Pump-controlled retrograde trial off for weaning from adult veno-arterial extracorporeal membrane oxygenation – a retrospective observation cohort

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Abstract

Background

The optimal strategy of weaning veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO) remains poorly described. Pump-controlled retrograde trial off (PCRTO) involves serial decremental pump revolutions until a retrograde flow from the arterial to venous ECMO cannula is achieved. It has been reported as a feasible weaning strategy in the pediatric population, but its application in adults has not been widely reported.

Methods

This was a retrospective observational study including all adult patients who underwent PCRTO during weaning from V-A ECMO at a tertiary ECMO center between January 2019 and July 2021. Hemodynamic characteristics during PCRTO and clinical outcomes were reported. The clinical and echocardiographic parameters of successful and unsuccessful PCRTO runs were compared.

Results

A total of 57 runs of PCRTO in 36 patients were analyzed – 45 (78.9%) of the trials were successful. The median blood flow rate during PCRTO was 0.6 L/min, and the median duration of PCRTO was 240 minutes in the successful group compared with 35 minutes in the unsuccessful group. Patients who tolerated the trial had higher systolic blood pressure (105 vs 96 mmHg, p=0.042) and mean arterial pressure (78 vs 63 mmHg, p=0.008) at the end of PCRTO. The left ventricular outflow tract velocity-time integral measured during PCRTO was greater in the successful group (17.5 vs 12.9 cm, p=0.021).

Of the 35 patients who had at least one session of successful PCRTO, 31 (88.6%) ultimately underwent ECMO decannulation. In adjusted analysis, baseline alanine aminotransferase (OR 8.16, 95% CI 1.31-50.9, p=0.025) and serum creatinine (OR 7.15, 95% CI 1.04-49.2, p=0.046) were significantly associated with increased probability of successful PCRTO.

Conclusions

PCRTO is a feasible strategy for trialing off V-A ECMO with a low risk of adverse events and high rate of predicting eventual successful ECMO decannulation. Laboratory parameters that reflect the degree and recovery of end-organ ischemic injury were useful for predicting a successful PCRTO. The application of PCRTO should be studied in multi-centered studies.

Background

The utilization of veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO) has been surging in recent years. It serves as a promising temporary cardiopulmonary support or a bridge to various types of therapies[1]. However, a systematic approach to weaning V-A ECMO remains to be well-established.

To the best of knowledge, decremental flow reduction and arteriovenous bridging recirculation remain the commonest adopted strategies to trial a patient off V-A ECMO[2–10]. Nevertheless, limitations of these strategies include variability in circuit arrangement between institutions, and risk of thromboembolic events during clamping of the circuit[11, 12]. More importantly, the evaluation of native left and right ventricular function is incomprehensive under a minimal residual ECMO flow[13]. A novel weaning strategy, pump-controlled retrograde trial off (PCRTO), has emerged as a potential remedy to the captioned problems[13]. PCRTO can be efficiently executed by turning down the pump head revolutions until blood flows in a “retrograde” manner from the arterial cannula through the ECMO circuit and returning to the venous cannula without requiring any modification of the existing circuit[12–14]. The ability of the left heart to generate sufficient cardiac output for systemic oxygen delivery, as well as the tolerance of the right heart to near-normal venous return, can be tested simultaneously during PCRTO. If hemodynamic instability is encountered during the trial, full ECMO support can be resumed instantaneously by increasing the pump head revolutions and restoring veno-arterial flow. PCRTO was originally reported in the pediatric population[12], its use has not been more broadly adopted in the adult population in part due to a scarcity of published data and lack of standardized procedures[13–15].

In this study, we aimed to investigate the application of PCRTO in adult patients undergoing a V-A ECMO weaning trial and examine physiological parameters that may predict successful weaning.

Methods

Study population

We retrospectively reviewed all patients admitted with cardiogenic shock and received V-A ECMO support (Cardiohelp, Maquet, Hirrlingen, Germany; Rotaflow, Maquet, Rastatt, Germany) at a tertiary level adult ECMO center between January 2019 and July 2021. This center did not manage post-cardiotomy patients. All patients who had PCRTO performed as part of an ECMO weaning trial were included. There were no exclusion criteria for the study. The study was approved by the Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) (IRB Reference Number: UW 20–573). A waiver of informed consent was granted due to the retrospective nature of the study.

ECMO characteristics

V-A ECMO was cannulated peripherally with a femoral-femoral configuration. A distal reperfusion catheter was routinely inserted to the superficial femoral artery and connected to the return cannula to maintain lower limb perfusion adequacy. For anticoagulation, systemic unfractionated heparin infusion was used to maintain a target partial thromboplastin time (APTT) at 1.5–2.5 times the normal value unless contraindicated.

PCRTO protocol

PCRTO has been adopted as a routine strategy in weaning patients from V-A ECMO support under a written protocol (Fig. 1). PCRTO starts with reducing the pump head revolutions in a controlled fashion until reaching a retrograde flow of 0.5–1.0 L/min. The distal reperfusion catheter would be connected to a pressurized normal saline infusion to maintain its patency and allow continuous pressure monitoring (Fig. 1). An APTT at 1.5–2.5 times the normal value had to be attained before initiation of PCRTO[9, 10, 12, 13], a bolus of unfractionated heparin would be given if the target clotting profile is not met. The sweep gas flow to the oxygenator is turned off once the retrograde ECMO flow is achieved.

Hemodynamic and respiratory parameters were closely monitored during PCRTO, and serial echocardiography to assess the left and right heart function were performed by trained intensivists before and during the institution of trial. The adequacy of organ perfusion was evaluated using composite assessment of urine output, serum pH, lactate level, and vasoactive-inotropic score (VIS) before and after the initiation of PCRTO. Cerebral and lower limb perfusion adequacy were closely monitored with near-infrared spectroscopy (NIRS) using the Root® with O3® Regional Oximetry (Masimo Corporation, Irvine, USA). The sensors were attached to the forehead and bilateral lower limb to monitor regional saturations.

Outcomes and definitions

The primary study outcome was whether the PCRTO was successfully completed. Patients were divided into two groups, which were successful PCRTO (“successful” group) and premature termination of the trial (“unsuccessful” group). A trial was successful if it ran its intended duration and was terminated electively with evidence of satisfactory end-organ perfusion. Patients with any manifestations of cardiac decompensation necessitating early termination of PCRTO were assigned to the remaining group. These manifestations included clinically significant deterioration in hemodynamic and respiratory profiles, evidence of end-organ hypoperfusion such as seizure episodes, and impaired lower limb circulation detected by near-infrared spectroscopy (NIRS).

Secondary outcomes include the rate of ECMO decannulation, ICU survival rate, and duration from ECMO initiation to the first PCRTO trial.

Data collection

All data were collected retrospectively from electronic medical charts and records. Physiological parameters, including heart rate, systolic and diastolic blood pressure, pulse pressure, and biochemical markers such as serum pH and lactate level, were retrieved at 1 hour before PCRTO, 1 hour after the trial initiation, and at the end of the trial.

Physiological parameters, organ function, and VIS were compared between the successful and unsuccessful groups. The VIS was calculated as a weighted sum of all vasopressors and inotropes (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 (unit/kg/min) + 100 × norepinephrine dose (μg/kg/min))[16]. PCRTO-related measurements, including blood flow rate and duration of PCRTO runs were collected. Bilateral lower limb regional saturations by NIRS were retrieved. The sequential organ

failure assessment (SOFA) score and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were used as measures of disease severity[17–19].

The baseline pulmonary function was measured by the PF ratio and the number of quadrants of lung infiltrates on daily chest radiograph[20]. Liver function was assessed by hepatic transaminases and was further categorized based on the Child-Pugh score[21]. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI creatinine equation, and patients were divided into six different stages of acute kidney injury according to the KDIGO criteria[22, 23]. The urine output 1 hour before and after each PCRTO trial were collected. Patients who were supported by continuous renal replacement therapy (CRRT) were not excluded from weaning trials[4], and the use of CRRT was documented.

One of three trained intensivists performed all echocardiographic assessments using the Vivid q cardiovascular ultrasound system (GE Medical, Freiburg, Germany). Assessment of the systolic and diastolic function of the heart was carried out using two-dimensional echocardiogram, Doppler flow, tissue Doppler imaging, and speckle tracking echocardiography[24]. Echocardiography was performed at various time points during ECMO care delivery, including after initiation of ECMO support, prior to, and during PCRTO.

Statistical analysis

Data were described as mean ± standard deviation if it was normally distributed, and median (interquartile range) for skewed data. The Shapiro-Wilk test was used to evaluate the normality of all non-categorical data, followed by independent t-test for normally distributed continuous variables, while the Wilcoxon rank-sum test was used for non-normally distributed variables. The Fisher exact test was performed for categorical variables unless otherwise specified. First, univariate analysis was used to compare variables between the “successful” and “unsuccessful” groups. A multivariable logistic regression was performed including variables with p-value < 0.05 in univariate analysis and any clinically important parameters. These included baseline end-organ and hemodynamic parameters, and echocardiographic measures of left ventricular function such as left ventricular outflow tract velocity-time integral (LVOT VTI) and left ventricular ejection fraction (LVEF). The variables were dichotomized using the cohort mean or median as the cut-off point. A subgroup analysis in patients with complete echocardiography measurements was performed. All data analyses were undertaken in Stata version 16 (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC).

Results

Patient population

Over the study period, there were a total of 86 patients who had V-A ECMO. A total of 57 runs of PCRTO were performed in 36 (41.9%) patients – 45 (78.9%) of the trials were successful. Of the remaining 50 patients who did not undergo PCRTO, 46 (92%) of them were deemed unsuitable for any form of weaning

trial. The remaining patients were bridged to other forms of advanced mechanical circulatory support or transplantation. The study flow diagram is shown in Fig. 2.

The median age was 57 years old (45–65), and 27 (75.0%) of the patients were male. The mean body weight was 70.2 ± 15.5 kg. The main indications for V-A ECMO were acute myocardial infarction (n = 14), myocarditis (n = 6), cardiomyopathy (n = 4), malignant arrhythmia (n = 4), and heart failure secondary to metabolic derangements including electrolyte disturbances and thyrotoxicosis (n = 3). The median SOFA score was 6 (4–12) and 11 (6-12.5) in the successful and unsuccessful groups, respectively (p = 0.30). The mean APACHE II score was 111.7 ± 29.0 among the successful and 114 ± 37.4 among the unsuccessful group (p = 0.87). Baseline characteristics are shown in Table 1.

Table 1
– Baseline characteristics of all enrolled patients

Characteristics	All patients (n = 36)
Age, years	57 (45–65)
Gender, male	27 (75%)
Body weight, kg	70.2 ± 15.5
Indications for V-A ECMO:	
Acute myocardial infarction	14 (38.9%)
Myocarditis	6 (16.7%)
Cardiomyopathies	4 (11.1%)
Endocrine-related heart failure	3 (8.3%)
Malignant arrhythmias	4 (11.1%)
Septic shock	1 (2.8%)
Miscellaneous	4 (11.1%)
Number of PCRTO sessions carried out per patient	
1 session	20 (55.6%)
2 sessions	14 (38.9%)
3 sessions	0
4 sessions	1 (2.8%)
5 sessions	1 (2.8%)
Invasive mechanical ventilation	22 (61.1%)
APACHE II score	112.1 ± 30.0
Decannulation of ECMO	32 (88.9%)
ICU survival	25 (78.1%)

A total of 32 (88.9%) patients were successfully decannulated from ECMO, and 25 (78.1%) of them survived the ICU admission. The causes of death after successful ECMO decannulation included sepsis (n = 6) and multiple organ failure (n = 1).

Baseline organ function

A total of 22 (61.1%) patients were mechanically ventilated. The mean PF ratio prior to PCRTO was 372.1 ± 168.1 mmHg, and not significantly different between the two groups (381.9 ± 169.5 vs 335.7 ± 163.4

mmHg, p = 0.40). There was no significant difference in the number of quadrants of infiltrates on chest radiographs between the two groups (p = 0.99).

The median ALT prior to the initiation of PCRTO was 125 (64–260) u/L, and was significantly lower in the successful group compared with the unsuccessful group (107 vs 356 u/L, p = 0.008). The median AST before the PCRTO trial was 150 (80–273) u/L, and was significantly lower in patients who tolerated the trial compared with patients who did not (118 vs 329 u/L, p = 0.001). The severity of liver failure according to the Child-Pugh score was distributed to A (33.3% vs 33.3%), B (46.7% vs 41.7%), C (20.0% vs 25.0%), in the successful and unsuccessful groups respectively (p = 0.92).

There were no significant differences in the degree of acute kidney injury between both groups based on the KDIGO criteria (p = 0.24). In addition, the fraction of patients requiring continuous renal replacement therapy was similar (p = 0.46).

The median creatine kinase preceding the start of PCRTO was 662 IU/L, and was significantly lower in patients who successfully tolerated a PCRTO trial (592 vs 1437 IU/L, p = 0.048). Similarly, troponin T was significantly lower in the successful group (1563 vs 8963 ng/ml, p = 0.010). Other laboratory parameters are shown in Table 2.

Table 2
Baseline organ function and laboratory results prior to PCRTO

Characteristics	All cohort (n = 57)	Successful group (n = 45)	Unsuccessful group (n = 12)	p-value
Pulmonary function:				
PF ratio, mmHg	372.1 ± 168.1	381.9 ± 169.5	335.7 ± 164.3	0.40
Chest X-ray: quadrant of infiltrates				
No quadrants		3 (6.7%)	1 (8.3%)	
1 quadrant		8 (17.8%)	1 (8.3%)	
2 quadrants		11 (24.4%)	4 (33.3%)	
3 quadrants		12 (26.7%)	3 (25.0%)	
4 quadrants		11 (24.4%)	3 (25.0%)	0.99
Liver function:				
ALT, u/L	125 (64–260)	107 (57–179)	356 (128–592)	0.008
AST, u/L	150 (80–273)	118 (67–210)	329 (194–736)	0.001
ALP, u/L	87 (69–133)	88 (69–140)	85 (75–116)	0.70
Child-Pugh Score:				
Child-Pugh A		15 (33.3%)	4 (33.3%)	
Child-Pugh B		21 (46.7%)	5 (41.7%)	
Child-Pugh C		9 (20.0%)	3 (25.0%)	0.92
Renal function:				
Stage of AKI:				
Stage I		7 (15.6%)	1 (8.3%)	
Stage II		8 (17.8%)	1 (8.3%)	
Stage IIIa		5 (11.1%)	0	
Stage IIIb		8 (17.8%)	3 (25%)	
Stage IV		5 (11.1%)	5 (41.7%)	
Stage V		12 (26.7%)	2 (16.7%)	0.24
Use of CRRT		7 (15.6%)	1 (8.3%)	0.46

Characteristics	All cohort (n = 57)	Successful group (n = 45)	Unsuccessful group (n = 12)	p-value
Serum creatinine, μmol/L	174 (109–374)	159 (100–381)	201 (172–271)	0.64
Partial thromboplastin time, seconds	47.5 (43.4–51.9)	48.7 (44.8–52.4)	45.1 (41-48.2)	0.18
Laboratory markers:				
Creatine kinase, IU/L	662 (335–2100)	592 (310–1607)	1437 (622–7853)	0.048
Troponin T, ng/L	3825 (569–9439)	1563 (385–7525)	8963 (6890–15861)	0.010
SOFA score	8 (5–12)	6 (4–12)	11 (6-12.5)	0.30

PCRTO characteristics

A total of 57 runs of PCRTO trials were performed – 20 patients had 1 session of PCRTO, 14 patients had 2 sessions, 1 patient had 4 sessions, and 1 patient had 5 sessions. During the PCRTO, the median blood flow rate was 0.6 (0.5–0.7) L/min. The mean heart rate was 100 ± 24 bpm, mean pulse pressure was 55 ± 18 mmHg, and median mean arterial pressure (MAP) was 80 (71–91) mmHg.

A total of 45 (78.9%) of the PCRTO were successful. The reasons for unsuccessful PCRTO included suspected RV failure (n = 4), evidence of transient end-organ hypoperfusion with poor lower limb perfusion reflected by the drop in NIRS reading (n = 4), seizure attacks accompanied by loss of consciousness (n = 3), and coincidental acute obstruction of the endotracheal tube (n = 1). There were no major patient or ECMO circuit complications arising from PCRTO. The median duration from initiation of ECMO to the first attempt of PCRTO was 87 (54–121) hours in the successful group and 69 (46–141) hours in the unsuccessful group ($p = 0.82$). The median duration of each PCRTO trial was 240 minutes in the successful group and 35 minutes in the unsuccessful group ($p < 0.001$). Patients who tolerated the trial had higher systolic blood pressure (105 vs 96 mmHg, $p = 0.042$) and MAP (78 vs 63 mmHg, $p = 0.008$) at the end of the trial compared with patients who did not. There were no differences in other hemodynamic parameters. Other parameters of end-organ perfusion including urine output, serum pH, lactate level, VIS, and lower limb NIRS measurements were similar between the successful and unsuccessful groups. Detailed data during PCRTO are presented in Table 3.

Table 3
ECMO and physiological parameters during PCRTO

Characteristics	All cohort (n = 57)	Successful group (n = 45)	Unsuccessful group (n = 12)	p-value
Heart rate, bpm:				
1-hour pre-trial	92 ± 20	90 ± 21	98 ± 14	0.23
1-hour after start of trial	100 ± 24	99 ± 24	107 ± 30	0.56
End of trial	100 ± 24	101 ± 24	97 ± 24	0.58
Systolic blood pressure, mmHg:				
1-hour pre-trial	110 (97–125)	111 (97–125)	106.5 (98–126)	0.97
1-hour after start of trial	105 (96–121)	105 (96–122)	102.5 (92–108)	0.46
End of trial	104 (93–129)	105 (95–139)	96 (81–114)	0.042
Diastolic blood pressure, mmHg:				
1-hour pre-trial	68 ± 14	68 ± 14	70 ± 17	0.62
1-hour after start of trial	56 ± 11	56 ± 12	53 ± 8	0.61
End of trial	58 ± 13	59 ± 13	54 ± 12	0.22
Pulse pressure, mmHg:				
1-hour pre-trial	46 ± 24	46 ± 22	44 ± 30	0.82
1-hour after start of trial	55 ± 18	55 ± 19	50 ± 14	0.60
End of trial	53 ± 19	55 ± 20	43 ± 15	0.053
Mean arterial pressure, mmHg:				
1-hour pre-trial	80 (71–91)	81 (71–91)	77 (73–93)	0.81
1-hour after start of trial	72 (65–84)	72 (64–84)	66 (66–69)	0.70
End of trial	73 (63–88)	78 (69–93)	63 (59–69)	0.008
Urine output, ml/hr:				
1-hour pre-trial	40 (16–100)	40 (15–100)	50 (30–95)	0.54
1-hour after start of trial	50 (15–70)	40 (10–70)	60 (37.5–75)	0.24

Characteristics	All cohort (n = 57)	Successful group (n = 45)	Unsuccessful group (n = 12)	p-value
pH:				
Pre-trial	7.49 (7.46–7.53)	7.5 (7.47–7.54)	7.46 (7.44–7.51)	0.055
During trial	7.48 (7.44–7.53)	7.5 (7.45–7.53)	7.4 (7.4–7.4)	0.17
Post-trial	7.50 (7.44–7.52)	7.5 (7.44–7.53)	7.45 (7.43–7.50)	0.36
Serum lactate, mmol/L:				
Pre-trial	2.1 (1.5–2.6)	2 (1.4–2.5)	2.8 (2-3.8)	0.12
Post-trial	2.4 (1.5–3.9)	2.4 (1.5–3.5)	2.5 (2.1–5.7)	0.43
Vasoactive-inotropic score (VIS):				
Pre-trial	0 (0–5)	0 (0-2.6)	3.4 (0-7.6)	0.19
During trial	0 (0-8.4)	0 (0–5)	6.6 (0-10.5)	0.13
Duration of each PCRTO run, minutes	180 (120–240)	240 (120–240)	35 (10–105)	< 0.001
Blood flow rate during PCRTO, LPM,				
Maximum blood flow rate	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.5 (0.5–0.7)	0.001
Minimum blood flow rate	0.5 (0.5–0.6)	0.5 (0.5–0.6)	0.5 (0.4–0.5)	0.032
Mean blood flow rate	0.6 (0.5–0.7)	0.6 (0.5–0.7)	0.5 (0.5–0.6)	0.025
Duration of ECMO to 1st run of PCRTO, hours:	81 (53–130)	87 (54–121)	69 (46–141)	0.82
NIRS reading:				
Left lower limb, %:				
Pre-trial	65 ± 6	66 ± 7	65 ± 5	0.70
During trial	61 (57–65)	62 (57–66)	60 (57–64)	0.33
Right lower limb, %:				
Pre-trial	65 ± 7	64 ± 7	66 ± 6	0.47
During trial	60 ± 8	60 ± 7	59 ± 11	0.64

Of the 35 patients who at least had one successful PCRTO, 31 (88.6%) ultimately underwent ECMO decannulation successfully. The reason for unsuccessful decannulation was hypoxic brain injury (n = 3), and concurrent multiple organ failure leading to a withdrawal of life-sustaining therapy (n = 1). There was 1 patient who was decannulated despite not having tolerated any attempts of PCRTO.

Echocardiographic parameters

A subgroup of 27 (47.4%) PCRTO runs had full echocardiographic data, including 23 successful and 4 unsuccessful runs. Prior to PCRTO, the median LVEF was 29.7 (25.1–39) %, LVOT VTI was 9.1 (7.5–13.2) cm, and peak systolic tissue velocity at lateral mitral annulus was 0.05 (0.04–0.06) m/s. Only LVOT VTI measured during PCRTO was significantly different between the successful and unsuccessful groups (17.5 vs 12.9 cm, p = 0.021). There were no significant differences in other echocardiography parameters including LVEF or mitral annulus peak systolic tissue velocity between the successful and unsuccessful groups. Echocardiography data are presented in Table 4.

Table 4
Subgroup of patients with detailed echocardiography data

Echo parameters	All cohort (n = 27)	Successful run with ECHO (n = 23)	Unsuccessful run with ECHO (n = 4)	p-value
LVEF (Teich) (%):				
T_1	14.1 (7.1–23.8)	16.5 (7.1–27.2)	11.5 (8.5–13.3)	0.32
T_2	29.7 (25.1–39)	30.6 (23.1–46.8)	30.6 (27.4–35.2)	0.95
T_3	43.9 (37-56.9)	45.3 (37.6–70.5)	49.5 (37.5–58.5)	0.78
LVESV (ml):				
T_1	58.5 (38.9–90.2)	51.1 (29.6-103.5)	59.3 (56.3–71.7)	0.72
T_2	70.8 (33.1–92.6)	48.0 (25.1-112.4)	49.5 (14.3–74.0)	0.54
T_3	55.5 (26.7–74.3)	42.1 (19.4–72.7)	47.6 (21.3–64.9)	0.89
LVEDV (ml):				
T_1	73 (61.4-116.6)	70.2 (44.4-124.4)	66.4 (65.2–77.4)	0.94
T_2	98.2 (72.3-119.8)	90.6 (50.9-144.9)	82.8 (55.2-102.7)	0.63
T_3	101.7 (58.3-114.3)	77.9 (47.2-130.4)	86.3 (40.6-103.5)	0.57
LVOT VTI (cm):				
T_1	4.8 (2.9–8.7)	6.8 (4.0-12.3)	2.9 (2.5–3.7)	0.055
T_2	9.1 (7.5–13.2)	10.5 (8.1–17.5)	6.1 (1.6–11.2)	0.12
T_3	14.4 (12–19)	17.5 (14.5–21.7)	12.9 (9.9–14.1)	0.021
FS (%):				
T_1	6.3 (3.1–10.9)	7.4 (3.1–12.6)	4.6 (3.2–5.8)	0.29
T_2	14.1 (11.7–19.7)	16.5 (11.1–23.2)	12.9 (11.4–16.2)	0.45
T_3	21.5 (17.7–29)	22.6 (17.9–39.6)	24.7(17.9–30.1)	0.83

Echo parameters	All cohort (n = 27)	Successful run with ECHO (n = 23)	Unsuccessful run with ECHO (n = 4)	p-value
CO (L/min):				
T_1	1.1 (1.0-2.4)	1.8 (0.9–3.4)	1.1 (0.9–1.2)	0.29
T_2	2.6 (2.5–3.3)	2.9 (2.5–4.2)	2.6 (2.5-3.0)	0.34
T_3	4.2 (3.5–6.3)	5.1 (3.8–6.8)	3.6 (3.4-5.0)	0.14
Lateral s' (cm/s):				
T_1	0.05 ± 0.02	0.05 ± 0.02	0.03 ± 0.02	0.11
T_2	0.05 (0.04–0.06)	0.05 (0.05–0.07)	0.06 (0.05–0.06)	0.65
T_3	0.10 (0.07–0.1)	0.10 (0.06–0.12)	0.09 (0.08–0.1)	0.97
Medial s' (cm/s):				
T_1	0.03 (0.03–0.04)	0.04 (0.03–0.05)	0.03 (0.03–0.04)	0.53
T_2	0.04 (0.04–0.06)	0.05 (0.04–0.07)	0.05 (0.04–0.06)	0.61
T_3	0.07 (0.05–0.09)	0.07 (0.06–0.1)	0.05 (0.05–0.07)	0.33
Mitral E/A:				
T_1	1.0 (0.68–1.4)	0.9 (0.7–1.6)	0.7 (0.4–1.3)	0.34
T_2	0.8 (0.6–1.3)	0.7 (0.6–1.4)	0.8 (0.4–1.3)	0.89
T_3	1.0 (0.7–1.2)	1.1 (0.8–1.3)	0.9 (0.6–1.1)	0.26
GLPSS (%):				
T_1	-2.3 (-5.3-0)	-3.6 (-6.2-0)	-1.7 (-2.3- -0.6)	0.23
T_2	-6.3 (-8.7- -4.4)	-7.1 (-10.6- -4.4)	-5.3 (-6.1- -4.0)	0.23
T_3	-9.9 ± 4.6	-11.5 ± 5.2	-9.9 ± 2.6	0.55
T_1: at the initiation of ECMO; T_2: prior to start of PCRTO; T_3: during PCRTO				

Echo parameters	All cohort (n = 27)	Successful run with ECHO (n = 23)	Unsuccessful run with ECHO (n = 4)	p-value

Abbreviations: CO, cardiac output; FS, fractional shortening; GLPSS: global left ventricular peak systolic strain; lateral s', lateral mitral annuls peak systolic velocity; medial s': medial mitral annulus peak systolic velocity; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVOT VTI, left ventricular outflow tract velocity-time integral; mitral E/A, mitral peak E/A wave velocity ratio.

Predictors of PCRTO success

In multivariable logistic regression including baseline hemodynamic and organ function parameters, ALT < 125 u/L [OR 8.16, 95% CI (1.31–50.9), p = 0.025] and serum creatinine level < 174 µmol/L [OR 7.15, 95% CI (1.04–49.2), p = 0.046] were significantly associated with increased probability of PCRTO success. The area under receiving operating characteristic curve (AUC) of this model was 0.83. A second model incorporating baseline organ function and echocardiographic parameters had better discrimination for successful PCRTO (AUC 0.90), although it was not possible to identify independently significant predictors.

Based on the observed significance of LVOT VTI in univariate analysis, the utility of LVOT VTI measured at different timepoints was examined. PCRTO was likely successful when the LVOT VTI prior to the trial was greater than 10.7 cm. The Youden index was 0.652 and the AUC was 0.83. Details of the full regression models are shown in Table 5.

Table 5
Multivariable logistic regression analyses

Characteristics	All patients (n = 36)
Age, years	57 (45–65)
Gender, male	27 (75%)
Body weight, kg	70.2 ± 15.5
Indications for V-A ECMO:	
Acute myocardial infarction	14 (38.9%)
Myocarditis	6 (16.7%)
Cardiomyopathies	4 (11.1%)
Endocrine-related heart failure	3 (8.3%)
Malignant arrhythmias	4 (11.1%)
Septic shock	1 (2.8%)
Miscellaneous	4 (11.1%)
Number of PCRTO sessions carried out per patient	
1 session	20 (55.6%)
2 sessions	14 (38.9%)
3 sessions	0
4 sessions	1 (2.8%)
5 sessions	1 (2.8%)
Invasive mechanical ventilation	22 (61.1%)
APACHE II score	112.1 ± 30.0
Decannulation of ECMO	32 (88.9%)
ICU survival	25 (78.1%)
Association between baseline organ function and PCRTO successfulness	

Discussion

This is the largest reported cohort that evaluated the practicality of PCRTO as the primary weaning strategy for V-A ECMO in the adult population. During the recruited period, 41.9% of all patients supported with V-A ECMO had weaning by PCRTO. Nearly all patients who completed a PCRTO went on to have eventual successful ECMO decannulation. We demonstrated that PCRTO was a feasible and reproducible

strategy for trialing off V-A ECMO with a low risk of adverse events. Laboratory parameters that reflect the degree and recovery of end-organ ischemic injury, including serum ALT and creatinine levels, were useful for predicting a successful PCRTO.

Over the recent decades since the widespread utilization of V-A ECMO, multiple weaning strategies exist, of which decremental pump flow reduction and arteriovenous bridging recirculation technique are the mainstream approaches[2–10]. Nevertheless, variations in practice exist among institutions, and there are no consensus guidelines to standardize the weaning algorithms. Pump flow reduction is simple to implement, usually involving reducing ECMO flow to 33–50% of full support[2, 4, 25, 26]. However, as ECMO is still providing a small amount of veno-arterial flow, assessment of the native heart function may be inadequate, especially of right ventricular function in light of a reduced preload[13, 27]. Arteriovenous bridging recirculation technique could resemble a complete trial off of V-A ECMO support, yet it requires extra reconfiguration of the ECMO circuit by adding a parallel limb between the inflow and outflow cannula, and its utilization is limited by a short trial time and an increased risk of clot formation[9, 28].

The concept of PCRTO originated in pediatric ECMO[12], and has some obvious advantages over the previous two methods discussed. It mimics a complete cessation of V-A ECMO support while obviating the need to clamp off the circuit. PCRTO merely involves reducing the pump head revolutions in a controlled fashion until blood flows in a retrograde manner from the arterial to the venous cannulae. During retrograde blood flow, the systemic cardiac output is entirely taken over by native heart function, and the centrifugal pump serves as a braking system to prevent excessive arterial to venous shunting of the retrograde flow. In this physiological state, the effects of restoring normal cardiopulmonary circulation including increased RV filling, increased LV preload, and reduced LV afterload can be tested.

The feasibility of PCRTO was broadly evaluated in one of the largest reported series of adult patients supported with V-A ECMO in this study. We showed that PCRTO is highly practicable, safe, and has excellent prognostic value for ECMO weaning success. Importantly, it was able to discriminate patients who go on to be successfully decannulated. In order to routinely adopt PCRTO as a weaning strategy, ECMO caregivers need to acquire the skills in managing the distal limb reperfusion catheter to prevent clotting and the catastrophic complication of distal embolism when veno-arterial flow is reinstituted. Moreover, the process of PCRTO requires intensive monitoring to detect and manage adverse events promptly. The utility of repeated echocardiographic assessment, such as documentation of LVOT VTI during PCRTO, may differentiate weaning success and failure in patients with marginal cardiac recovery. Other hemodynamic assessment tools include insertion of the Swan-Ganz catheter have also been proposed as adjunctive techniques to facilitate determination of readiness to wean[2–5, 25, 26]. Future studies should aim to delineate the optimal number and duration of trials, and the feasibility of PCRTO in complex ECMO configurations such as V-AV and the presence of LV venting[4, 25, 29].

The determination of readiness to wean is another controversy in ECMO weaning, and multiple studies have suggested that stabilization of end-organ function including hemodynamic profile, respiratory parameters, and liver function is essential for successful weaning[2, 7, 25]. Other reports advocate the use of

surrogate markers such as serum lactate level and mixed venous saturation to adjudicate adequacy of oxygen delivery[13]. Perhaps most importantly, echocardiographic features including aortic VTI > 10 cm, lateral mitral annulus peak systolic velocity > 6 cm/s, and a LVEF > 20% have been shown to have high specificity for weaning success[2, 7, 25]. In our cohort, serum levels of hepatic transaminases and cardiac enzymes were satisfactory predictors of successful PCRTO, suggesting that weaning attempts should only be made after allowing adequate time for organ recovery.

This study had several inherent limitations of a retrospective cohort design. PCRTO was used entirely as the weaning approach in all recruited patients, and a matched control group was not included. Second, this was a single-center study, and subsequent generalizability of PCRTO to other ECMO configurations and care settings remains to be examined. Third, the sample size was limited in the cohort, especially in the subgroup of patients with detailed echocardiographic data, possibly precluding detection of significant differences.

Conclusion

We showed that PCRTO is a feasible weaning strategy for adult patients with peripheral V-A ECMO support. The use of liver parenchymal and cardiac enzymes prior to a weaning trial together with an LVOT VTI > 10.7cm can predict the successfulness of a PCRTO. Future studies to evaluate the broader application of PCRTO and its merits over conventional weaning strategies are needed.

Declarations

Author contributions

(1) Concept or design: FML, WKC and PYN

(2) Acquisition of data: FML, WKC and PYN

(3) Analysis or interpretation of data: FML, WKC and PYN

(4) Drafting of the article: FML, WKC and PYN

(5) Critical revision for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of Interest

All authors have disclosed no conflict of interest.

Acknowledgement

Not applicable.

Declaration

This research has not been presented or published in any form prior to submission.

Consent of publication

Not applicable.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

Not applicable.

Ethics approval

This study was approved by the Institutional Review Board of The University of Hong Kong with a waiver of informed consent (IRB reference number: UW 20-573). The study was conducted in accordance with the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study.

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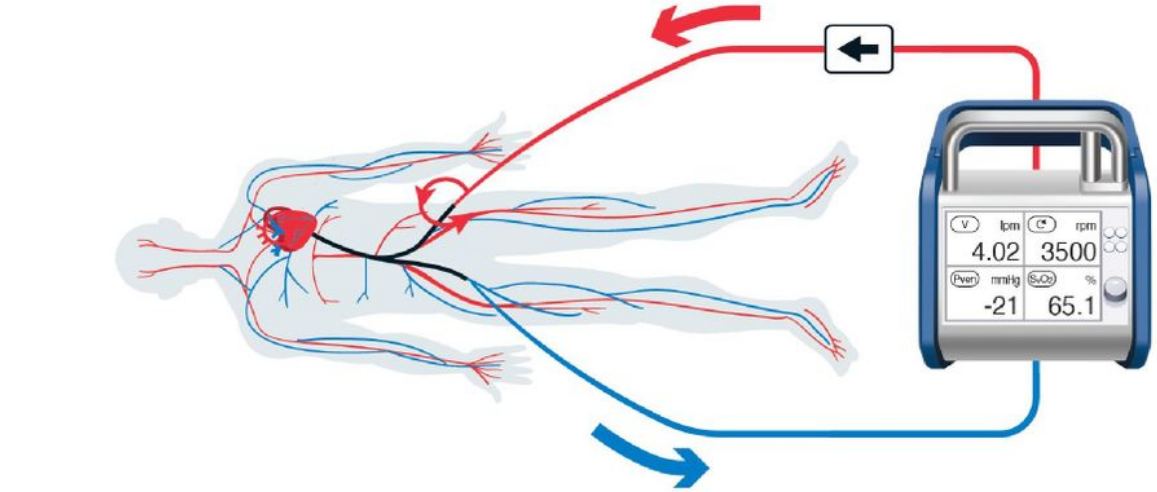
Figures

Figure 1.



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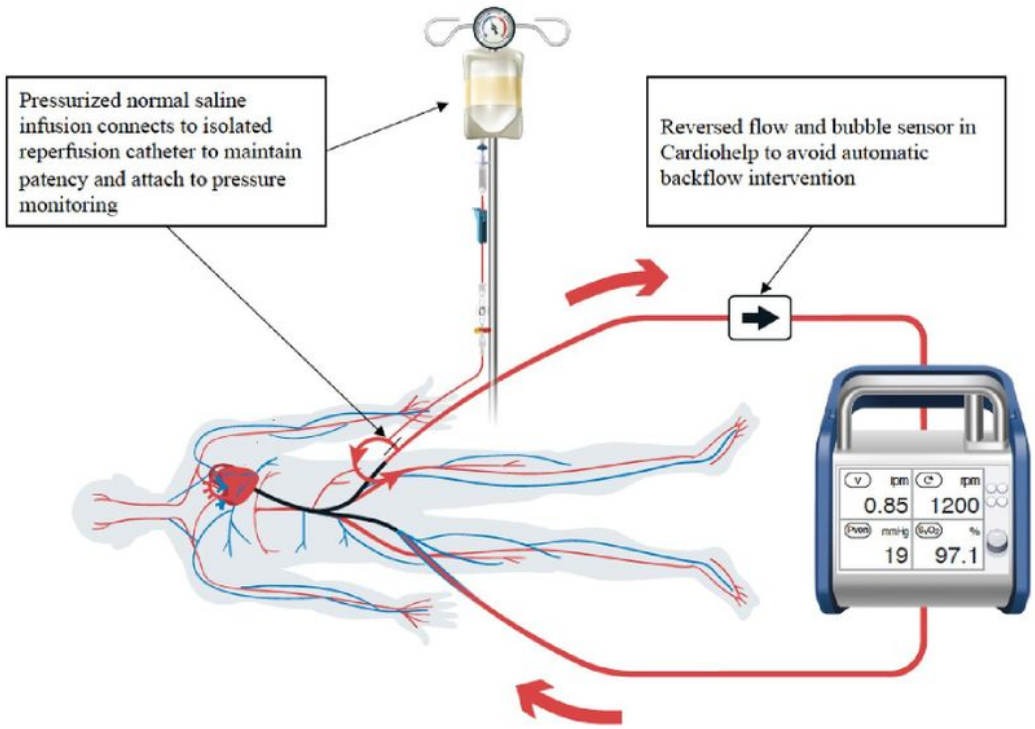

b、

Figure 1

Schematic diagram of V-A ECMO and PCRTO

(Panel A) A typical configuration of femoro-femoral V-A ECMO circuit consists of blood flow from the access cannula (blue) exiting the common femoral vein, passing through the ECMO pump head and oxygenator, and returning via the return cannula (red) inserted into the common femoral artery.

(Panel B) During PCRTO, systemic arterial blood flows from the cannula in the common femoral artery, through the ECMO pump head and oxygenator, and is shunted to the venous system via the cannula in the common femoral vein. The distal limb reperfusion catheter is isolated from the circuit and connect to pressured normal saline.

Figure 2.

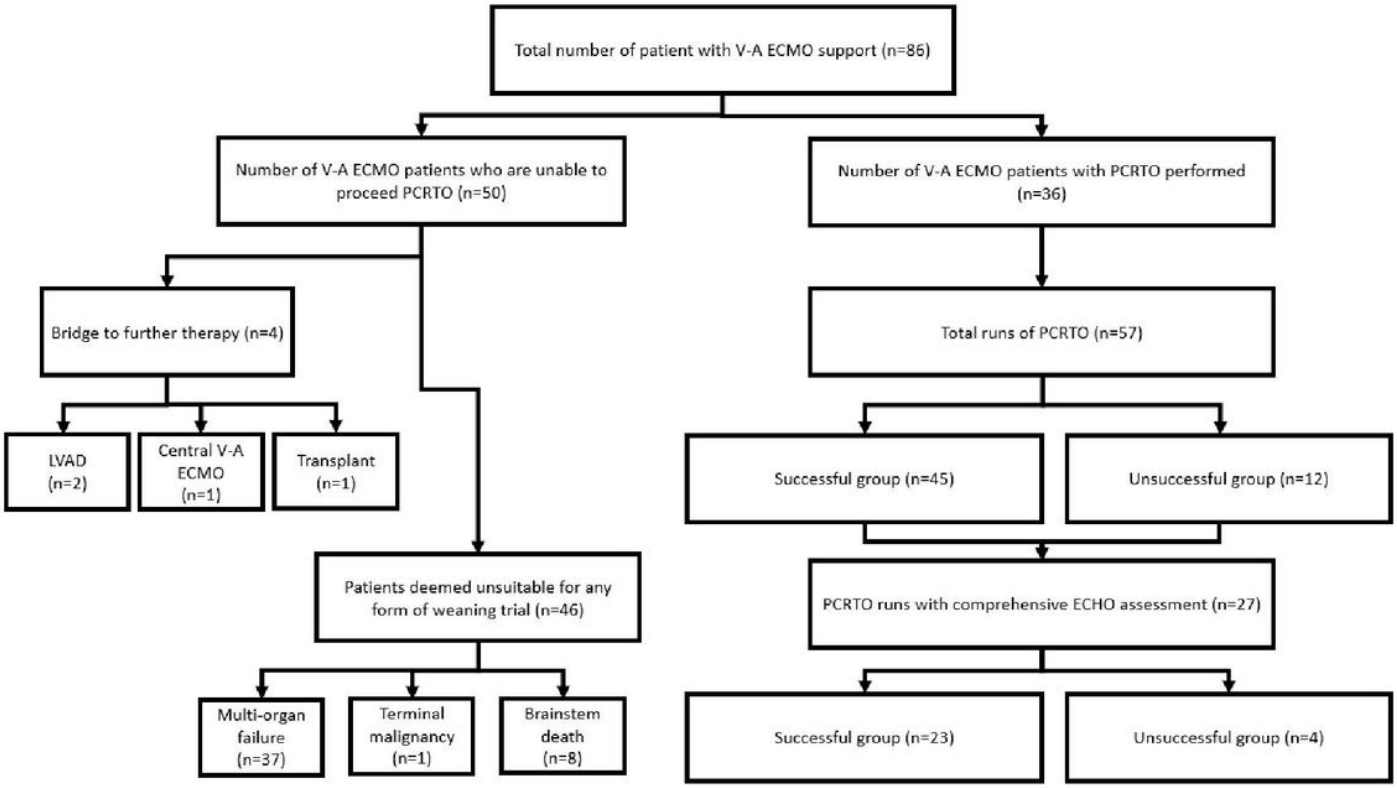

Figure 2

Study flow diagram

There was a total of 86 patients who received V-A ECMO during the study period. A total of 36 patients received at least 1 PCRTO trial, and the total number of PCRTO runs was 57.