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

Jean Bonnemain1*, Denise Auberson2, Tobias Rutz2, Patrick Yerly2, John-David Aubert3, Aurélien Roumy4, Olivier Pantet1, Marco Rusca1, Lucas Liaudet1† and Lise Piquilloud1†

1The Service of Adult Intensive Care Medicine, University Hospital and Faculty of Biology and Medicine, University of Lausanne, Rue du Bugnon 46, Lausanne, CH-1011, Switzerland; 2The Service of Cardiology, University Hospital and Faculty of Biology and Medicine, University of Lausanne, Rue du Bugnon 46, Lausanne, CH-1011, Switzerland; 3The Service of Pneumology, University Hospital and Faculty of Biology and Medicine, University of Lausanne, Rue du Bugnon 46, Lausanne, CH-1011, Switzerland; 4The Service of Cardiac Surgery, University Hospital and Faculty of Biology and Medicine, University of Lausanne, Rue du Bugnon 46, Lausanne, CH-1011, Switzerland

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

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 ($F_{shunt-Tot}$)

$$F_{shunt-Tot} = \frac{Q_s}{Q_t} = \frac{(C_{pO_2} - C_{aO_2})}{(C_{pO_2} - C_{vO_2})}$$

where $Q_s$: shunt flow; $Q_t$: systemic cardiac output; $C_{pO_2}$: 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: $(1.39 \times \text{[haemoglobin]} \times SO_2) + (0.031 \times PO_2)$. 
2. Calculation of right ventricular oxygen content under VV-ECMO (CRVO₂)

\[ CRVO₂ = \frac{[QEC/Q_t] \times CECO₂]}{[1 - (QEC/Q_t)] \times CvpO₂} \] (2)

where \( CECO₂ \): O₂ content in blood exiting the oxygenator; \( CvpO₂ \): central O₂ content in venous blood bypassing the oxygenator; \( QEC \): ECMO flow (assuming no recirculation); and \( Q_t \): systemic venous return (= systemic cardiac output).

3. Calculation of systemic arterial oxygen content under VV-ECMO (CaO₂-ECMO)

\[ CaO₂-ECMO = \left( F_{shunt-tot} \times CRVO₂ \right) + \left[ \left( 1 - F_{shunt-tot} \right) \times CCO₂ \right] \] (3)

\( CaO₂-ECMO \) is the sum of O₂ content in shunted blood and in non-shunted blood exiting the lung. We assume no alveolo-capillary diffusion impairment and equilibrium between alveolar (\( P_{A}O₂ \)) and capillary O₂ pressures (\( P_{c}O₂ \)). 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 (\( F_{shunt-Lung} \)), and determine the O₂ content exiting the lungs (left atrium, \( C_{LA}O₂ \), Equation 4). The corrected fraction of cardiac shunt (\( F_{shunt-Heart} = F_{shunt-tot} - F_{shunt-Lung} \)) should be used to calculate \( C_{aO₂-ECMO} \) (Equation 5).

\[ C_{LA}O₂ = CCO₂ \times (F_{shunt-Lung} \times (C_{LA}O₂ - CRVO₂)) \] (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 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.
4. Calculation of predicted $S_aO_2$ and $P_aO_2$ under VV-ECMO

$$S_aO_2 = \frac{C_aO_2 - (0.031 \times P_aO_2)}{(1.39 \times Hb)} \quad (6)$$

$$P_aO_2 = \sqrt{\frac{1}{2}(-y_N + \sqrt{y_N^2 - h^2})} + \sqrt{\frac{1}{2}(-y_N - \sqrt{y_N^2 - h^2})} \quad (7)$$

where

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

Hb: haemoglobin concentration (g/L).

We can use here a $P_aO_2$ of 70 mmHg to calculate dissolved oxygen ($0.031 \times P_aO_2$, which is negligible). Equation 7 is the inverse Severinghaus equation, which yields $S_aO_2$ (s) from $P_aO_2$. 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.
| Parameter | Measured | Basal condition (before ECMO) | Formula |
|-----------|----------|-------------------------------|---------|
| \(P_O2\)  | 30       |                               |         |
| \(P_2O\)  | 37       |                               |         |
| \(P_CO2\) | 40       |                               |         |
| \(S_O2\)  | 0.72     |                               |         |
| \(S_2O2\) | 0.56     |                               |         |
| \(Hb\)    | 151      |                               |         |
| \(F_2O\)  | 1        |                               |         |
| \(P_h\)   | 710      |                               |         |
| \(P_H2O\) | 47       |                               |         |

\[
P_{AO2} = \frac{P_h \times P_{H2O} \times F_2O}{P_{CO2}}
\]

\[
P_{CO2} = P_{AO2}
\]

\[
S_{CO2} = 1
\]

\[
C_{CO2} = (Hb \times S_{CO2} \times 1.39) + (P_{CO2} \times 0.031)
\]

\[
C_{VO2} = (Hb \times S_{VO2} \times 1.39) + (P_{VO2} \times 0.031)
\]

\[
F_{shunt-Tot} = \frac{C_{CO2} - C_{CO2}}{C_{CO2} - C_{CO2}}
\]

| Parameter | Measured | Under VV-ECMO | Formula |
|-----------|----------|---------------|---------|
| \(F_2O\)  | 0.8      |               |         |
| \(Q_{EC}\) | 4.5      |               |         |
| \(P_{ECO2}\) | 400     |               |         |
| \(S_{ECO2}\) | 1       |               |         |
| \(Q\)     | 7        |               |         |
| \(C_{ECO2}\) | 222.3   |               |         |
| \(C_{RV2}\) | 185.2   |               |         |
| \(C_{O2}\) | 198.5    |               |         |
| \(S_{O2\ ECMO}\) | 0.93 (actual) | 0.94 (predicted) |         |
| \(P_{O2\ ECMO}\) | 67 (actual) | 69 (predicted) |         |

\[
C_{ECO2} = (Hb \times S_{ECO2} \times 1.39) + (P_{ECO2} \times 0.031)
\]

\[
C_{RV2} = \frac{Q_{EC}}{C_{ECO2}}
\]

\[
C_{O2} = \frac{Q_{EC}}{C_{RV2}}
\]

\[
S_{O2\ ECMO} = \frac{[C_{O2\ ECMO} - 0.31 \times P_{O2}]/(Hb \times 1.39)}{[C_{ECO2} - 0.31 \times P_{O2}]/(Hb \times 1.39)}
\]

\[
P_{O2\ ECMO} = \text{inverse Severinghaus equation}
\]

| Parameter | Measured | Under VV-ECMO: intrapulmonary shunt 10% \((F_{shunt-Lung}: \text{estimated fraction of } F_{shunt-Tot})\) | Formula |
|-----------|----------|---------------------------------------------------------------|---------|
| \(C_{A2\ ECMO}\) | 0.59 | \(F_{shunt-Heart} = F_{shunt-Tot} - F_{shunt-Lung}\) |         |
| \(C_{O2\ ECMO}\) | 224 | \(C_{A2\ ECMO} = C_{O2} - [F_{shunt-Lung} \times (C_{CO2} - C_{RV2})]\) |         |
| \(S_{O2\ ECMO}\) | 0.93 (actual) | 0.95 (predicted) |         |
| \(P_{O2}\) | 67 (actual) | 74 |         |

Under VV-ECMO: intrapulmonary shunt 20% \((F_{shunt-Lung}: \text{estimated fraction of } F_{shunt-Tot})\)

| Parameter | Measured | Under VV-ECMO: intrapulmonary shunt 20% \((F_{shunt-Lung}: \text{estimated fraction of } F_{shunt-Tot})\) | Formula |
|-----------|----------|---------------------------------------------------------------|---------|
| \(C_{A2\ ECMO}\) | 0.49 | \(F_{shunt-Heart} = F_{shunt-Tot} - F_{shunt-Lung}\) |         |
| \(C_{O2\ ECMO}\) | 219.7 | \(C_{A2\ ECMO} = C_{O2} - [F_{shunt-Lung} \times (C_{CO2} - C_{RV2})]\) |         |
| \(S_{O2\ ECMO}\) | 0.93 (actual) | 0.96 (predicted) |         |
| \(P_{O2}\) | 67 (actual) | 79 |         |
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% O₂ by high nasal flow (PₐO₂/FiO₂ O₂: 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 decompenated 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 vasopressor (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 O₂ saturation obtained from the right atrium as a surrogate of mixed venous O₂ saturation. Cardiac output (Qₜ) was not directly measured but was estimated using the Krovetz–Goldbloom equation of O₂ consumption: VO₂ = \left(138.1 - (17.04 \times \ln(\text{age}))\right) + (0.378 \times \text{HR}), and the arteriovenous O₂ difference, Cₐ(a–v)O₂ (Qₜ = VO₂/Cₐ(a–v)O₂). Estimated Qₜ was 7.1 L/min, which was close to the latest Qₜ determined by cardiac catheterization at steady state, several weeks before current hospitalization (8 L/min).

Using this value of Qₜ, we predicted that ECMO flow of 4.5 L/min with a delivered sweep gas O₂ fraction of 0.8–1.0 (producing a post-membrane PO₂ of 300–500 mmHg) would result in a SₐO₂ of 0.94 and PₐO₂ of 69 mmHg (Equation 7). The actual values of SₐO₂ and PₐO₂ 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 SₐO₂ increased by 0.01–0.02) (Table 2).

The clinical condition improved, allowing weaning from VV-ECMO after 29 days. FiO₂ was progressively reduced to 0.28 (2 L/min O₂ flow), with maintenance of arterial O₂ 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.

**References**

1. Combes A, Hajage D, Capellier G, Demoule A, Lavoue S, Guerilly C, Da Silva D, Zafrani L, Tirot P, Veber B, Maury E, Levy B, Cohen Y, Richard C, Kalfon P, Bouadma L, Mehtaoui H, Beduneau G, Lebreton G, Brochard L, Ferguson ND, Fan E, Slutsky AS, Brodie D, Mercat A, Eolia Trial Group R, Ecmonet. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; 378: 1965–1975.

2. Quintel M, Bartlett RH, Grocott MPW, Combes A, Ranieri MV, Baicchi M, Nava S, Brodie D, Camporota L, Vasques F, Busana M, Marinji JJ, Gattinoni L. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *Adv Physiol Educ* 2001; 25: 159–166.

3. Bigeleisen PE. Models of venous admixture. *Adv Physiol Educ* 2001; 25: 159–166.

4. Arvanitaki A, Giannakoulas G, Baumgartner H, Lammers AE. Eisenmenger syndrome: diagnosis, prognosis and clinical management. *Heart* 2020; 106: 1638–1645.

5. Javidfar J, Brodie D, Sonett J, Bacchetta M. Venovenous extracorporeal membrane oxygenation using a single cannula in patients with pulmonary hypertension and atrial septal defects. *J Thorac Cardiovasc Surg* 2012; 143: 982–984.

6. Rosenzweig EB, Abrams D, Biscotti M, Kerstein D, Drasinower D, Brodie D, Bacchetta M. Eisenmenger syndrome and pregnancy: novel ECMO configuration as a bridge to delivery and recovery utilizing a multidisciplinary team. *ASAIO J* 2018; 64: e8–e10.

7. Udi J, Kohler TC, Grohmann J, Baum M, Grundmann S, Bode C, Biever P, Duerschmied D. A challenging case of severe pulmonary bleeding in a patient with congenital ventricular septal defect (VSD) and Eisenmenger syndrome: extracorporeal membrane oxygenation (ECMO) support and weaning strategies. *Clin Res Cardiol* 2020; 109: 403–407.

8. Nickalls RWD. Inverse solutions of the Severinghaus and Thomas equations which allow PO2 to be derived directly from SO2. 2011. www.nickalls.org/dick/papers/anes/severinghaus.pdf (Accessed on October 16th 2020).

9. Walley KR. Use of central venous oxygen saturation to guide therapy. *Am J Respir Crit Care Med* 2011; 184: 514–520.

10. Krovetz LJ, Goldblom S. Normal standards for cardiovascular data. I. Examination of the validity of cardiac index. *Johns Hopkins Med J* 1972; 130: 174–186.

11. Pierro MA, Daneshmand MA, Bartz RR. Perioperative management of the adult patient on venovenous extracorporeal membrane oxygenation requiring non-cardiac surgery. *Anesthesiology* 2018; 128: 181–201.

**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**

---

*ESc Heart Failure 2021; 1637–1642 DOI: 10.1002/ehf2.13253*