory bleeding, timely initiation of ECMO and appropriate regimen management is a reliable choice. Further research is needed in the future to validate the findings for the use of VA-ECMO in other types of hemorrhage, and investigating the long-term impact of ECMO on pediatric patients' recovery and quality of life.

Limitations

The small sample size of six patients isn't enough for statistical analysis and the potential for selection bias limits the generalizability of the findings. Expanding the study to include more patients or conducting a multi-center study would provide more robust data.

Conclusion

In summary, postcardiotomy refractory hemorrhage is no longer a relative contraindication to ECMO. VA-ECMO could provide effective respiratory and circulatory support in such a case. Choosing the appropriate timing of ECMO implantation is critical. Moreover, a reasonable anticoagulation regimen and auxiliary measures could reduce hemorrhage and facilitate patient recovery.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

JinL, XD and YJ designed the research study. YJ performed the research. YJ, YC, ZF, HW, and JiaL analyzed the data. All authors read and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study is in compliance with the declaration of Helsinki. This study was approved by the Institutional Review Board of Fuwai Hospital. Approval Number: 2020-1346. Our institutional review board approved the study with a waiver of informed consent due to its retrospective nature.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.59958/hsf.7761.

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