Sensitivity of ventricular systolic function to afterload during veno-arterial extracorporeal membrane oxygenation

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Abstract

Aims Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) increases afterload to the injured heart and may hinder myocardial recovery. We aimed to compare the sensitivity of left ventricular (LV) systolic function to the afterload effects of peripheral V-A ECMO during the acute and delayed stages of acute myocardial dysfunction.

Methods and results A total of 46 adult patients who were supported by peripheral V-A ECMO between April 2019 and June 2021 were analysed. Serial cardiac performance parameters were measured by transthoracic echocardiography (TTE) on mean day 1 ± 1 of V-A ECMO initiation (n = 45, ‘acute phase’) and mean day 4 ± 2 of V-A ECMO initiation (n = 36, ‘delayed phase’). Measurements were obtained at 100%, 120%, and 50% of ECMO target blood flow (TBF). LV global longitudinal strain (GLS) significantly improved from /C06.1 (%GLS) to /C08.8 (%) during 120% TBF to /C04.0 (%) during 50% TBF (P < 0.001). The sensitivity of LV GLS to changes in ECMO flow was significantly greater in the acute phase of myocardial injury compared with the delayed phase [median (IQR) percentage change: 72.7 (26.8–100.0)% vs. 22.5 (14.9–43.8)%; P < 0.001]. Findings from other echocardiographic parameters including LV ejection fraction [43.0 (29.1–56.8)% vs. 22.8 (9.2–42.2)%; P = 0.012] and LV outflow tract velocity-time integral [45.8 (18.6–58.7)% vs. 24.2 (12.6–34.0)%; P = 0.001] were similar. A total of 24 (52.2%) patients were weaned off ECMO successfully.

Conclusions We demonstrated that LV systolic function was significantly more sensitive to the afterload effects of V-A ECMO during the acute stage of myocardial dysfunction compared with the delayed phase. Understanding the evolution of the heart–ECMO interaction over the course of acute myocardial dysfunction informs the clinical utility of echocardiographic assessment in patients on V-A ECMO.

Keywords Extracorporeal membrane oxygenation; Transthoracic echocardiography; Left ventricular systolic function; Afterload

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Introduction

Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) is an established method of temporary mechanical circulatory support in patients with cardiogenic shock. Due to the ‘retrograde’ flow of oxygenated blood from the return cannulae, commonly inserted through the femoral artery into the aorta, left ventricular (LV) afterload is invariably increased during peripheral V-A ECMO support, and the subsequent increased wall stress may hinder the recovery of the injured myocardium.1 The current range of mechanical circulatory support devices including intra-aortic balloon pumps, catheter-based intravascular blood pumps, and surgically-placed external centrifugal pumps have not been compared in head-to-head physiological studies, and the incomplete understanding of their relative merits and limitations undermines the lack of well-defined selection criteria and translation to improved patient outcomes.2,3

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Transthoracic echocardiography (TTE) has been widely used to assess the haemodynamic status and myocardial performance of patients in the intensive care unit (ICU) setting. Observational studies using echocardiographic parameters have demonstrated an effect of ECMO flow on myocardial systolic function at different ECMO blood flow rates. Specifically, left ventricular ejection fraction (LVEF) and aortic velocity-time integral (VTI) were shown to increase at lower ECMO flows, where there are concurrent increases in LV preload and decreases in afterload. However, this heart–ECMO interaction was only studied during the recovery phase of myocardial injury upon weaning of V-A ECMO. It is not known whether the effect of peripheral V-A ECMO on native LV systolic function differs during different phases of myocardial dysfunction, and the evolution of the heart–ECMO interaction has implications on optimal flow titration and predicting successful weaning.

In this prospective observational study, we aimed to examine the sensitivity of LV systolic function to the afterload effects of peripheral V-A ECMO during various stages of acute myocardial dysfunction. We hypothesised that LV systolic function is more sensitive to changes in ECMO blood flow during the acute stage compared with the delayed stage.

Methods

Study population

This was a single-centre prospective observational study of all adult patients (≥18 years old) admitted to the ICU with cardiogenic shock and received peripheral V-A ECMO in Queen Mary Hospital between April 2019 and June 2021. Patients were excluded if they met one of the following criteria: (i) clinically unstable haemodynamics including unstable ECMO blood flow; (ii) presence of pathological intracardiac shunt, for example, ventricular septal defect; (iii) presence of iatrogenic shunt, for example, left ventricular vent; (iv) surgical patients; (v) echocardiographic image quality unsatisfactory for data processing; or (vi) absence of patient or surrogate consent. Patients were put on V-A ECMO as part of extracorporeal cardiopulmonary resuscitation (ECPR) if they were determined to have a potentially reversible cause of cardiac arrest but did not have return of spontaneous circulation after more than 30 min of conventional CPR. The study conforms with the principles outlined in the Declaration of Helsinki and 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 17-449). Informed consent was obtained from all participants or their surrogates if they were deemed unfit to consent.

Material, equipment, and procedures

The first set (‘acute phase’) of TTE measurements were taken within the first 48 h after initiation of V-A ECMO support, followed by the second set (‘delayed phase’) taken during trial of weaning from V-A ECMO, or 7–10 days after initiation of V-A ECMO in patients without signs of myocardial recovery. Examinations were performed by one of the three trained physicians in detailed cardiac echocardiography with a commercially available system (General Electric Healthcare Vivid q cardiovascular ultrasound system). Two-dimensional sequences with three beats were obtained using a 3.5 MHz ultrasound transducer probe at a frame rate of 50 frames/sec and stored digitally in Digital Imaging and Communications in Medicine (DICOM) format. All echocardiographic measurements were performed according to current recommendations, and were repeated 5 min after adjusting to three ECMO flow settings at 100%, 120%, and 50% target blood flow (TBF; defined as 50–80 mL/kg/ideal body weight), respectively. During the second set of echocardiography in the delayed phase, measurements were also obtained during pump-controlled retrograde trial off (PCRTO) in patients who tolerated initial weaning. Measurements were abandoned, and further flow adjustments were not attempted if the patient developed any clinical signs of acute haemodynamic deterioration.

Assessment of LV systolic function included LVEF using the modified Simpson’s rule, fractional shortening (FS), left ventricular outflow tract (LVOT) VTI, left ventricular index of myocardial performance (LIMP), and peak systolic tissue velocity at the mitral annulus (s’). Myocardial strain for each of the cardiac segments were measured by two-dimensional speckle tracking echocardiography in longitudinal 3-chamber, 4-chamber, and 2-chamber planes. The LV global longitudinal strain (GLS) was measured as the average of all segmental strain values. All echocardiographic measurements were analysed offline by a single investigator blinded to clinical data and subsequent analysis. Detailed definitions of these measurements are shown in Supporting Information, Table S1.

Haemodynamic data were obtained by continuous invasive measurements of arterial blood pressure and estimated by TTE parameters according to current recommendations. Cardiac power output (CPO) was calculated as the product of mean arterial pressure (MAP) and cardiac output divided by 451.0

Outcomes and definitions

The primary outcome was the sensitivity of LV systolic function to ECMO blood flow, measured by the percentage change in LV GLS at different ECMO flow rates. Secondary outcomes were percentage changes in other measures of LV systolic function, including LVEF, LVOT VTI, LIMP, and s’ at the lateral and septal mitral annular levels.

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Patients who had evidence of myocardial recovery and tolerated initial weaning to 50% TBF proceeded to PCRTO, these patients were considered potentially ‘weanable’ from ECMO. The final decision to wean depended on myocardial recovery and extent of coexisting organ failure, in particular, evidence of irreversible neurological impairment and the decision to limit care. Patients were considered successfully ‘weaned’ from ECMO if they had ECMO decannulation by operative vascular repair and did not require further mechanical support in the next 30 days.

Statistical analysis

All analyses were performed with pre-specified endpoints and statistical methods. Contingent on demonstrating inverse association between the LV systolic function and ECMO blood flow during different stages of myocardial injury, the primary analysis was to compare the sensitivity of heart–ECMO interaction during the acute and delayed phases. Shapiro–Wilk tests were performed to test for normality of continuous variables, and data expressed either as means with standard deviations or medians with interquartile ranges (IQR). The percentage change in LV parameters during the acute and delayed stages were compared using paired t-tests or Wilcoxon signed rank tests as appropriate.

Sensitivity analyses included examining the difference in sensitivity to ECMO blood flow only in the subgroup of patients who were considered weanable and had proceeded to PCRTO. The primary analysis was also performed in patients with ischaemic cardiomyopathy, who theoretically have similar trends in myocardial injury and recovery.

We performed exploratory analyses to examine predictors of ECMO weaning success. The discrimination and calibration of two prediction models were assessed by the concordance C statistic (area under receiver operating characteristic [AUROC] curve) and the Hosmer–Lemeshow test. Model 1 included commonly adopted echocardiographic cut-offs of LVEF >20%, aortic VTI ≥10 cm, and s/ at lateral mitral annulus ≥6 cm/s. Model 2 was the Survival after Veno-Arterial ECMO (SAVE) score.11

Data management and statistical analyses were performed in Stata MP, version 16.1 (StataCorp, College Station, TX). A two-tailed $P$ value <0.05 was defined as statistically significant.

Results

Patients and characteristics

Between 1 April 2019 and 30 June 2021, 76 adult patients were admitted to the ICU with cardiogenic shock and received peripheral V-A ECMO (Figure 1). Eighteen patients who had unstable haemodynamics and could not tolerate ECMO flow adjustment, three patients who had LV venting, two surgical patients, two patients requiring urgent cardiomyotomy, two patients who had unsatisfactory echocardiographic image quality, one patient with ventricular septal defect, and two patients who did not give informed consent were excluded.

The final cohort for analysis included 46 patients. The median age was 58 (50–64) years and 33 (71.7%) were males. There were 6 (13.0%) patients with a history of ischaemic heart disease, 2 (4.3%) patients had known dilated cardiomyopathy, and 1 (2.2%) patient had chronic rheumatic heart disease. The most common indications of V-A ECMO were acute myocardial infarction (25, 54.3%) and myocarditis (6, 13.0%).

Baseline demographics of the study population are presented in Table 1. A total of 10 patients were not included in echocardiographic studies during the delayed phase: 8 patients had died and 2 patients had unsatisfactory echocardiographic image quality.

A total of 33 (71.7%) patients received V-A ECMO during ECPR, amongst whom 15 (45.5%) suffered from out-of-hospital cardiac arrest. The median no-flow time, defined as the duration from cardiac arrest to beginning of cardiopulmonary resuscitation, was 0 (0–0) min, and the median low-flow time, defined as the duration from cardiopulmonary resuscitation to initiation of ECMO blood flow or sustained return of spontaneous circulation, was 47 (35–56) min. Clinical data of patients who received ECPR are detailed in Supporting Information, Table S2.

Clinical outcomes

The median duration of V-A ECMO was 5.3 (3.2–7.9) days. A total of 24 (52.2%) patients were ultimately weaned from ECMO, while 2 (4.3%) patients were bridged to cardiac transplantation. The median length of stay in ICU was 7.6 (5.1–13.0) days. The rates of ICU and hospital survival were 47.8% ($n = 22$) and 45.7% ($n = 21$), respectively. 1 (2.2%) patient developed ischaemic limb requiring fasciectomy, and 3 (6.5%) patients developed ischaemic stroke. Major bleeding, defined according to ELSO definitions,12 were observed in 10 (21.7%) patients. The clinical outcomes are presented in Supporting Information, Table S3.

Heart–extracorporeal membrane oxygenation interaction at delayed phase

Transthoracic echocardiography during the delayed phase was performed on mean day $4 \pm 2$ of V-A ECMO initiation. Similar to that observed during the acute phase of myocardial injury,13 echocardiographic parameters of LV systolic function were significantly better at 50% compared with 100% and

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120% TBF during the delayed phase. Systolic function measured by LV GLS was significantly better at 50% TBF compared with 100% and 120% TBF, respectively [−8.8 (−11.5 to −6.0) vs. −5.8 (−9.4 to −3.5)%, P < 0.001; −8.8 (−11.5 to −6.0) vs. −6.1 (−8.9 to −4.0)%, P < 0.001]. Similar differences were demonstrated in other parameters of LV systolic function, including LVEF measured by biplane method [43.0 (28.4–54.8) vs. 29.8 (18.6–40.9)%, P < 0.001; 43.0 (28.4–54.8) vs. 25.5 (17.7–46.2)%, P < 0.001], LVOT VTI [10.9 (7.3–16.1) vs. 9.7 (6.3–14.0) cm, P < 0.001; 10.9 (7.3–16.1) vs. 9.4 (5.8–11.9) cm, P < 0.001], and s’ measured at the medial [0.06 (0.04–0.07) vs. 0.05 (0.04–0.07) m/s, P = 0.003; 0.06 (0.04–0.07) vs. 0.05 (0.04–0.06) m/s, P = 0.005] and lateral mitral annulus [0.07 (0.05–0.08) vs. 0.05 (0.04–0.06) m/s, P < 0.001; 0.07 (0.05–0.08) vs. 0.05 (0.04–0.07) m/s, P < 0.001]. Details of echocardiographic parameters at various ECMO flow rates are presented in Table 2.

During the delayed phase of myocardial injury, haemodynamic parameters were significantly different at different ECMO flows. The MAP was significantly lower at 50% TBF compared with 100% and 120% TBF (73 ± 20 vs. 81 ± 21 mmHg, P < 0.001; 73 ± 20 vs. 82 ± 21 mmHg, P < 0.001; respectively). ECMO at 50% TBF were associated with higher stroke volume (SV) [37 (23–49) vs. 32 (18–43) mL, P < 0.001; 37 (23–49) vs. 29 (17–39) mL, P < 0.001] and cardiac index (CI) [1.8 (1.3–2.3) vs. 1.5 (1.1–2.0) L/min/m², P < 0.001; 1.8 (1.3–2.3) vs. 1.3 (1.0–1.8) L/min/m², P < 0.001] when compared with 100% and 120% TBF, respectively. The CPO was higher at 50% TBF compared with 100% and 120% TBF [0.47 (0.35–0.79) vs. 0.46 (0.33–0.77), P = 0.027; 0.47 (0.35–0.79 vs. 0.42 (0.27–0.64), P < 0.001].

The heart–ECMO interaction between 50% TBF and retrograde ECMO flow in PCRTO during the delayed phase was compared. This analysis included 28 (60.9%) patients who were deemed potentially weanable and had underwent PCRTO, and the median retrograde flow achieved was 0.6 (0.5–0.7) L/min. LV systolic function measured by GLS was −8.8 (−11.5 to −6.0)% at 50% TBF and −10.7 (−13.6 to −7.0)% during PCRTO (P = 0.003). Similar differences in other LV parameters between 50% TBF and PCRTO were observed, including LVEF measured by biplane method [43.0 (28.4–54.8) vs. 49.9 (32.7–60.8)%, P = 0.001], LVOT...
Table 1 Baseline demographics of the study population

| Demographics | Unweaned | Weaned | P-value |
|--------------|----------|--------|---------|
| **Age**      | 60 (53–64) | 56 (47–64) | 0.38 |
| **Sex, male** | 16 (72.7%) | 17 (70.8%) | 0.89 |
| **Mean body mass index, kg/m²** | 25.6 ± 3.7 | 24.9 ± 4.3 | 0.56 |
| **Mean body surface area, m²** | 1.8 ± 0.2 | 1.8 ± 0.2 | 0.55 |
| **Hospital stay before ECMO initiation, h** | 1.9 (0.8–15.5) | 26.0 (1.3–116.9) | 0.25 |

**Co-morbidities**

| Active smoker | 8 (36.4%) | 7 (29.2%) | 0.60 |
| Hypertension | 6 (27.3%) | 9 (37.5%) | 0.46 |
| Hypercholesterolemia | 6 (27.3%) | 6 (25.0%) | 0.86 |
| Diabetes mellitus | 6 (27.3%) | 4 (16.7%) | 0.38 |
| Ischaemic stroke | 0 | 1 (4.2%) | 0.33 |
| Ischaemic heart disease | 2 (9.1%) | 2 (8.3%) | 0.71 |
| Valvular heart disease | 1 (4.5%) | 1 (4.2%) | 0.95 |
| Cardiomyopathy | 1 (4.5%) | 0 | 0.33 |
| Obstructive sleep apnoea | 0 | 1 (4.2%) | 0.33 |
| Congestive heart failure | 2 (9.1%) | 3 (12.5%) | 0.71 |
| Intracranial haemorrhage | 2 (9.1%) | 0 | 0.13 |

**Indications for V-A ECMO**

| Myocardial infarction | 12 (54.5%) | 13 (54.2%) | 0.98 |
| Infective myocarditis | 1 (4.5%) | 5 (20.8%) | 0.10 |
| Malignant arrhythmia | 1 (4.5%) | 3 (12.5%) | 0.34 |
| Thyrotoxic heart failure | 2 (9.1%) | 1 (4.2%) | 0.50 |
| Decompensated heart failure | 3 (13.6%) | 1 (4.2%) | 0.25 |

**Clinical scores**

| APACHE IV score | 134.1 ± 24.9 | 113.4 ± 28.8 | 0.013 |
| APACHE II score | 33.6 ± 7.5 | 30.3 ± 8.5 | 0.17 |
| SAVE score | –5.1 ± 3.6 | –4.3 ± 5.1 | 0.52 |

**Vasopressor/inotrope use (highest dose on day 1 of ECMO)**

| VISa | 24.4 (6.6–52.8) | 17.5 (4.5–44.4) | 0.55 |
| Noradrenaline, mcg/min/kg | 0.3 (0.1–0.4) | 0.3 (0.1–0.3) | 0.72 |
| Adrenaline, mcg/min/kg | 0.2 (0.2–0.3) | 0.1 (0.0–0.3) | 0.71 |
| Dobutamine, mcg/min/kg | 11.9 (2.0–30.9) | 3.4 (2.6–5.8) | 0.44 |
| Dopamine, mcg/min/kg | 21.0 (21.0–21.0) | 13.2 (11.0–15.4) | 0.22 |

**Biochemistry (worst values on day 1 of ECMO)**

| Creatinine, μmol/L | 210.5 (137.0–296.0) | 165.0 (125.0–258.0) | 0.41 |
| Arterial blood pH | 7.0 ± 0.2 | 7.1 ± 0.2 | 0.25 |
| Bicarbonate, mmol/L | 13.5 ± 6.5 | 13.4 ± 4.9 | 0.94 |
| Base excess, mmol/L | –16.3 ± 8.7 | –15.8 ± 6.5 | 0.81 |
| Bilirubin, μmol/L | 17.3 (10.4–30.0) | 19.8 (9.6–27.1) | 0.96 |
| Alanine transaminase, U/L | 222.5 (108.0–639.0) | 180.0 (68.0–333.0) | 0.41 |
| International normalized ratio | 1.5 (1.2–2.6) | 1.6 (1.3–1.9) | 0.98 |

All data are presented as frequency with percentages, mean ± standard deviation, or median with interquartile range unless specified.

aThe Vasoactive Inotropic Score was calculated as: Dopamine dose (μg/kg/min) + Dobutamine dose (μg/kg/min) + 100 × Adrenaline dose (μg/kg/min) + 1000 × Vasopressin dose (unit/kg/min) + 10 × Noradrenaline dose (μg/kg/min); using the highest dose for each vasopressor/inotrope.

APACHE II score, acute physiology and chronic health evaluation II score; APACHE IV score, acute physiology and chronic health evaluation IV score; ECMO, extracorporeal membrane oxygenation; PaO2, partial pressure of oxygen; PaCO2, partial pressure of carbon dioxide. SAVE, Survival after Veno-Arterial ECMO score; V-A ECMO, veno-arterial extracorporeal membrane oxygenation; VIS, Vasoactive Inotropic Score.
Table 2  Echocardiographic parameters at various ECMO flow rates

| Target blood flow | Acute phase N = 45 | Delayed phase N = 36 |
|-------------------|--------------------|---------------------|
|                   | 100% | 120% | 50% | 100% | 120% | 50% |
| **Left ventricle size** |                   |                   |     |                   |                   |     |
| LVIddd, cm        | 4.3 (3.6–4.8)     | 4.1 (3.5–4.8)     | 4.0 (3.2–4.8) | 3.8 (3.1–4.9)     | 4.1 (3.4–5.0)     | 4.0 (3.5–4.8) |
| LVIdds, cm        | 4.0 (3.3–4.6)     | 3.7 (3.1–4.7)     | 3.5 (2.8–4.2) | 3.2 (2.4–4.4)     | 3.6 (2.8–4.4)     | 3.2 (2.4–4.1) |
| LVEDV, mL         | 70.0 (44.4–113.7) | 59.6 (44.2–109.4) | 78.0 (41.0–108.7) | 89.3 (44.7–117.2) | 82.0 (46.9–126.5) | 66.7 (50.2–116.9) |
| LVESV, mL         | 55.2 (29.6–88.9)  | 54.9 (32.0–94.7)  | 51.4 (26.3–92.2) | 52.7 (23.7–95.5)  | 63.2 (27.1–97.1)  | 42.3 (26.3–81.1) |
| **Strain values**  |                   |                   |     |                   |                   |     |
| Global longitudinal strain, % | –2.8 (–5.4–0) | 0 (–4.8–0) | –4.7 (–8.2 to –1.1) | –5.8 (–9.4 to –3.5) | –6.1 (–8.9 to –4.0) | –8.8 (–11.5 to –6.0) |
| Longitudinal 3-chamber strain, % | –3.5 (–6.2–0) | 0 (–5.5–0) | –4.8 (–8.5–0) | –6.4 (–8.7 to –3.8) | –6.5 (–10.0 to –4.0) | –8.9 (–14.4 to –5.3) |
| Longitudinal 2-chamber strain, % | –3.5 (–6.0–0) | 0 (–3.8–0) | –4.5 (–8.7–0) | –5.7 (–10.0 to –4.4) | –6.2 (–8.6 to –4.3) | –8.7 (–11.5 to –6.5) |
| Longitudinal 4-chamber strain, % | 0 (–5.2–0) | 0 (–5.0–0) | –3.7 (–7.2–0) | –4.9 (–8.6 to –3.7) | –6.0 (–7.8 to –3.4) | –7.7 (–10.1 to –5.3) |
| **Left ventricular systolic function** |                   |                   |     |                   |                   |     |
| LVEF, %           |                   |                   |     |                   |                   |     |
| Linear method     | 14.1 (7.8–24.5)   | 12.1 (5.3–20.9)   | 22.9 (14.8–34.1) | 30.1 (21.3–46.9)   | 29.5 (16.2–46.5)   | 39.3 (25.5–54.2) |
| Biplane           | 16.8 (10.0–28.5)  | 13.1 (8.3–26.3)   | 28.2 (18.0–35.5) | 29.8 (18.6–40.9)   | 25.5 (17.7–46.2)   | 43.0 (28.4–54.8) |
| LVOT VTI, cm      | 4.7 (2.7–7.8)     | 3.5 (1.9–7.8)     | 7.7 (3.9–11.3)   | 9.7 (6.3–14.0)     | 9.4 (5.8–11.9)     | 10.9 (7.3–16.1) |
| LIMP, %           | 1.6 (1.1–2.3)     | 1.7 (1.2–2.3)     | 1.1 (0.8–1.6)    | 1.1 (0.8–1.5)      | 1.0 (0.8–1.5)      | 1.0 (0.6–1.4)   |
| s – medial mitral annulus, m/s | 6.2 (3.3–10.9) | 5.2 (2.4–9.3) | 10.9 (6.7–15.7) | 14.2 (10.6–23.8) | 13.4 (7.3–22.7) | 19.0 (11.6–26.7) |
| s – lateral mitral annulus, m/s | 0.03 (0.03–0.05) | 0.03 (0.03–0.04) | 0.04 (0.03–0.06) | 0.05 (0.04–0.07) | 0.05 (0.04–0.06) | 0.06 (0.04–0.07) |
| e’ – mean         | 11.9 (8.4–18.3)   | 11.1 (7.6–18.5)   | 11.1 (7.7–17.0)  | 11.1 (6.8–17.1)    | 13.0 (9.7–16.9)    | 11.7 (9.1–17.1) |
| **Haemodynamic parameters** |                   |                   |     |                   |                   |     |
| SBP, mmHg         | 92 (77–105)       | 100 (82–112)      | 85 (71–107)      | 108 (95–127)       | 108 (95–127)       | 104 (82–115) |
| DBP, mmHg         | 74 ± 17           | 71 ± 17           | 60 ± 16          | 69 ± 19            | 70 ± 19            | 60 ± 15       |
| MAP, mmHg         | 75 ± 18           | 78 ± 18           | 67 ± 20          | 81 ± 21            | 82 ± 21            | 73 ± 20 |
| Pulse pressure, mmHg | 17 (8–31)       | 25 (11–38)       | 24 (15–39)       | 43 (30–55)         | 39 (30–51)         | 42 (27–61) |
| HR, b.p.m         | 93 ± 19           | 91 ± 19           | 94 ± 19          | 91 ± 20            | 90 ± 20            | 90 ± 18 |
| Stroke volume, mL | 15 (8–25)         | 12 (6–22)         | 21 (13–34)       | 32 (18–43)         | 29 (17–39)         | 37 (23–49) |
| Cardiac output, L/min | 1.3 (0.8–2.2) | 1.0 (0.5–2.3) | 2.0 (1.2–3.1) | 2.6 (1.8–3.7) | 2.4 (1.7–3.2) | 3.1 (2.3–4.3) |
| Cardiac index, L/min/m² | 0.8 (0.5–1.3) | 0.5 (0.3–1.4) | 1.2 (0.7–1.7) | 1.5 (1.1–2.0) | 1.3 (1.0–1.8) | 1.8 (1.3–2.3) |
| Cardiac power output, Watts | 0.24 (0.11–0.38) | 0.17 (0.08–0.41) | 0.30 (0.17–0.49) | 0.46 (0.33–0.77) | 0.42 (0.27–0.64) | 0.47 (0.35–0.79) |

All data were presented as median with interquartile range or mean ± standard deviation unless specified. P values are provided for comparisons of echocardiographic parameters during the delayed phase.

1DBP, diastolic blood pressure; e', early diastolic tissue velocity at mitral annulus; E/A, early to late diastolic transmitral flow velocity; E/e', early diastolic transmitral flow velocity to e'; ECMO, extracorporeal membrane oxygenation; FS, fractional shortening; HR, heart rate; LIMP, left ventricular index of myocardial performance; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVIddd, left ventricular internal diameter in diastole; LVIdds, left ventricular internal diameter in systole; LVOT, left ventricular outflow tract; MAP, mean arterial pressure; s, peak systolic tissue velocity at mitral annulus; SBP, systolic blood pressure; TBF, target blood flow; VT1, velocity time integral.
| Target blood flow | P value for mean change between 100% and 50% | P value for mean change between 120% and 50% | Retrograde | P value for mean change between 50% and retrograde | P value for mean change between 120% and retrograde |
|------------------|---------------------------------------------|---------------------------------------------|------------|-----------------------------------------------|-----------------------------------------------|
| **Left ventricle size** |                                            |                                            |            |                                              |                                              |
| LVId, cm         | 0.50                                        | 0.42                                        | 4.4 (3.6–5.2) | 0.018                                         | 0.26                                          |
| LVIDs, cm        | <0.001                                      | <0.001                                      | 3.3 (2.5–4.1) | 0.64                                          | <0.001                                        |
| LVEDV, mL        | 0.10                                        | 0.092                                       | 77.9 (52.7–122.3) | 0.71                                         | 0.49                                          |
| LVESV, mL        | 0.043                                       | <0.001                                      | 47.5 (21.0–71.3) | 0.39                                          | 0.001                                        |
| **Strain values** |                                            |                                            |            |                                              |                                              |
| Global longitudinal strain, % | <0.001                                      | <0.001                                      | −10.7 (−13.6 to −7.0) | 0.003                                        | <0.001                                        |
| Longitudinal 3-chamber strain, % | <0.001                                      | <0.001                                      | −10.3 (−13.3 to −6.2) | 0.42                                         | <0.001                                        |
| Longitudinal 2-chamber strain, % | <0.001                                      | <0.001                                      | −10.0 (−14.3 to −7.5) | 0.14                                         | <0.001                                        |
| Longitudinal 4-chamber strain, % | <0.001                                      | <0.001                                      | −9.9 (−12.8 to −7.0) | <0.001                                      | <0.001                                        |
| **Left ventricular systolic function** |                                            |                                            |            |                                              |                                              |
| LVEF, %          | Linear method                              | <0.001                                      | 45.3 (37.3–62.2) | <0.001                                      | <0.001                                        |
|                  | Biplane                                     | <0.001                                      | 49.9 (32.7–60.8) | 0.001                                        | <0.001                                        |
|                  | LVOT VTI, cm                                | <0.001                                      | 15.6 (12.8–19.9) | <0.001                                      | <0.001                                        |
| LIMP, %          | 0.19                                        | 0.26                                        | 0.9 (0.7–1.1) | 0.85                                          | 0.26                                          |
| FS, %            | <0.001                                      | 22.6 (17.8–30.1) | <0.001                                      | <0.001                                        |
| s – medial mitral annulus, m/s | 0.003                                       | 0.005                                       | 0.07 (0.05–0.09) | 0.009                                        | <0.001                                        |
| s – lateral mitral annulus, m/s | <0.001                                      | <0.001                                      | 0.10 (0.06–0.12) | <0.001                                      | <0.001                                        |
| **Left ventricular diastolic function** |                                            |                                            |            |                                              |                                              |
| E/A              | 0.14                                        | 0.48                                        | 1.0 (0.8–1.3) | 0.25                                          | 0.06                                          |
| e’ – medial, m/s | <0.001                                      | 0.004                                       | 0.07 (0.05–0.08) | 0.017                                        | <0.001                                        |
| e’ – lateral, m/s | 0.50                                        | 0.060                                       | 0.09 (0.06–0.10) | 0.001                                        | 0.003                                        |
| E/e’ – mean      | 0.20                                        | 0.44                                        | 10.7 (8.4–14.6) | 0.39                                          | 0.18                                          |
| **Haemodynamic parameters** |                                            |                                            |            |                                              |                                              |
| SBP, mmHg        | <0.001                                      | 0.002                                       | 104 (91–127) | 0.75                                          | 0.046                                        |
| DBP, mmHg        | <0.001                                      | <0.001                                      | 56 ± 13 | 0.007                                        | <0.001                                        |
| MAP, mmHg        | <0.001                                      | <0.001                                      | 69 ± 21 | 0.038                                        | <0.001                                        |
| Pulse pressure, mmHg | 0.57                                        | 0.07                                        | 52 (40–63) | 0.15                                          | 0.006                                        |
| HR, b.p.m.       | 0.82                                        | 0.95                                        | 96 ± 18 | 0.002                                        | <0.001                                        |
| Stroke volume, mL | <0.001                                      | <0.001                                      | 54 (41–63) | <0.001                                      | <0.001                                        |
| Cardiac output, L/min | <0.001                                      | <0.001                                      | 4.5 (3.6–6.4) | <0.001                                      | <0.001                                        |
| Cardiac index, L/min/m² | <0.001                                      | <0.001                                      | 2.4 (2.0–3.5) | <0.001                                      | <0.001                                        |
| Cardiac power output, Watts | 0.027                                       | <0.001                                      | 0.69 (0.50–1.15) | 0.60                                          | 0.034                                        |

All data were presented as median with interquartile range or mean ± standard deviation unless specified. P values are provided for comparisons of echocardiographic parameters during the delayed phase.

'*E/A ratio only measured if patient was in sinus rhythm.'

DBP, diastolic blood pressure; e', early diastolic tissue velocity at mitral annulus; E/A, early to late diastolic transmitral flow velocity; E/e', early diastolic transmitral flow velocity to e'; ECMO, extracorporeal membrane oxygenation; FS, fractional shortening; HR, heart rate; LIMP, left ventricular index of myocardial performance; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MAP, mean arterial pressure; s, peak systolic tissue velocity at mitral annulus; SBP, systolic blood pressure; TBF, target blood flow; VTI, velocity time integral.
VTI [10.9 (7.3–16.1) vs. 15.6 (12.8–19.9) cm, \( P < 0.001 \)] and \( s' \) measured at lateral mitral annulus [0.07 (0.05–0.08) vs. 0.10 (0.06–0.12) m/s, \( P < 0.001 \)]. Detailed plots of echocardiographic parameters of LV systolic function against ECMO blood flow are shown in Supporting Information, Figure S1.

Heart–extracorporeal membrane oxygenation interaction at different phases of myocardial injury

Left ventricular systolic function was significantly more sensitive to the change in ECMO blood flow during the acute phase compared with the delayed phase. The percentage change in LV systolic function between 50% and 120% TBF measured by LV GLS were 72.7 (26.8–100.0)% in the acute phase and 22.5 (14.9–43.8)% in the delayed phase (\( P < 0.001 \)). Similar differences were observed in the percentage change in LVEF measured by biplane method (43.0 (29.1–56.8)% vs. 22.8 (9.2–42.2)%, \( P = 0.012 \)) and LVOT VTI (45.8 (18.6–58.7)% vs. 24.2 (12.6–34.0)%, \( P = 0.001 \)) during acute and delayed phases, respectively (Figure 2). There were no significant differences in the percentage change in \( s' \) measured at the medial and lateral mitral annulus. The sensitivity of haemodynamic parameters was similarly more significant with greater percentage changes in MAP, SV, CI, and CPO during the acute compared with delayed phase. Details of the sensitivity of echocardiographic and haemodynamic parameters to ECMO blood flow during the acute and delayed phases are presented in Table 3.

Sensitivity analyses

In a subgroup analysis including only 28 (60.9%) patients who were considered potentially weanable from ECMO and proceeded to PCrTO, the sensitivity of LV systolic function at different stages of myocardial dysfunction was significantly different. The percentage change in LV systolic function between 50% and 120% TBF measured by LV GLS were 45.3 ± 45.4% in the acute phase and 27.3 ± 19.3% in the delayed phase (\( P = 0.016 \)). Similar differences were observed in the percentage change in LVEF [44.0 ± 21.9 vs. 27.2 ± 17.1%, \( P = 0.002 \)] and LVOT VTI [39.0 ± 26.4 vs. 18.3 ± 17.1 cm, \( P = 0.002 \)]. Details of the sensitivity of echocardiographic and haemodynamic parameters to ECMO blood flow during the acute and delayed phases in this subgroup of patients are shown in Supporting Information, Table S4.
Table 3  Sensitivity of echocardiographic and haemodynamic parameters to ECMO blood flow during the acute and delayed phases

| Parameter                      | Percentage differences between 50% and 100% TBF | Percentage differences between 50% and 120% TBF |
|--------------------------------|-----------------------------------------------|-----------------------------------------------|
|                                | Acute phase N = 45                           | Acute phase N = 500                            |
|                                | Delayed phase N = 36                          | Delayed phase N = 36                            |
|                                | P-value                                       | P-value                                       |
| LVIdd                          | –3.4 (–12.7 to 2.2)                           | –0.7 (–8.8 to 7.1)                             |
| LVIDs                          | –6.4 (–18.3 to –0.2)                          | –6.3 (–13.0 to –1.3)                           |
| LVEDV                          | –0.8 (–26.0 to 15.3)                          | –7.0 (–33.1 to 14.6)                           |
| LVESV                          | –7.4 (–46.5 to 5.3)                           | –20.1 (–60.4 to 4.3)                           |
| Strain values                  |                                               |                                               |
| – Global longitudinal strain   | 31.1 (13.8–58.2)                              | 72.7 (26.8–100.0)                              |
| – Longitudinal 3 chamber strain| 30.8 (3.6–53.1)                               | 43.0 (12.5–100.0)                              |
| – Longitudinal 2 chamber strain| 26.8 (5.1–100.0)                              | 100.0 (43.5–100.0)                             |
| – Longitudinal 4 chamber strain| 26.9 (3.8 to 100.0)                           | 60.7 (8.6–100.0)                               |
| Left ventricular systolic function | LVEF                                       |                                               |
| – Linear method                | 29.6 (19.4–52.1)                              | 45.5 (28.2–57.9)                               |
| – Biplane                      | 30.4 (10.3–48.1)                              | 43.0 (29.1–56.8)                               |
| – LVOT VTI                     | 31.0 (16.9–46.9)                              | 45.8 (18.6–58.7)                               |
| – FS                           | 23.1 (5.0–35.0)                               | 26.2 (19.3–39.1)                               |
| – s − medial mitral annulus    | 10.7 ± 30.7                                   | 14.6 ± 30.3                                   |
| – s − lateral mitral annulus   | 12.1 (0–29.2)                                 | 18.3 (0–33.3)                                 |
| Left ventricular diastolic function | E/A,           |                                               |
| – early to late diastolic      | 4.3 (–6.4 to 35.4)                            | 14.7 (–17.1 to 27.7)                           |
| – early to early diastolic     | 0 (0–33.3)                                    | 0 (0–33.3)                                    |
| – early to late diastolic      | 0 (–25.0 to 26.8)                             | 22.5 (0–33.3)                                 |
| Haemodynamic parameters        |                                               |                                               |
| – SBP                          | –9.0 (–22.1 to 4.2)                           | –9.0 (–31.3 to 0)                              |
| – DBP                          | –21.3 (–35.0 to –3.6)                         | –17.2 (–34.0 to 1.8)                           |
| – MAP                          | –13.2 (–27.5 to –1.6)                         | –15.6 (–32.4 to 3.3)                           |
| – Pulse pressure               | 20.2 (5.1–44.4)                               | 8.1 (21.4 to 37.3)                             |
| – HR                           | 1.1 (–4.9 to 5.3)                             | 2.5 (–2.2 to 7.3)                              |
| – Stroke volume                | 28.7 ± 29.8                                   | 430 ± 29.9                                    |
| – Cardiac output               | 30.7 (16.4–47.2)                              | 48.3 (28.0–61.9)                               |
| – Cardiac index                | 30.7 (16.4–47.2)                              | 48.3 (28.0–61.9)                               |
| – Cardiac power output         | 27.1 (8.9–40.6)                               | 47.2 (9.9–58.9)                                |

All data were presented as median with interquartile range or mean ± standard deviation unless specified.

DBP, diastolic blood pressure; e, early diastolic tissue velocity at mitral annulus; E/A, early to late diastolic transmitral flow velocity; E/e0, early diastolic transmitral flow velocity to e0; ECMO, extracorporeal membrane oxygenation; FS, fractional shortening; HR, heart rate; LIMP, left ventricular index of myocardial performance; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVId2, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; LVOT, left ventricular outflow tract; MAP, mean arterial pressure; s, peak systolic tissue velocity at mitral annulus; SBP, systolic blood pressure; VTI, velocity time integral.
In the 25 (54.3%) patients with ischaemic cardiomyopathy, LV systolic function was similarly more sensitive to ECMO flow during the acute phase compared with the delayed phase (LV GLS: 59.3 ± 44.1% vs. 30.3 ± 24.4%, \( P = 0.019 \); LVEF: 45.9 ± 23.1% vs. 30.2 ± 20.8%, \( P = 0.09 \); LVOT VTI: 45.5 ± 26.0% vs. 21.8 ± 20.1%, \( P = 0.006 \), respectively) (Supporting Information, Table S5).

**Exploratory analyses**

We examined the performance of two clinical models to predict ECMO weaning success. The widely accepted echocardiographic criteria in Model 1, which included LVEF >20%, aortic VTI ≥ 10 cm and s at lateral mitral annulus ≥ 6 cm/s, had a better discriminatory value compared with Model 2, which was the SAVE score, in predicting potentially weanable patients (AUROC 0.86, 95% CI 0.73–0.98 vs. 0.58, 95% CI 0.38–0.78) as well as eventual ECMO decannulation (AUROC 0.68, 95% CI 0.51–0.85 vs. 0.54, 95% CI 0.36–0.71), respectively. Hosmer–Lemeshow tests showed that all models were well-calibrated with \( P > 0.05 \). Comparisons of AUROC are provided in Figure 3.

**Discussion**

In this prospective observational study of patients on V-A ECMO, we examined the relationship between LV systolic function and ECMO blood flow during various phases of acute myocardial injury. An increased ECMO blood flow was associated with a significantly decreased LV systolic function during the delayed phase of ECMO support. We demonstrated for the first time that this sensitivity in LV systolic function to the afterload effects of ECMO was significantly greater during the acute phase compared with the delayed phase of myocardial dysfunction. These findings highlight an evolution of the heart–ECMO interaction over the course of illness, which adds to our current understanding of ECMO physiology, and should be incorporated to guide flow titration, medication management, and the utilization of echocardiographic assessment to optimize outcomes after support with V-A ECMO.

The sensitivity of LV systolic function to ECMO flow can be attributed to changes in venous return and LV afterload, and the overall effect on LV systolic function depends on the balance between the titrated ECMO flow and the performance of the myocardium. When the ECMO blood flow is decreased, more blood passes through the native cardio-
pulmonary circulation, challenging the ability of the right and left ventricles to handle the increased preload. Meanwhile, the afterload effect of peripheral V-A ECMO have been demonstrated using echocardiographic parameters in clinical studies, and different strategies to counteract LV distension during ECMO support have evolved. The optimal ECMO flow needs to be titrated to the most favourable preload on the Frank–Starling curve while limiting unnecessary afterload to the acutely-impaired LV. While most strategies have focused on the acute stage of myocardial injury, we now provide the evidence that LV systolic function remains sensitive to the ECMO blood flow even upon the delayed or recovery stage. The finding that different metrics of LV systolic function, including commonly used parameters such as LVEF, are in fact partial derivatives of the titrated ECMO flow, suggests that static measures of LV function during a weaning study may not provide adequate information about myocardial function and hence should be interpreted with caution. For instance, despite widespread adoption of conventional echocardiographic cut-offs for the prediction of ECMO weaning success, findings from a recent paper showed that dynamic changes in lateral e' and tricuspid annular s' velocities were possibly better clinical predictors, highlighting the need to identify parameters that accurately characterize dynamic changes in LV function during peripheral V-A ECMO.

Our data provided novel echocardiographic evidence that detailed the change in heart–ECMO interaction over the duration of mechanical circulatory support, where LV systolic function was more sensitive to ECMO flow titration, with significantly greater percentage increases in LV GLS, LVEF, and LVOT VTI at lower ECMO blood flows, during the acute phase of myocardial injury compared with the delayed phase. This can be explained from a mechanical point of view, and previous models have shown that the effect of afterload on ejection fraction, simulated by titration of systemic vascular resistance, was more pronounced in the impaired left ventricle compared with a normal-functioning heart. LV remodeling after myocardial injury is a complex and dynamic process, and during the late phase (beyond 72 h) involves progressive LV dilatation and mural hypertrophy to attenuate the effect of afterload and subsequent wall stress, further lending a pathophysiological explanation of the differential afterload sensitivity observed in our cohort. The amplified afterload effect on depressing LV systolic function in the acute phase of ECMO implantation deserves special consideration during setting a ECMO target blood flow after implantation, for which a knowledge gap exists and the optimization is often left to individual clinical discretion. Higher ECMO flows aimed to maintain adequate systemic perfusion to support end-organ function must be balanced against the risk of LV distension and its complications. Apart from LV function, the optimal ECMO blood flow demands a fine balance between effects on microvascular and macrovascular parameters of tissue ischaemia, cerebral blood flow, haemolysis and platelet destruction, and centrifugal pump efficacy.

In our exploratory analysis, echocardiographic parameters had satisfactory performance in predicting potentially weanable patients with AUROC 0.86, which however drops to 0.68 for predicting patients who were ultimately decannulated from ECMO. This lends indirect evidence that recovery after V-A ECMO support requires a successful chain of events that extend beyond myocardial recovery. The patient outcome depends on the totality of concurrent organ failure, neurological insult, and quality of life considerations.

This study was limited by its single-centre design. However, all bedside echocardiographic examinations and subsequent analyses were performed by one of three experienced ECMO providers, resulting in high internal data consistency. The modest cohort size obligated pooling analyses of different cardiac pathologies, and it remains possible that certain disease conditions do not share similar evolution of the heart–ECMO interaction. Third, systemic vascular resistance was not maintained at stable levels by dose titration of vasopressors during ECMO flow changes, lending potential interaction with the LV systolic function. Finally, the haemodynamic estimates were not systematically validated by other invasive quantification methods such as the pulmonary arterial catheter.

To conclude, the afterload effects of ECMO blood flow on LV systolic function are demonstrable in both the acute and delayed phases of myocardial injury, with heightened sensitivity experienced during the early stage of mechanical circulatory support. These data suggest that a comprehensive assessment of myocardial function with judicious interpretation of static measures during weaning studies is necessary.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.
Table S1. Two-dimensional echocardiographic measurements and normal values.

Table S2. Clinical data of patients who had ECMO-CPR.

Table S3. Clinical outcomes of the study population.

Table S4. Sensitivity of Echocardiographic and Hemodynamic Parameters to ECMO Blood Flow during the Acute and Delayed Phases in Weanable Patients.

Table S5. Sensitivity of Echocardiographic and Hemodynamic Parameters to ECMO Blood Flow during the Acute and Delayed Phases in Patients with Ischemic Cardiomyopathy.

Figure S1. Spaghetti plots for echocardiographic parameters of left ventricular systolic function against ECMO blood flow.

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