Journal of Critical Care 36 (2016) 178–186

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

A mathematical model of oxygenation during venovenous extracorporeal membrane oxygenation support☆,☆☆,★,★★

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ARTICLE INFO

Available online xxxx

Keywords:
Extracorporeal circulation
Extracorporeal membrane oxygenation
Oxygen consumption
Blood circulation
Cardiac output
Theoretical models

ABSTRACT

Purpose: To develop a mathematical model of oxygenation during venovenous extracorporeal membrane oxygenation (vv-ECMO).

Material and methods: Total oxygen consumption, cardiac output, blood flow, recirculation, intrapulmonary shunt, hemoglobin, natural lung, and membrane lung oxygen fractions were chosen as inputs. Content, partial pressure, and hemoglobin saturation of oxygen in arterial, venous, pulmonary, and extracorporeal blood were outputs. To assess accuracy and predictive power of the model, we retrospectively analyzed data of 25 vv-ECMO patients. We compiled 2 software (with numerical, 2D and 3D graphical outputs) to study the impact of each variable on oxygenation.

Results: The model showed high accuracy and predictive power. Raising blood flow and oxygen fraction to the membrane lung or reducing total oxygen consumption improves arterial and venous oxygenation, especially in severe cases; raising oxygen fraction to the natural lung improves oxygenation only in milder cases; raising hemoglobin always improves oxygenation, especially in the venous district; recirculation fraction severely impairs oxygenation. In severely ill patients, increasing cardiac output worsens arterial oxygenation but enhances venous oxygenation. Oxygen saturation of ECMO inlet is critical to evaluate the appropriateness of oxygen delivery.

Conclusions: The model with the software can be a useful teaching tool and a valuable decision-making aid for the management of hypoxic patients supported by vv-ECMO.

1. Introduction

Venovenous extracorporeal membrane oxygenation (vv-ECMO) has been proven clinically effective for the treatment of patients with severe hypoxic respiratory failure [1-3]. During vv-ECMO, blood oxygenation is depending on the complex interaction between the function of the patient pulmonary system (natural lung [NL]) and the ECMO support (membrane lung [ML]). Several factors affect blood oxygenation during vv-ECMO: cardiac output (CO), NL intrapulmonary shunt (Qs), oxygen fraction to the natural lung (FiO_2NL), oxygen fraction to the membrane lung (FiO_2ML), total oxygen consumption (VO_2TOT), extracorporeal blood flow (BF), hemoglobin (Hb) concentration, membrane lung shunt (QsML), and recirculation (R) [4-6]. Therefore, during vv-ECMO, common clinical interventions may have unpredictable effects on oxygenation. Moreover, assessing the adequacy of oxygen delivery in patients supported by vv-ECMO is particularly complex because the parameters commonly used to assess oxygenation (ie, mixed venous or central venous oxygen saturation [7]) are highly affected by the extracorporeal support [8].

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☆☆ Authors' contributions: All authors provided substantial contributions to the conception and design, acquisition of data, analysis, and interpretation of findings. AZ developed the mathematical model and performed analyses of data. SD, EC, and PC compiled the mathematical model. VS and EC retrospectively collected and performed analyses of data. MG, LC, and FM contributed in data collection and analyses. NP contributed in the development of the mathematical model. AZ, VS, MB, GG, and AP drafted the manuscript, and all authors contributed substantially to revisions. All authors gave approval for the final version submitted for publication.

★ Financial Support: Funding for this study was provided by the in-house research funds from the School of Medicine and Surgery, University of Milan-Bicocca, Monza (MB), Italy.

★★ Disclosures and Conflict of Interest: We acknowledge the following potential conflicts of interest: Dr Pesenti received payment for lectures and service on speaker bureau from Maquet (Maquet Cardiopulmonary, Rastatt, Germany) and Novalung (Novalung, Heilbronn, Germany); Dr Pesenti has received consulting honoraria from Maquet (Maquet Cardiopulmonary, Rastatt, Germany) and Novalung (Novalung, Heilbronn, Germany). The remaining authors have disclosed that they do not have any potential conflicts of interest.

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http://dx.doi.org/10.1016/j.jcrc.2016.07.008
0883-9441/

We present a mathematical model of blood oxygenation during vv-ECMO, which can be used as a teaching tool and a decision-making aid for physicians. This model is based on the principle of conservation of mass and standard equations describing uptake and delivery of oxygen [9-11]. By this model, given a set of the variables above, it is possible to obtain oxygen content, Po_2, and hemoglobin saturation (So_2) of the different circulatory districts of a patient during vv-ECMO.

We assessed the accuracy and the predictive capability of the model with a retrospective analysis of blood gas analyses of patients treated with vv-ECMO admitted to San Gerardo Hospital (Monza, Italy) intensive care unit (ICU) for respiratory failure. We analyzed how different physiologic variables independently affect oxygenation during vv-ECMO and evaluated which individual physiologic parameter may better describe the appropriateness of oxygen delivery.

2. Material and methods

2.1. ECMO model

Our model describes a simplified circulatory system of a patient connected to a vv-ECMO support (see Fig. 1). The model is suitable for neonatal, pediatric, and adult patients, provided that the circulatory system is fully transitioned from the fetal circulation to a newborn circulation (closure of the ductus arteriosus and venosus as well as foramen ovale). We used the Riley's model of gas exchange [9] to describe the patient pulmonary system. Thus, the Qs (L/min)—the fraction of CO (L/min) perfusing nonventilated alveoli—is the only determinant of inadequate oxygenation of blood exiting the NL. The Riley's model is also used to describe the function of the ML.

We choose as input of the model the actual primary independent determinants of oxygenation during vv-ECMO support:

- Vo_2TOT (mL/min) that is the oxygen expenditure of the whole body;
- CO (L/min);
- extracorporeal BF (L/min);
- recirculation fraction [12] (R/BF, %; R is the blood flow recirculating from the ECMO output into the ECMO input, L/min);
- intrapulmonary shunt fraction (Qs/CO, %);
- Fio_2NL (%);
- Fio_2ML (%);
- Hb concentration (g/dL);
- membrane lung shunt fraction (QsML/BF, %) [13].

From the variables above, following standard equations [14-17], our model computes the oxygen content, Po_2 and So_2 of the various circulatory districts of a patient supported vv-ECMO support, as well as the oxygen loaded by the patient lung (Vo_2NL) and the oxygen loaded by the membrane lung (Vo_2ML). We identified 7 different blood districts (ie, arterial [Ca], venous, ECMO inlet, ECMO outlet, mixed venous, pulmonary capillary, and ML capillary), with 7 correspondent oxygen contents: Ca, venous, ECMO inlet, ECMO outlet, mixed venous, ideal pulmonary capillary, and ideal ML capillary. For further details about the mathematical model compilation, see *ECMO model* (Additional Methods, Supplementary Material).

2.2. Software

We implemented the model into 2 software, freely for academic and research purposes at www.ecmomodel.unimi.it. In both programs, the user enters numerical values for input variables. The "patient oxygenation" program provides the Po_2 and So_2 of all the patient's blood districts. The "graph builder" plots the relationship between 2 and 3 variables in a 2D or 3D graph. For further details, see Figs. S1 and S2 and *Software* and *Software Installation* (Additional Methods, Supplementary Material).

2.3. Accuracy and predictability test

To evaluate the accuracy and predictability of the model, we retrospectively analyzed data from selected 25 adult and 3 pediatric patients admitted to the ICU of San Gerardo Hospital (Monza, Italy) after diagnosis of severe respiratory failure and thus connected to vv-ECMO support, from January 2003 to January 2013 (see Table 1 for adult patients' demographics and table S3 for pediatric data). Electronic charts were scrutinized for the following inclusion criteria: (1) diagnosis of respiratory failure, (2) connection to a vv-ECMO circuit, (3) availability of simultaneous measurement of Fio_2NL, Fio_2ML, BF, core temperature, CO by thermodilution technique and the collection of arterial, mixed venous, ECMO inlet, and ECMO outlet blood gas analyses. The institutional review board approved the study. Written informed consent was waived

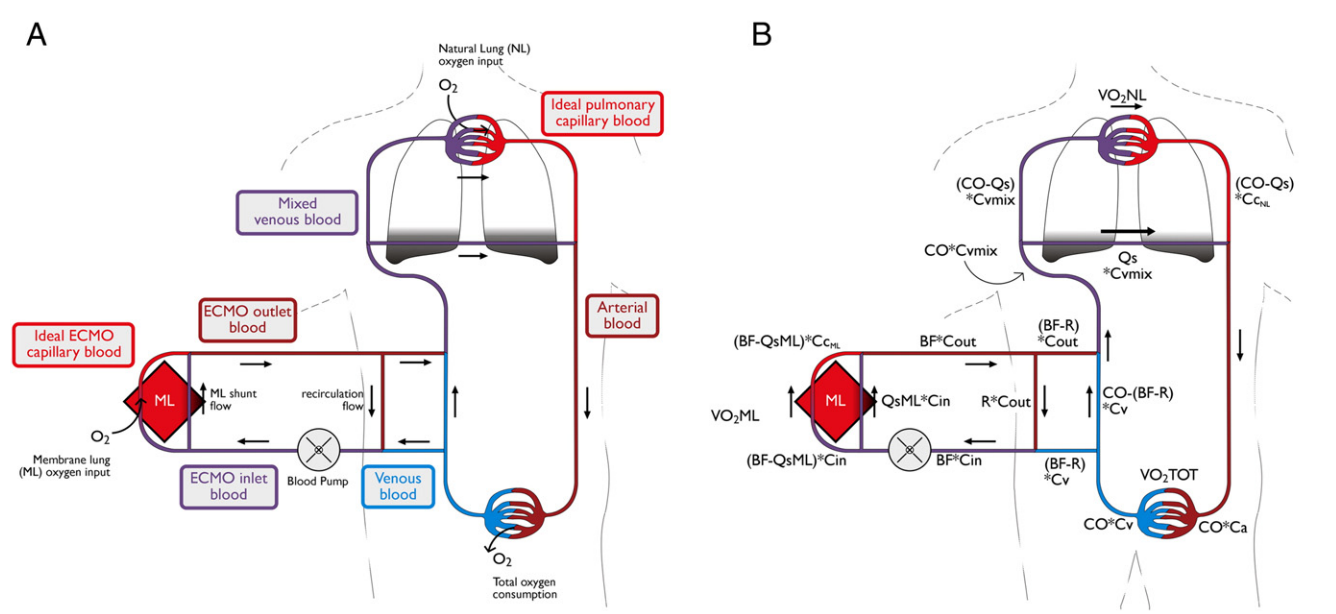

Fig. 1. Schematic representation of a patient connected to vv-ECMO. Panel A, All the different blood districts are depicted. Panel B, The oxygen delivery of each circulatory district is depicted. Cvmix indicates mixed venous content of oxygen; Cc_{NL}, ideal pulmonary capillary content of oxygen; Cin, ECMO inlet content of oxygen; Cout, ECMO outlet content of oxygen; Cc_{ML}, ideal ML capillary content of oxygen.