Renal Replacement Therapy

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No predialysis treatment of blood primes in pediatric continuous kidney replacement therapy

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Abstract

Background Pediatric continuous kidney replacement therapy (CKRT) uses blood as the priming fluid in the CKRT circuit to prevent hemodilution and hypotension and is dialyzed using a dialysate before the start of CKRT. This study aimed to investigate the safety of CKRT using a protocol of no predialysis after blood priming in underweight infants, based on hemodynamic and laboratory data changes.

Methods This single-center retrospective cohort study included children weighing < 5 kg after cardiac surgery treated with CKRT from March 2019 to February 2022. Our protocol is as follows. We used 6-Fr vascular access, 20 mL priming volume of 0.3 m^2 cellulose triacetate membrane, 37 mL priming volume of the pediatric extracorporeal circuit, and 57 mL of total extracorporeal volume. Heparin saline was prefilled with the extracorporeal circuit, and then, 30 mL of packed red blood cells was used to prime. Subsequently, the therapy was started without predialysis treatment of blood primes and vasopressin was used as a vasopressor for hypotension. Hemodynamic and laboratory data changes were studied.

Results CKRT was performed in 8 patients, and 19 circuit connections were analyzed. Hypotension was observed in 10/19 (52.6%) connections, but all patients recovered within approximately 10 min. Ionized calcium, bicarbonate, and pH values were significantly decreased ($p = 0.001$, < 0.001, and < 0.001, respectively) before dialysis. However, 60 min after dialysis, pH recovered to predialysis levels and ionized calcium and bicarbonate recovered to > 95% of the levels before extracorporeal circulation. Moreover, potassium levels, which were not significantly different between extracorporeal circulation and dialysis initiation ($p = 1.000$), were significantly decreased after dialysis ($p = 0.046$). Lactate and hematocrit did not significantly change either before dialysis ($p = 0.131$ and 0.071, respectively) or after dialysis compared to the time of extracorporeal circulation ($p = 1.000$ and 0.591, respectively).

Conclusions CKRT, using our protocol, could be safely performed without predialysis treatment of blood primes in children weighing < 5 kg.

Keywords Infant, Continuous kidney replacement therapy, Blood prime, Priming volume, Hypotension

Background

Continuous kidney replacement therapy (CKRT) is a well-established therapy for a pediatric intensive care unit for the management of patients with severe acute kidney injury (AKI), which is the most common diagnosis

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in neonates and infants who receive CKRT following cardiac surgery [1].

Blood should be used as the priming fluid for CKRT in children weighing < 5 kg before starting therapy to prevent hemodilution and hypotension [2]. Blood bank blood contains nonphysiological electrolyte concentrations and acid–base equilibrium and must be pretreated to obtain physiological blood priming fluid [3]. Usually, the outflow and return tubes are connected by a three-way stopcock to form a closed-loop system, and the blood bank blood in the CKRT circuit is dialyzed or ultrafiltrated using dialysate before starting CKRT [3, 4]. At our institution, hemodialysis was previously performed using blood as the priming fluid. However, owing to the concerns that the negative pressure in the circuit over time would induce hemolysis as well as damage the hemofilter, CKRT has been performed for > 5 years based on a protocol that does not require predialysis treatment after blood priming. No adverse events were observed with CKRT using this protocol, but the hematology data were not immediately confirmed after treatment initiation.

This study investigated the safety of CKRT using a protocol of no predialysis after blood priming in underweight infants, based on hemodynamic and laboratory data changes.

Methods

The study was conducted at the Pediatric Intensive Care Unit of the Kanagawa Children's Medical Center (Yokohama) from March 2019 to February 2022. The Kanagawa Children's Medical Center Institutional Review Board approved this study with a waiver of consent (144-4).

This single-center retrospective cohort study included children (weight < 5 kg) with AKI after cardiac surgery treated with CKRT from March 2019 to February 2022. A high percentage of patients requiring CKRT and invariably requiring blood priming weighed < 5 kg and had undergone cardiac surgery with extracorporeal membranous oxygenation (ECMO) or pacemakers [1, 2], and it was difficult to assess vital signs during CKRT because of an increased impact on blood pressure and heart rate. The inclusion criteria were as follows: patients with AKI requiring CKRT, postoperative patients with congenital heart disease weighing less than 5 kg, and patients requiring blood priming. The exclusion criteria were as follows: patients receiving ECMO, those with a pacemaker, those with incomplete data, those weighing > 5 kg, and those who underwent procedures other than cardiac surgery.

Data regarding clinical characteristics were collected from the electronic medical records, including underlying disease, hemodynamic data (mean arterial pressure [MAP] and heart rate [HR]), available laboratory values (pH, potassium, ionized calcium, bicarbonate, lactate, and hematocrit), pediatric logistic organ dysfunction (PELOD) score [5], and vasopressor use (vasoactive inotropic score [VIS]) at CKRT filter change. VIS was calculated as follows: VIS = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min) + 10,000 × vasopressin dose (U/kg/min) + 100 × norepinephrine dose (μg/kg/min) [6]. Blood samples and hemodynamic data (invasive arterial blood pressure) were collected before the start of extracorporeal circulation (before EC), before the start of dialysis (before DIAL), and 60 min after the start of EC (after DIAL).

No predialysis treatment of blood primes protocol

Vascular access, using a 6-Fr flexible double-lumen catheter, was placed in the femoral or internal jugular vein. All CKRT were performed with TR-55X II (Toray Medical Co., Ltd., Tokyo, Japan) machines. Cellulose triacetate (CTA) membrane, UT-300S (surface area 0.3 m^2, Nipro Co., Ltd., Osaka, Japan), was used as the hemofilter. The total priming volume was approximately 57 mL (hemofilter of 20 mL and extracorporeal circuit volume of 37 mL).

The operation processes were as follows: heparin saline (1 U/mL) was prefilled with the extracorporeal circuit and hemofilter, and then, 30 mL of packed red blood cells was used to prime the circuit. CKRT parameters: initial blood flow rate (QB) was 10 mL/min and was increased to 20 mL/min. Only extracorporeal circulation was performed for the first approximately 10 min, and dialysis and filtration were initiated after obtaining blood samples. The initial dialysate flow rate (QD) was 200 mL/kg/h and was gradually decreased to 50 mL/kg/h within 48 h. The replacement flow rate (QS) was 20 mL/h. Sublood-BSG (FUSO Pharmaceutical Industries Ltd., Osaka, Japan) was used in dialysate and replacement fluid. The composition of Sublood-BSG was K^+ of 2.0 mEq/L, Ca^{2+} of 3.5 mEq/L, HCO_3^- of 35 mEq/L, and CH_3COO^- of 0.5 mEq/L. Nafamostat mesylate was administered as an anticoagulant at an initial dose of 0.5 mg/kg/h and adjusted to maintain an activated coagulation time of 180–200 s.

Most patients who required CKRT after cardiac surgery had hypotension. Vasopressin (0.02–0.1 U/kg/h) was administered as a vasopressor drug, with the target systolic blood pressure values of 60 and 70 mmHg in neonates and infants, respectively. A bolus dose of vasopressin (0.01–0.02 U/kg/dose) was administered after initiating EC in CKRT if systolic blood pressure decreased to > 20% from the start.

The perioperative hematocrit goal was 50%, and red blood cell transfusions were administered as needed before starting CKRT.

Estimation

The primary outcome was clinically significant hypotension, and secondary outcomes were changes in HR and laboratory findings before EC, before DIAL (approximately 10 min after starting EC), and after DIAL. Hypotension was defined as a > 20% decrease from the MAP before EC, meaning that intravenous vasopressin was required. A change in HR of ≥ 20% compared to before EC was considered a significant change. Data regarding vital signs (MAP and HR) and laboratory findings were expressed as a ratio to values before EC.

Statistical analysis

Continuous variables are expressed as medians and interquartile ranges (IQR, Q1–Q3). Statistical significance of categorical data was tested using Fisher's exact test with the validation of hemodynamic data and changes in laboratory findings. The Mann–Whitney *U* test was used for comparisons between two groups, and the Kruskal–Wallis test followed by post hoc Steel's test was used for comparisons among three groups. The results of the analysis were considered significant for p values of < 0.05. Statistical tests were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 43 patients underwent CKRT, and the characteristics of the connection to CKRT were studied in eight patients (4 males and females, respectively) with a mean weight of 2.4 (2.2–3.1) kg (Fig. 1). Overall, 19 circuit connections were analyzed. All patients developed hypotension; hence, vasopressin was started, and the dose of vasopressin was adjusted to maintain the target systolic blood pressure at the start of CKRT. Table 1 shows the demographic characteristics of study participants. All patients were on mechanical ventilation and were receiving vasopressors (VIS = 11 [8.3–19]) for hypotension; their PELOD scores were 20 (12–22) before EC. The mortality rate predicted using the PELOD score was 16.2%.

Primary outcomes

Figure 2 shows the evolution of hemodynamic parameters before EC, before DIAL, and after DIAL. Hypotension was observed in 10/19 (52.6%) connections within 5 min of the treatment, and no patient exhibited significant hypotension before DIAL. Of the 10 hypotension cases, 7 required a single dose of vasopressin, 2 required two doses, 1 required three doses, and only the last case required volume resuscitation.

Secondary outcomes

HR tended to decrease over time, but it did not significantly change by > 20% (Fig. 2). The assessment results of the variables are shown in Table 2. Ionized calcium, bicarbonate, and pH values were significantly decreased ($p = 0.001$, < 0.001, and < 0.001, respectively) before DIAL. After DIAL, ionized calcium and bicarbonate continued to exhibit significant decreases ($p = 0.016$ and < 0.001, respectively), but the pH improved ($p = 0.592$). Potassium levels were not increased before DIAL, but they were significantly decreased after DIAL ($p = 0.046$). Lactate and hematocrit levels did not significantly change

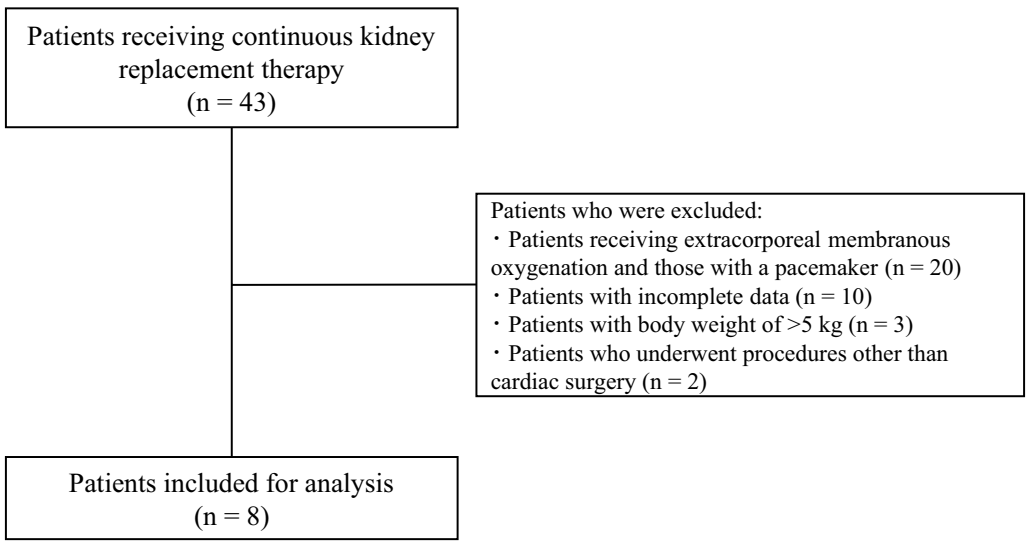

Fig. 1 Patient flow diagram

Table 1 Clinical details of patients

Case	1	2	3	4	5	6	7	8
Age	9 months	27 days	2 months	3 days	6 months	2 months	5 days	6 days
Sex	F	F	M	F	M	M	M	F
Weight (kg)	4.8	2.4	2.2	3.1	4.7	2.0	2.1	3.0
Underlying disease	TOF	TAPVC/PVO	TOF	HLHS	VSD	TOF	CoA/C	PA/IVS
VIS at admission	18.3	29.5	9.5	12.6	18	7	10	14.3
PELOD score at admission	22	30	12	21	20	12	20	22
PMR in terms of PELOD score	0.26	0.79	0.02	0.21	0.16	0.02	0.16	0.26
28-day outcome (the day of death)	Survival	Death (3)	Survival	Survival	Survival	Survival	Survival	Death (18)
90-day outcome	Survival	–	Survival	Survival	Survival	Survival	Survival	–

TOF, tetralogy of Fallot; TAPVC, total anomalous pulmonary venous connection; PVO, pulmonary venous obstruction; HLHS, hypoplastic left heart syndrome; VSD, ventricular septal defect; CoA/C, coarctation complex; PA, pulmonary atresia; IVS, intraventricular septum; VIS, vasoactive inotropic score; PMR, predicted mortality rate; PELOD, pediatric logistic organ dysfunction

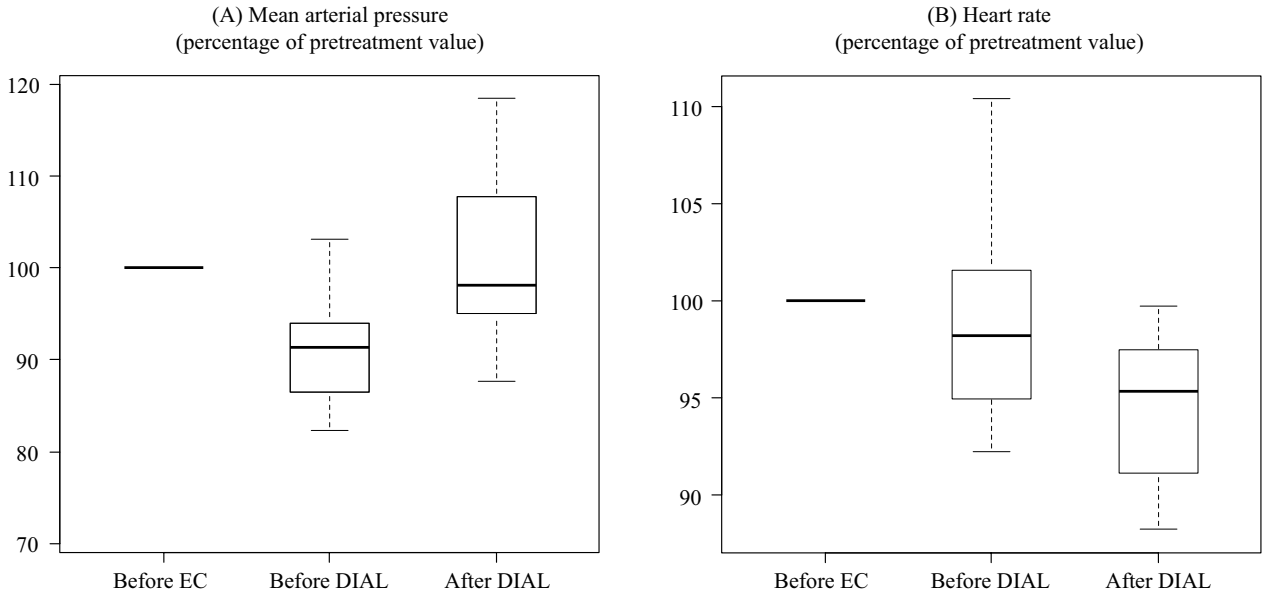

Fig. 2 Changes in hemodynamic parameters. Data are expressed as percentage values before EC. No patient exhibited significant hypotension before DIAL. Before EC, before the start of extracorporeal circulation; before DIAL, before the start of dialysis; after DIAL, 60 min after the start of extracorporeal circulation

Table 2 Changes in laboratory parameters in the overall cohort

Variable	Before EC	Before DIAL	*p*	After DIAL	*p*
pH	100	99.4 [99.2–99.8]	< 0.001	99.9 [99.4–101]	0.592
Potassium	100	100 [91.9–106]	1.000	97.4 [94.3–105]	0.046
Ionized calcium	100	90.6 [87.4–93.2]	0.001	96.3 [93.9–100]	0.016
Bicarbonate	100	87.2 [85.3–90.8]	< 0.001	95.9 [89.3–98.5]	< 0.001
Lactate	100	111 [95.7–122]	0.131	100 [88.5–112]	1.000
Hematocrit	100	96.4 [95.7–122]	0.071	101 [94.8–105]	0.591

Data are presented as median percentage [interquartile range] of the value before the start of extracorporeal circulation

Before EC, before the start of extracorporeal circulation; before DIAL, before the start of dialysis; after DIAL, 60 min after the start of extracorporeal circulation

p values are determined by the Kruskal–Wallis test followed by the post hoc Steel's test

either before ($p=0.131$ and 0.071, respectively) or after ($p=1.000$ and 0.591, respectively) DIAL.

Discussion

Overall, 19 CKRT sessions were performed on 8 children weighing < 5 kg, as well as postcardiac surgery without predialysis treatment of blood primes. Hypotension occurred in 52.6% of sessions, but a bolus dose of vasopressin, when the mean blood pressure dropped to > 20%, allowed blood pressure to recover by the start of CKRT (approximately 10 min later), and CKRT could be performed at all sessions. CKRT following our protocol could be safely performed in children weighing < 5 kg without dialyzing the priming blood.

Blood priming of the circuit is considered in smaller children due to the significant circuit volume to patient blood volume ratio [4]. Especially in infants weighing < 5 kg, 96.5% of circuits have been initiated with a blood prime [7]. The use of blood as a priming fluid for extracorporeal circulation can have detrimental consequences because blood derived from blood banks can be acidemic, hyperkalemic, and hypocalcemic [8]. The use of our protocol, in which only 30 mL or 50% of the priming volume was replaced with red blood cells, led to a significant decrease in pH, ionized calcium, and bicarbonate ($p<0.001$, 0.001, and < 0.001, respectively) values before DIAL; however, after DIAL, the pH recovered to pre-EC levels ($p=0.592$) and ionized calcium and bicarbonate levels recovered to > 95% of pre-EC levels ($p=0.016$ and < 0.001, respectively). There were no significant increases in lactate and potassium levels before DIAL ($p=0.131$ and 1.000, respectively), whereas there was a significant decrease in potassium levels after DIAL ($p=0.046$). Hematocrit levels decreased within 5% and did not demonstrate a significant change either before ($p=0.071$) or after ($p=0.591$) DIAL.

The patients were classified into two groups: those with ($n=10$) and without ($n=9$) hypotension, and the variables were compared between the two groups (Table 3). Only the PELOD score and VIS before DIAL were significantly different between the two groups ($p=0.020$ and 0.002, respectively), suggesting that hypotension at the start of CKRT in pediatric patients was more dependent on disease severity and vasopressor drug dosage than on electrolyte and acid–base abnormalities in the blood obtained from the blood bank. A study of hemodynamic changes during connection to CKRT in pediatric patients revealed hypotension in 53 of 174 patients (mean weight, 17.6 kg; mean PELOD score, 22.2) [9], 80 of 161 treatments in 36 patients (median weight, 9.95 kg; median PELOD score, 21) [10], and 9 of 16 patients (median weight, 7.6 kg; median PELOD score, 19.8) [11]; however, there was no significant difference in the probability of hypotension between the previous and present studies ($p=0.070$, 1.000, and 0.361, respectively). In the present study, the mean and median PELOD scores were 18.7 and 20, respectively, which were comparable to the previously reported PELOD scores, suggesting that the current study protocol did not increase the risk of hypotension.

Table 3 Changes in laboratory parameters of patients with or without hypotension

Variables	Time	Patients with hypotension ($n=10$)	Patients without hypotension ($n=9$)	*p*
pH	Before EC	7.39 [7.35–7.42]	7.40 [7.36–7.42]	0.713
	Before DIAL	7.37 [7.30–7.40]	7.34 [7.32–7.39]	1.000
Potassium	Before EC	3.65 [3.42–3.92]	3.50 [3.30–3.70]	0.566
	Before DIAL	3.50 [3.18–3.88]	3.50 [3.40–3.80]	0.741
Ionized calcium	Before EC	1.21 [1.12–1.34]	1.23 [1.20–1.27]	0.902
	Before DIAL	1.10 [1.02–1.19]	1.11 [1.08–1.17]	0.935
Bicarbonate	Before EC	24.0 [22.9–27.9]	23.5 [23.5–24.4]	0.623
	Before DIAL	21.1 [19.8–23.7]	20.7 [20.6–22.0]	0.806
Lactate	Before EC	2.35 [1.70–2.72]	1.60 [1.30–2.00]	0.205
	Before DIAL	2.50 [1.90–3.05]	2.00 [1.40–2.50]	0.219
Hematocrit	Before EC	49.9 [48.1–51.4]	46.9 [43.5–47.6]	0.086
	Before DIAL	46.3 [45.3–47.5]	45.9 [45.5–49.0]	0.967
Weight	Before EC	3.10 [2.40–4.30]	2.20 [2.20–3.00]	0.070
PELOD score	Before EC	22.0 [21.0–22.0]	12.0 [12.0–22.0]	0.020
VIS	Before EC	18.7 [13.0–24.3]	8.30 [7.00–10.3]	0.002

Data are presented as median percentage [interquartile range] of the value before the start of extracorporeal circulation

Before EC, before the start of extracorporeal circulation; before DIAL, before the start of dialysis; after DIAL, 60 min after the start of extracorporeal circulation; PELOD, pediatric logistic organ dysfunction; VIS, vasoactive inotropic score

p values are determined using the Mann–Whitney *U* test

Children are at a high risk of developing hypotension while receiving CKRT because of the high extracorporeal volume relative to total blood volume [10]. In the present study, there was no significant difference in the frequency of hypotension despite the lower weight of the patients compared with previous studies, suggesting that our protocol is feasible for clinical use.

Vasopressin was used as a vasopressor drug for hypotension, and it has recently been suggested to be useful as a perioperative vasopressor in congenital heart disease [12]. Vasopressin is considered a superior vasopressor agent for patients with congenital heart disease because of its minimal effect on pulmonary vascular resistance, and the present study revealed no findings of increased pulmonary vascular resistance such as elevated central venous pressure or decreased oxygenation after bolus administration of vasopressin (data not shown).

Brophy et al. [13] noted that the hypotension seen in children may be due to bradykinin production.

Bradykinin production is enhanced when in contact with low pH-packed red blood cells because polyacrylonitrile (AN-69) membrane is exquisitely pH sensitive, suggesting that the marked hypotension in children may be due to the unique property of AN-69 membrane. Sutherland et al. [14] revealed no severe hypotension in infants at the start of CKRT after changing from AN-69 filters to polyarylethersulfone membranes. Predialysis treatment of blood primes may not be always necessary when combined with the results of our study, if AN69 membranes are not used, at least as long as CTA membranes are used.

Limitation

Our study has several limitations. First, this retrospective study was based on accurate documentation of medical interventions by the medical team. Second, this study included a small number of cases, which was not sufficient to prove the safety of the current protocol. However, we could safely perform CKRT in neonates and infants using the same protocol before conducting the current study. Third, because this was a single-center study, our results might not be generalizable without the inclusion of a control group; thus, randomized controlled trials are needed to confirm the advantages of our protocol. Fourth, we were unable to account for medications frequently received by critically ill patients, such as sedation, that might lead to hemodynamic changes. Similarly, we were unable to obtain real-time echocardiograms; thus, assessing for changes in cardiac function that would affect hemodynamics was impossible.

Conclusions

Our protocol of replacing approximately 50% of the priming volume of the extracorporeal circulation with packed red blood cells allowed us to safely perform CKRT without predialysis treatment of blood primes even in children weighing < 5 kg.

Abbreviations

AKI	Acute kidney injury
CKRT	Continuous kidney replacement therapy
CoA/C	Coarctation complex
CTA	Cellulose triacetate
DIAL	Dialysis
EC	Extracorporeal circulation
HLHS	Hypoplastic left heart syndrome
HR	Heart rate
IVS	Intraventricular septum
MAP	Mean arterial pressure
PAES	Polyarylethersulfone
PELOD	Pediatric logistic organ dysfunction
PMR	Predicted mortality rate
PVO	Pulmonary venous obstruction
QB	Blood flow rate
QD	Dialysate flow rate
QS	Replacement flow rate
SMR	Standardized mortality rate
TAPVC	Total anomalous pulmonary venous connection
TOF	Tetralogy of Fallot
TMP	Transmembrane pressure
VIS	Vasoactive inotropic score
VSD	Ventricular septal defect

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Author contributions

HN wrote the initial draft of the manuscript. KS, HS, KY, AK, SM, and KS managed the patients during this study. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Kanagawa Children's Medical Center (144-4), and according to the principles of the Declaration of Helsinki, informed consent was obtained from the patient's parents and the personal data of patients were rendered anonymous.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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