ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 1637–1642
Published online 25 February 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13253

CASE REPORT

Simple equations to predict the effects of veno-venous ECMO in decompensated Eisenmenger syndrome

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Abstract

Adult patients with uncorrected congenital heart diseases and chronic intracardiac shunt may develop Eisenmenger syndrome (ES) due to progressive increase of pulmonary vascular resistance, with significant morbidity and mortality. Acute decompensation of ES in conditions promoting a further increase of pulmonary vascular resistance, such as pulmonary embolism or pneumonia, can precipitate major arterial hypoxia and death. In such conditions, increasing systemic oxygenation with veno-venous extracorporeal membrane oxygenation (VV-ECMO) could be life-saving, serving as a bridge to treat a potential reversible cause for the decompensation, or to urgent lung transplantation. Anticipating the effects of VV-ECMO in this setting could ease the clinical decision to initiate such therapeutic strategy. Here, we present a series of equations to accurately predict the effects of VV-ECMO on arterial oxygenation in ES and illustrate this point by a case of ES decompensation with refractory hypoxaemia consecutive to an acute respiratory failure due to viral pneumonia.

Keywords Extracorporeal membrane oxygenation; ECMO; Veno-venous; Hypoxaemia; Eisenmenger syndrome

Received: 19 October 2020; Revised: 15 January 2021; Accepted: 26 January 2021
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Introduction

In case of refractory hypoxaemia due to intrapulmonary shunt (e.g. severe acute respiratory distress syndrome), veno-venous extracorporeal membrane oxygenation (VV-ECMO) is an option when other strategies have failed.[1] VV-ECMO improves systemic oxygenation by rising venous oxygen content,[2] mitigating the consequences of venous admixture.[3] Physiologically, the same concept could apply to cardiac right-to-left shunt, such as in Eisenmenger syndrome (ES). The latter develops in patients with unrepaired congenital heart disease and chronic left-to-right shunt, with progressive increase in pulmonary vascular resistance and progression towards a predominant right-to-left shunt.[4] Although not classically considered in ES, VV-ECMO could be life-saving during acute decompensation as a bridge to recovery, surgery, or transplantation.[5–7] Anticipating the effects of VV-ECMO in decompensated ES could ease the decision to initiate ECMO. We present simple equations that can be used for this purpose and illustrate our point by a case presentation. An Excel fill-in spreadsheet (Supporting Information, *Table S1*) is provided with this report for solving all the relevant equations.

1. Calculation of the total (cardiac plus intrapulmonary) shunt fraction ($F_{shunt\text{-}Tot}$)

$$F_{shunt\text{-}Tot} = Q_s/Q_t = (C_cO_2 - C_aO_2)/(C_cO_2 - C_vO_2) \quad (1)$$

where Q_s: shunt flow; Q_t: systemic cardiac output; C_cO_2: pulmonary capillary O_2 content; C_aO_2: systemic arterial O_2 content; and C_vO_2: mixed venous O_2 content. The content equation is as follows: (1.39 × [haemoglobin] × SO_2) + (0.031 × PO_2).

2. Calculation of right ventricular oxygen content under VV-ECMO ($C_{RV}O_2$)

$$C_{RV}O_2 = [(Q_{EC}/Q_t) \times C_{EC}O_2] + [[1 - (Q_{EC}/Q_t)] \times C_{cv}O_2] \quad (2)$$

where $C_{EC}O_2$: O_2 content in blood exiting the oxygenator; $C_{cv}O_2$: central O_2 content in venous blood bypassing the oxygenator; Q_{EC}: ECMO flow (assuming no recirculation); and Q_t: systemic venous return (= systemic cardiac output).

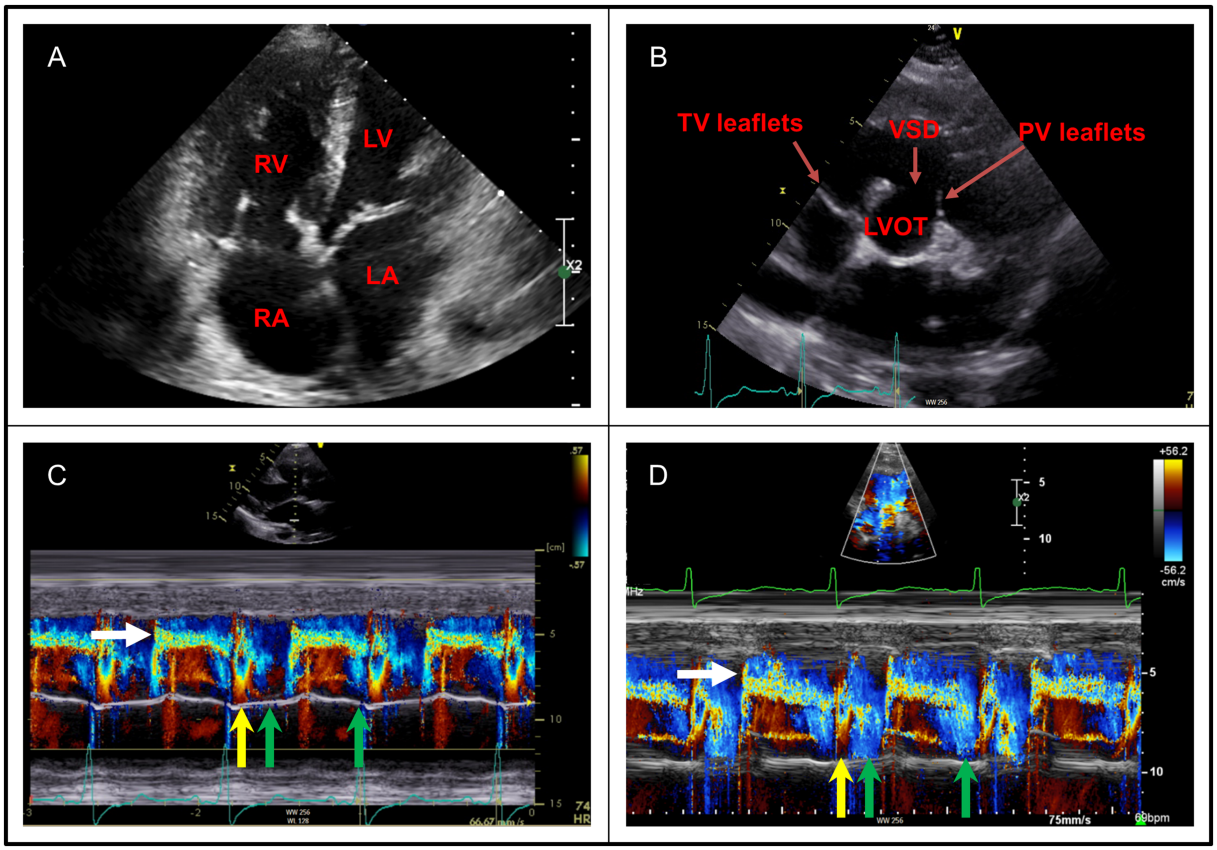
3. Calculation of systemic arterial oxygen content under VV-ECMO ($C_aO_{2\text{-ECMO}}$)

$$C_aO_{2\text{-ECMO}} = (F_{shunt\text{-}Tot} \times C_{RV}O_2) + [(1 - F_{shunt\text{-}Tot}) \times C_cO_2] \quad (3)$$

$C_aO_{2\text{-ECMO}}$ is the sum of O_2 content in shunted blood and in non-shunted blood exiting the lung. We assume no alveolo-capillary diffusion impairment and equilibrium between alveolar (P_AO_2) and capillary O_2 pressures (P_cO_2). We also consider that the cardiac shunt accounts for the total shunt, because we cannot separate intracardiac from intrapulmonary shunt, and the contribution of intrapulmonary shunt to total shunt is limited in conditions of massive cardiac right-to-left shunt. We can still introduce a correction factor, assuming a certain percentage of intrapulmonary shunt ($F_{shunt\text{-}Lung}$), and determine the O_2 content exiting the lungs (left atrium, $C_{LA}O_2$, Equation 4). The corrected fraction of cardiac shunt ($F_{shunt\text{-}Heart} = F_{shunt\text{-}Tot} - F_{shunt\text{-}Lung}$) should be used to calculate $C_aO_{2\text{-ECMO}}$ (Equation 5).

$$C_{LA}O_2 = C_cO_2 - [F_{shunt\text{-}Lung} \times (C_cO_2 - C_{RV}O_2)] \quad (4)$$

Figure 1 Echocardiographic investigations. (A) Four-chamber view showing a dilated, hypertrophied right ventricle and bi-atrial dilation. (B) Parasternal short-axis view at the level of the left ventricular outflow tract (LVOT) showing the doubly committed ventricular septal defect (VSD). (C) Colour Doppler M-mode performed during a routine visit before current hospitalization, showing a bidirectional shunt with a left-to-right shunt in early and mid-systole (yellow arrow) and a right-to-left shunt in late systole and in diastole (green arrows), as well as a pulmonary insufficiency (white arrow). (D) Colour Doppler M-mode performed on admission, showing an increase in the duration of the right-to-left shunt (green arrows), relative to the left-to-right shunt (yellow arrow). LA, left atrium; LV, left ventricle; PV, pulmonary valve; RA, right atrium; RV, right ventricle; TV, tricuspid valve.



DOI: 10.1002/ehf2.13253

$$C_aO_{2\text{-ECMO}} = (F_{\text{shunt-Heart}} \times C_{RV}O_2) + [(1 - F_{\text{shunt-Heart}}) \times C_{LA}O_2] \quad (5)$$

4. Calculation of predicted S_aO_2 and P_aO_2 under VV-ECMO

$$S_aO_2 = [C_aO_2 - (0.031 \times P_aO_2)]/(1.39 \times Hb) \quad (6)$$

$$P_aO_2 = \sqrt[3]{\frac{1}{2}\left(-y_N + \sqrt{{y_N}^2 - h^2}\right)} + \sqrt[3]{\frac{1}{2}\left(-y_N - \sqrt{{y_N}^2 - h^2}\right)} \quad (7)$$

where

$$h^2 = -500\,000$$
$$y_N = -23\,400s/(1 - s)$$

Hb: haemoglobin concentration (g/L).

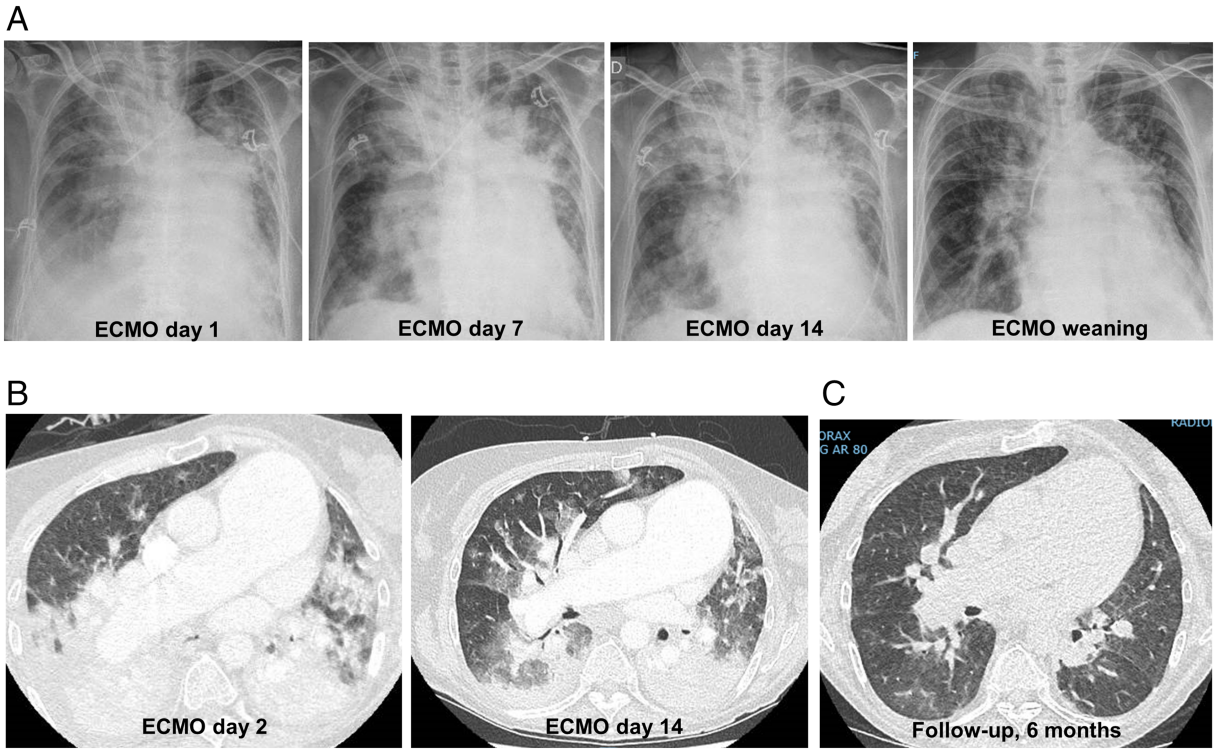
We can use here a P_aO_2 of 70 mmHg to calculate dissolved oxygen (0.031 × P_aO_2, which is negligible). Equation 7 is the inverse Severinghaus equation, which yields S_aO_2 (s) from P_aO_2.[8]

These equations help predict the effect of VV-ECMO on arterial oxygenation in patients with significant cardiac right-to-left shunt. The following case illustrates this concept.

Case Report

The patient was a 61-year-old female, known for partial ES due to a non-corrected doubly committed ventricular septal defect with bidirectional shunt and severe pulmonary arterial hypertension. She was treated with macitentan (10 mg/day) and oxygen (2 L/min). She was admitted after a 3 day history of increasing dyspnoea and low O_2 saturation (70–80%) despite increasing supplemental O_2. Electrocardiogram showed new onset atrial fibrillation, chest X-Ray displayed a right lower lobe infiltrate, and a transthoracic echocardiography showed severe right-to-left shunt. *Figure 1* shows echocardiographic morphological characteristics of the congenital pathology of the patient (*Figure 1A* and *1B*), as well as the baseline shunt analysis with colour Doppler M-mode during routine examination (*Figure 1C*), and its worsening on admission (*Figure 1D*). Right heart catheterization was not performed at this acute phase.

Figure 2 Radiological investigations. (A) Evolution of bilateral pneumonia on sequential chest X-rays obtained under veno-venous extracorporeal membrane oxygenation (VV-ECMO) at Day 1, Day 7, Day 14, and 1 day after VV-ECMO weaning. (B) Contrast-enhanced computed tomography scans of the chest showing massive bilateral pneumonia and severe dilation of the pulmonary artery trunk at Day 2 and Day 14 of VV-ECMO support. (C) Native computed tomography scan of the chest obtained at 6 months of follow-up showing resolution of the bilateral pneumonia.



DOI: 10.1002/ehf2.13253

Table 1 Equations used to predict arterial oxygen status following VV-ECMO initiation under conditions of intracardiac right-to-left shunt

Basal condition (before ECMO)			
Parameter	Measured	Calculated	Formula
P_VO_2	30		
P_aO_2	37		
P_aCO_2	40		
S_aO_2	0.72		
S_VO_2	0.56		
Hb	151		
F_IO_2	1		
P_B	710		
PH_2O	47		
P_AO_2		613	$P_AO_2 = [(P_B - PH_2O) \times F_IO_2] - (P_aCO_2/RQ)$
P_CO_2		613	$P_CO_2 = P_AO_2$
S_CO_2		1	$S_CO_2 = 1$
C_CO_2		228.3	$C_CO_2 = (Hb \times S_CO_2 \times 1.39) + (P_CO_2 \times 0.031)$
C_aO_2		152.2	$C_aO_2 = (Hb \times S_aO_2 \times 1.39) + (P_aO_2 \times 0.031)$
C_VO_2		118.4	$C_VO_2 = (Hb \times S_VO_2 \times 1.39) + (P_VO_2 \times 0.031)$
$F_{shunt\text{-}Tot}$		0.69	$F_{shunt\text{-}Tot} = (C_CO_2 - C_aO_2)/(C_CO_2 - C_VO_2)$
Under VV-ECMO			
Parameter	Measured	Calculated	Formula
F_SO_2	0.8		
Q_{EC}	4.5		
$P_{EC}O_2$	400		
$S_{EC}O_2$	1		
Q_T	7		
$C_{EC}O_2$		222.3	$C_{EC}O_2 = (Hb \times S_{EC}O_2 \times 1.39) + (P_{EC}O_2 \times 0.031)$
$C_{RV}O_2$		185.2	$C_{RV}O_2 = [(Q_{EC}/Q_T) \times C_{EC}O_2] + [(1 - (Q_{EC}/Q_T)) \times C_{cv}O_2]$
$C_aO_{2\ ECMO}$		198.5	$C_aO_{2\ ECMO} = (F_{shunt\text{-}Tot} \times C_{RV}O_2) + [(1 - F_{shunt\text{-}Tot}) \times C_CO_2]$
$S_aO_{2\ ECMO}$	0.93 (actual)	0.94 (predicted)	$S_aO_{2\ ECMO} = [(C_aO_{2\ ECMO} - 0.031 \times P_aO_2)]/(Hb \times 1.39)$
P_aO_2	67 (actual)	69 (predicted)	Inverse Severinghaus equation
Under VV-ECMO: intrapulmonary shunt 10% ($F_{shunt\text{-}Lung}$: estimated fraction of $F_{shunt\text{-}Tot}$)			
Parameter	Measured	Calculated	Formula
Intracardiac shunt ($F_{shunt\text{-}Heart}$)		0.59	$F_{shunt\text{-}Heart} = F_{shunt\text{-}Tot} - F_{shunt\text{-}Lung}$
$C_{LA}O_{2\ ECMO}$		224	$C_{LA}O_2 = C_CO_2 - [F_{shunt\text{-}Lung} \times (C_CO_2 - C_{RV}O_2)]$
$C_aO_{2\ ECMO}$		201	$C_aO_2 = (F_{shunt\text{-}Heart} \times C_{RV}O_2) + [(1 - F_{shunt\text{-}Heart}) \times C_{LA}O_2]$
$S_aO_{2\ ECMO}$	0.93 (actual)	0.95	$S_aO_{2\ ECMO} = [(C_aO_{2\ ECMO} - 0.031 \times P_aO_2)]/(Hb \times 1.39)$
P_aO_2	67 (actual)	74	$P_aO_{2\ ECMO}$ = inverse Severinghaus equation
Under VV-ECMO: intrapulmonary shunt 20% ($F_{shunt\text{-}Lung}$: estimated fraction of $F_{shunt\text{-}Tot}$)			
Parameter	Measured	Calculated	Formula
Intracardiac shunt ($F_{shunt\text{-}Heart}$)		0.49	$F_{shunt\text{-}Heart} = F_{shunt\text{-}Tot} - F_{shunt\text{-}Lung}$
$C_{LA}O_{2\ ECMO}$		219.7	$C_{LA}O_2 = C_CO_2 - [F_{shunt\text{-}Lung} \times (C_CO_2 - C_{RV}O_2)]$
$C_aO_{2\ ECMO}$		202.7	$C_aO_2 = (F_{shunt\text{-}Heart} \times C_{RV}O_2) + [(1 - F_{shunt\text{-}Heart}) \times C_{LA}O_2]$
$S_aO_{2\ ECMO}$	0.93 (actual)	0.96	$S_aO_{2\ ECMO} = [(C_aO_{2\ ECMO} - 0.031 \times P_aO_2)]/(Hb \times 1.39)$
P_aO_2	67 (actual)	79	$P_aO_{2\ ECMO}$ = inverse Severinghaus equation

Table 1 (continued)

Under VV-ECMO: intrapulmonary shunt 30% ($F_{shunt\text{-}Lung}$: estimated fraction of $F_{shunt\text{-}Tot}$)			
Parameter	Measured	Calculated	Formula
Intracardiac shunt ($F_{shunt\text{-}Heart}$)		0.39	$F_{shunt\text{-}Heart} = F_{shunt\text{-}Tot} - F_{shunt\text{-}Lung}$
$C_{LA}O_2$ ECMO		215.4	$C_{LA}O_2 = C_CO_2 - [F_{shunt\text{-}Lung} \times (C_CO_2 - C_{RV}O_2)]$
C_aO_2 ECMO		203.5	$C_aO_2 = (F_{shunt\text{-}Heart} \times C_{RV}O_2) + [(1 - F_{shunt\text{-}Heart}) \times C_{LA}O_2]$
S_aO_2 ECMO	0.93 (actual)	0.96	S_aO_2 ECMO = $[(C_aO_2$ ECMO $- 0.031 \times P_aO_2)]/(Hb \times 1.39)$
P_aO_2	67 (actual)	81	P_aO_2 ECMO = inverse Severinghaus equation

C_aO_2 (mL/L), arterial oxygen content; C_aO_2 ECMO (mL/L), arterial oxygen content under ECMO support; C_CO_2 (mL/L), pulmonary capillary oxygen content; $C_{CV}O_2$ (mL/L), central O_2 content in venous blood bypassing the oxygenator; $C_{EC}O_2$ (mL/L), ECMO outflow oxygen content; $C_{LA}O_2$ECMO (mL/L), left atrium oxygen content under ECMO; $C_{RV}O_2$ (mL/L), right ventricular oxygen content; C_VO_2 (mL/L), mixed venous oxygen content; F_IO_2, inspired fraction of oxygen; $F_{shunt\text{-}Heart}$, intracardiac shunt fraction; $F_{shunt\text{-}Lung}$, intrapulmonary shunt fraction; $F_{shunt\text{-}Tot}$, total shunt fraction (intracardiac + intrapulmonary); F_sO_2, fraction of sweep gas oxygen delivered by ECMO; Hb (g/L), haemoglobin concentration; P_aCO_2 (mmHg), arterial partial pressure of carbon dioxide; P_AO_2 (mmHg), alveolar partial pressure of oxygen; P_aO_2 (mmHg), arterial partial pressure of oxygen; P_B (mmHg), barometric pressure; P_cO_2 (mmHg), pulmonary capillary partial pressure of oxygen; $P_{EC}O_2$ (mmHg), ECMO outflow partial pressure of oxygen; PH_2O (mmHg), partial pressure of water vapour; P_VO_2 (mmHg), central venous partial pressure of oxygen; Q_{EC} (L/min), ECMO flow; Q_T (L/min), cardiac output; RQ, respiratory quotient (default value assumed to be 0.8); S_aO_2 ECMO, arterial oxygen saturation under ECMO support; S_aO_2, arterial oxygen saturation; S_cO_2, pulmonary capillary oxygen saturation; $S_{EC}O_2$, ECMO outflow oxygen saturation; S_VO_2, mixed venous oxygen saturation; VV-ECMO, veno-venous extracorporeal membrane oxygenation.

This table presents measured and calculated values at baseline, in a patient with massive intracardiac right-to-left shunt due to decompensated Eisenmenger syndrome. Knowing ECMO flow, cardiac output and calculated shunt fraction allows to accurately predict the arterial oxygen saturation after VV-ECMO initiation. The calculated predicted P_aO_2 value is obtained using the inverse solution of the Severinghaus equation (see text). The bottom of the table indicates the predicted values of arterial oxygenation taking into consideration intrapulmonary shunt contributing 10%, 20%, or 30% of total shunt.

Sinus rhythm was restored by amiodarone, and antibiotic therapy was initiated with piperacillin–tazobactam. The clinical condition worsened, with refractory hypoxaemia in spite of 100% O_2 by high nasal flow (P_aO_2/F_iO_2 O_2: 35–50 mmHg). A nasopharyngeal smear was positive for rhinovirus, and thoracic computed tomography scan revealed bilateral posterior condensations (*Figure 2*). A diagnosis of acute hypoxaemic respiratory failure due to viral pneumonia with worsening pulmonary hypertension and decompensated ES was made. Pulmonary vasodilators (intravenous iloprost and oral sildenafil and macitentan) were introduced to reduce pulmonary vascular resistance, together with intravenous diuretics (furosemide) without any improvement. Mean systemic arterial blood pressure was maintained at values between 70 and 80 mmHg, using intravenous vasopressin (0.5–1.5 U/H) and norepinephrine (0.1–0.3 μg/kg/min). Intubation and mechanical ventilation were not considered, due to the risks of right ventricular failure and increased right-to-left shunting. Owing to the potential for partial reversibility (viral pneumonia), we opted for VV-ECMO to improve systemic oxygenation.

The calculated shunt was 0.69 (*Table 1*), using central venous O_2 saturation obtained from the right atrium as a surrogate of mixed venous O_2 saturation.[9] Cardiac output (Q_T) was not directly measured but was estimated using the Krovetz–Goldbloom equation of O_2 consumption[10]: VO_2 = $[138.1 - (17.04 * \ln_{(age)})] + (0.378 \times HR)$, and the arteriovenous O_2 difference, $C_{(a\text{-}v)}O_2$ ($Q_T = VO_2/C_{(a\text{-}v)}O_2$). Estimated Q_T was 7.1 L/min, which was close to the latest Q_T determined by cardiac catheterization at steady state, several weeks before current hospitalization (8 L/min).

Using this value of Q_T, we predicted that ECMO flow of 4.5 L/min with a delivered sweep gas O_2 fraction of 0.8–1.0 (producing a post-membrane PO_2 of 300–500 mmHg[11]) would result in a S_aO_2 of 0.94 and P_aO_2 of 69 mmHg (Equation 7). The actual values of S_aO_2 and P_aO_2 after ECMO initiation at these settings were 0.93 and 67 mmHg, agreeing well with predicted values. Considering some degree of intrapulmonary shunt did not significantly modify the results (predicted S_aO_2 increased by 0.01–0.02) (*Table 1*).

The clinical condition improved, allowing weaning from VV-ECMO after 29 days. FiO_2 was progressively reduced to 0.28 (2 L/min O_2 flow), with maintenance of arterial O_2 saturation between 80% and 85%, corresponding to the patient's usual values. She was discharged from the intensive care unit after 40 days, from the hospital after 61 days, and was in stable condition at a follow-up visit 6 months after discharge.

Discussion

In the case presented here, decompensation of ES occurred in the context of an acute viral pneumonia, with some

potential for reversibility. Treating refractory hypoxaemia with positive pressure ventilation in this setting would likely worsen the shunt fraction and precipitate cardiovascular collapse. In such conditions, VV-ECMO appeared as the only viable strategy as a bridge to recovery, giving time to treat the reversible components and preventing the complications of major hypoxaemia. The effects of VV-ECMO on systemic oxygenation in this setting could be accurately predicted by the use of relatively simple equations, which can be solved easily using a fill-in Excel spreadsheet (*Table S1*). The ability to predict the influence of VV-ECMO on oxygenation even before its insertion adds an important clinical value, not only by providing significant help in the decision process but also by determining in advance the optimal settings of VV-ECMO for best expected results. Moreover, it is worth to underscore that the equations detailed in this report refer to fundamental principles of gas exchange, oxygen content, and shunt physiology. Therefore, they might also be considered to predict the effects of VV-ECMO in other clinical conditions associated with significant right-to-left shunt (both intracardiac and intrapulmonary) and refractory hypoxaemia, an assumption that will require further validation studies.

Conflict of interest

None declared.

Funding

This work was supported in part by the 'Emma Muschamp Foundation', Lausanne, Switzerland, to J.B.

Author contributions

J.B., L.P., and L.L. were involved in the design and the implementation of the work and in the analysis and interpretation of the results. J.B., L.P., and L.L. wrote the first draft of the manuscript with the contribution of D.A. and T.R. D.A., T.R., P.Y., J.D.A., A.R., O.P., and M.R. contributed to the analysis and interpretation of the results and critically revised the manuscript. All authors approved the final version of the manuscript.

Ethical statement

The patient's informed consent has been obtained for this publication.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Supporting Information

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