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Blood Gas Parameters and Acid–Base Balance during Extracorporeal Lung Support with Oxygenators: Semi-Empirical Evaluation

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Abstract: Membrane artificial lungs (oxygenators) are used in cardiopulmonary surgery as well as, in some cases, in severe lung disease to support the natural lung by means of ECMO (extracorporeal membrane oxygenation). The oxygen and carbon dioxide transfer rates of any oxygenator are usually assessed by considering several blood gas parameters, such as oxygen saturation, hemoglobin concentration, partial pressure of oxygen and carbon dioxide, bicarbonate concentration, and pH. Here, we report a set of semi-empirical equations that calculate such parameters directly from their partial pressures and assess the acid–base balance during ECMO. The implementation of this equation set permits the evaluation of any oxygenator, existing or prototypes in development, as well as the development of clinical decision-making tools for predicting the blood gas state and acid–base balance during surgical interventions and ECMO. The predicted results are then compared with experimental data obtained from in vitro gas exchange investigations with a commercial oxygenator using fresh porcine blood. The high correlation, $R^2 > 0.95$, between the predicted and the experimental data suggests a possibility of using such empirical equations in the simulation of gas transfer in a cardiopulmonary system with an oxygenator for any venous inlet blood gas data and also for estimating the acid–base balance during such therapy.

Keywords: oxygenator; oxygen transfer rate (OTR); carbon dioxide transfer rate (CTR); acid–base balance; semi-empirical model

MSC: 92-08

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1. Introduction

Oxygenators [1,2], today mainly capillary membrane artificial lungs, are used in cardiopulmonary surgery as well as in some cases of severe lung disease to support the natural lung by means of ECMO (extracorporeal membrane oxygenation). In addition, they are also used for some specific therapies, such as extracorporeal carbon dioxide removal ($ECCO_2R$) [3]. The partial pressure of oxygen pO_2, partial pressure of carbon dioxide pCO_2, oxygen saturation S, and oxygen and carbon dioxide transfer rates ($OTRs$ and $CTRs$), together with pH and other acid-base parameters, are the main blood gas parameters that represent the physiological state of the blood. The oxygen transfer rate (OTR) and carbon dioxide transfer rate (CTR) of an oxygenator have been established as the determining factors of any oxygenator's gas transfer performance. OTR depends primarily on the blood flow rate and blood saturation at the inlet of the oxygenator [4]. CTR, on the other hand, due to high diffusion capacity, is more affected by the gas flow rate and its ratio to the blood flow rate. The removal of carbon dioxide has a pronounced effect on pH and, subsequently, on the HCO_3^- level of blood. It is, thus, essential to determine, beforehand, the impact of the CTR on the acid–base state of the patient before applying $ECCO_2R$ therapy.

Usually, the gas transfer performance of oxygenator prototypes is evaluated through in vitro investigations in compliance with the International Organization for Standardization (ISO) 7199:2016 [5] before proceeding to any clinical trials. To calculate OTR and CTR, various blood gas parameters need to be measured frequently at both the inlet and outlet ports of the oxygenator in the course of these in vitro investigations, such as oxygen and carbon dioxide partial pressure (pO_2 mmHg and pCO_2 mmHg), oxygen saturation $S(\%)$, hemoglobin concentration c_{Hb} (g/dL), hematocrit Hct (%) , pH, bicarbonate concentration $[HCO_3^-]$ (mmol/L) etc. In this study, we evaluate the accuracy of semi-empirical equations for oxygen and carbon dioxide dissociation curves to directly calculate the OTR and CTR of an oxygenator from the pO_2 and pCO_2 at its inlet and outlet.

The oxygen dissociation curve expresses S as a function of pO_2 for defined pH, pCO_2, and temperature. Oxygen saturation S and hemoglobin concentration c_{Hb} are required for the estimation of chemically bound oxygen concentration $\left(c_{O_2,chemical}\ \text{mL/dL}\right)$ in blood. The concentration of physically dissolved oxygen $c_{O_2,physical}$(mL/dL) can be calculated directly from pO_2 using Henry's law of solubility [6]. The carbon dioxide dissociation curve relates pCO_2 with the total carbon dioxide content c_{CO_2} (mL/dL) in blood for defined pH and S.

Apart from the estimation of carbon dioxide content directly from its partial pressure, this article also takes into account the relationship between pH, pCO_2, and $[HCO_3^-]$ as according to the Henderson–Hasselbalch equation [7] to predict the acid–base state. The analysis further considers the initial condition of pH and $\left[HCO_3^-\right]$ and the slope of the corresponding buffer line. Such a prediction could help in predicting the direction and outcome of the respiratory compensation for pH balance, as provided by the extracorporeal carbon dioxide removal.

2. Materials and Methods

2.1. Estimation of Oxygen and Carbon Dioxide Content from Their Partial Pressure

Kelman subroutine [8] for the calculation of $S(\%)$ from pO_2 (mmHg) is given in Equations (1) and (2). The calculated S is then used for the calculation of oxygen concentration (c_{O_2}mL/dL) using Equation (3).

$$pO_{2,adj} = pO_2 \times 10^{0.024(37-temp)+0.40(pH-7.4)+0.06(log40-logpCO_2)} \tag{1}$$

$$S(\%) = 100 \times \frac{a_1x + a_2x^2 + a_3x^3 + x^4}{a_4 + a_5x + a_6x^2 + a_7x^3 + x^4};\ x = pO_{2,adj} \tag{2}$$

$$c_{O_2} = 1.34 \times c_{Hb}.\frac{S(\%)}{100} + \alpha_{O_2}pO_2\left(1 - \frac{Hct(\%)}{100}\right) \tag{3}$$

$$Hct(\%) = 3 \times c_{Hb} \tag{4}$$

a_1 to a_7 are the coefficients for oxygen dissociation curve, and their empirically derived values are $a_1 = -8532.2289$, $a_2 = 2121.401$, $a_3 = -67.073989$, $a_4 = 935,960.87$, $a_5 = -31,346.258$, $a_6 = 2396.1674$, and $a_7 = -67.104406$, $1.34ml_{O_2}/g_{Hb}$ is the Hüfner constant, c_{Hb}(g/dL) is the hemoglobin concentration, $Hct(\%)$ is the hematocrit value, which is estimated to be thrice the value of the hemoglobin concentration c_{Hb} (g/dL) [9], and $\alpha_{O_2} = 0.00317$mL/dL/mmHg is the solubility coefficient of oxygen at 37 °C.

Similarly, the equation for the calculation of carbon dioxide content (c_{CO_2}mL/dL) in blood from pCO_2 (mmHg) by Douglas et al. [10] is given in Equations (5) and (6).

$$c_{CO_2,plasma} = 2.226 \cdot \alpha_{CO_2} \cdot pCO_2 \cdot 10^{pH-pK} \tag{5}$$

$$c_{CO_2,blood} = c_{CO_2.plasma}\left(1 - \frac{0.0289c_{Hb}}{(3.352 - 0.00456S(\%))(8.142 - pH)}\right) \quad (6)$$

α_{CO_2} and pK in Equations (5) and (6) are 0.0307mmol/L/mmHg and 6.0907 [11], respectively, at 37 °C, and 2.226 is the conversion factor from mmol/L to mL/dL.

2.2. Estimation of Blood Gas Parameters Based on the Empirical Equations and Initial Conditions

It is apparent in Equation (5) that the concentration of carbon dioxide depends not only on the partial pressure of carbon dioxide but also on the pH value of the blood. The relation between pCO_2 mmHg, $\left[HCO_3^-\right]$ mmol/L and pH is further explored via Henderson–Hasselbalch equation (Equation (7)). The additional equation for the relationship between pH and HCO_3^- is obtained via the buffer line (Equation (8)).

$$pH = 6.1 + \log_{10}\frac{\left[HCO_3^-\right]}{[0.03pCO_2]} \quad (7)$$

$$\left[HCO_3^-\right] - H_i = m(pH - p_i) \quad (8)$$

Here, H_i and p_i are the initial bicarbonate concentration and pH. From Equations (7) and (8), for any pCO_2, pH value can be estimated based on the initial conditions. This, in return, will provide more accurate model for calculating the $c_{CO_2,blood}$ in blood. Furthermore, the buffer line Equation (8) determines the direction of acid–base state during the extracorporeal carbon dioxide removal.

2.3. Experimental Circuit

An in vitro experimental circuit (Figure 1) was assembled to evaluate the gas transfer performance of a hollow fiber oxygenator and to determine the influence of carbon dioxide removal on the overall acid–base balance, using two roller pumps (Stockert S3), a blood reservoir, adequate length of tubing, and two commercial oxygenators (one in the role of deoxygenator).

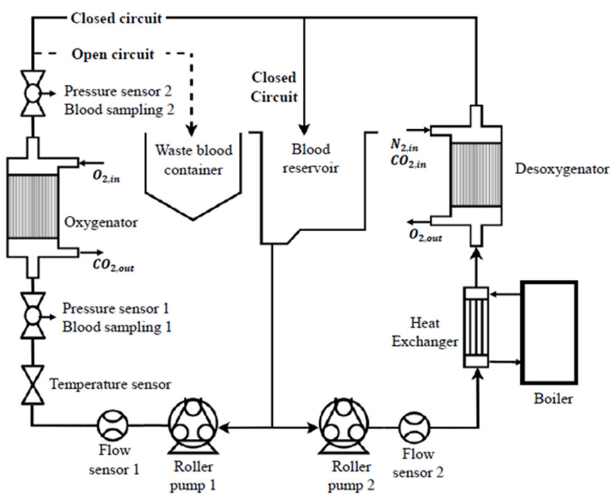


Figure 1. Schematic representation of an in vitro experimental circuit for the evaluation of an oxygenator. Two flow sensors constantly monitor the blood flow rate through the oxygenator and deoxygenator. The heat exchanger regulates the temperature of blood within the physiological range of 37 ± 1 °C. Blood samples are drawn from the equivalent ports in regular intervals to measure the blood gas parameters.

For the performance evaluation, the experiment was conducted in accordance with the established international standard for cardiovascular implants and artificial organ–blood–gas exchangers (ISO 7199:2016). A closed-loop in vitro circulation, with both oxygenator and deoxygenator being simultaneously perfused, is used until pO_2, oxygen saturation, pCO_2 and pH in the reservoir reach values of 40 ± 5 mmHg, 65 ± 5%, 45 ± 5 mmHg and 7.35 ± 0.5, respectively. Afterwards, the circuit is opened, and blood flow rates of 1, 3 , 5 and 7 L/min are implemented through the oxygenator. Blood samples are taken from sampling ports located at the oxygenator's inlet–outlet ports and analyzed using a blood gas analyzer (Radiometer ABL 800 FLEX) to measure the blood gas parameters of venous and arterial blood. Finally, the experimental data are compared with the predicted values to assess the accuracy and reproducibility of the empirical equations in calculating OTR and CTR.

$$OTR = 10 \times \dot{Q}_B \left(c_{O_2,Bout} - c_{O_2,Bin} \right) \tag{9}$$

$$CTR = 10 \times \dot{Q}_B \left(c_{CO_2,Bin} - c_{CO_2,Bout} \right) \tag{10}$$

where $\dot{Q}_B(\mathrm{L/min})$ is the blood flow rate through the oxygenator, and c_{O_2} and c_{CO_2} are the concentrations of oxygen and carbon dioxide in mL/dL. B_{in} and B_{out} indices are for blood inlet and outlet of the oxygenator.

During the $ECCO_2R$ experiment, the initial condition was set to a pCO_2 of around 70 mmHg, in order to mimic a clinical situation where, for instance, the patient is suffering from severe acidosis; CO_2 was removed at constant gas and blood flow rate of 1 L/min, each. Blood samples were taken from the sampling port and analyzed in the commercial blood gas analyzer (Radiometer ABL 800 FLEX).

3. Results

Description of Results

For oxygen saturation and carbon dioxide content, the correlation coefficients are $R^2 = 0.9964$ and $R^2 = 0.9905$, respectively, as shown in Figure 2a,b. However, in the case of the oxygen dissociation curve, the estimated result is consistently higher than the measured value; the average bias is 15.5% for saturations between 70% and 90%, but the bias decreases afterwards. The bias suggests a shift in the oxygen dissociation curve.

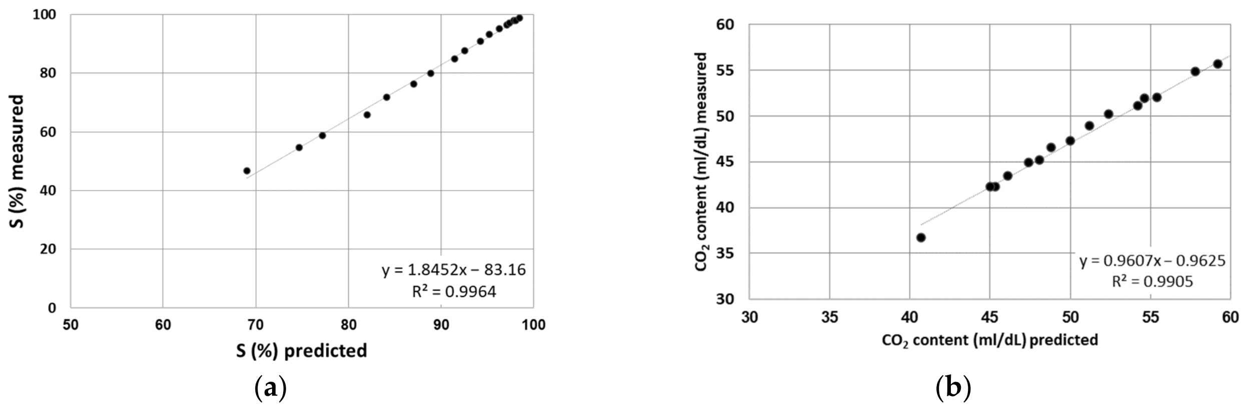


Figure 2. (**a**) Comparison between predicted and experimental oxygen saturation. pH, pCO_2, and temperature in the equations were set as 7.4, 40 mmHg and 37 °C. (**b**) Comparison between the predicted and measured carbon dioxide concentration. Hemoglobin concentration of 12.9g/dL and S(%) 60%, and pH is calculated through the non-linear system of equations (Equations (7) and (8)) using fsolve function in SciPy (version 1.10.0) package of Python (version 3.10.9).

The respiratory compensation for pH balance during extracorporeal CO_2 removal is shown in Figure 3. In this experiment, pCO_2 decreases from an initial 64.9 mmHg to an eventual 23 mmHg. And, during the course of CO_2 removal, pH decreases monotonically from an initial acidosis (pH 7.285) to a final alkalosis (pH 7.566) state along the buffer line AB (the direction of change is indicated by the arrow). The slope of the buffer line depends primarily on the concentration of hemoglobin. The slope is −32.527 for the hemoglobin concentration of 12.9 g/dL in the experiment. The red region shown in Figure 3 is the normal physiological acid–base region (pH around 7.4 and HCO_3^- around 24 mM) [7].

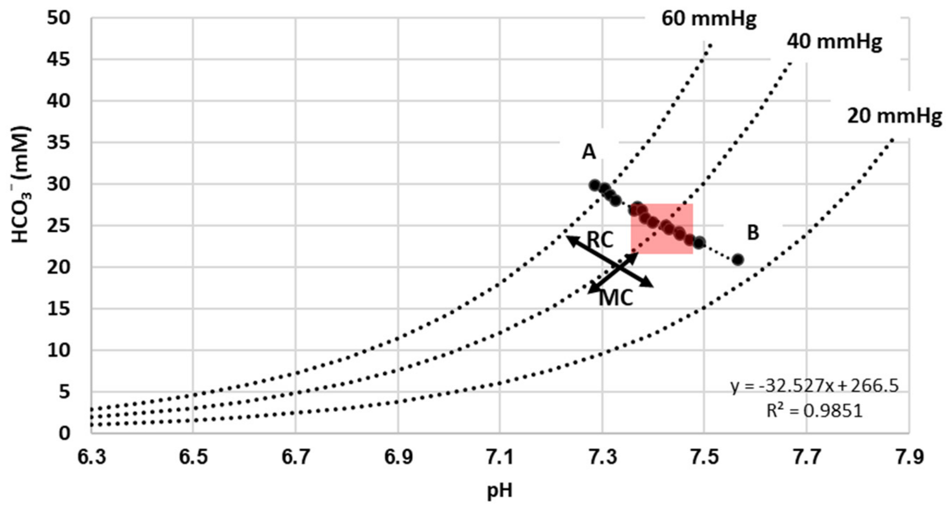
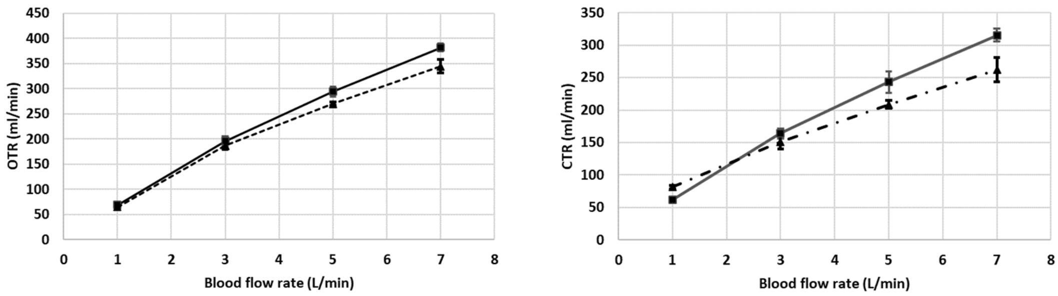


Figure 3. Change in pH during extracorporeal carbon dioxide removal provided in the Davenport diagram [7]. The red region represents the normal physiological pH and bicarbonate range. The arrow indicates the direction of change during carbon dioxide removal. The isobar 20 mmHg, 40 mmHg, and 60 mmHg depict the region of constant partial pressure of carbon dioxide. RC direction of respiratory compensation as provided by the buffer line, MC direction of metabolic compensation. A is the beginning of the experiment and B is the end of the experiment.

In the performance evaluation of the oxygenator, pO_2 and pCO_2 at the blood inlet and outlet at different blood flow rates are provided in Table 1. The measured OTR and CTR means (sd) for the oxygenator at 1 , 3 , 5, and 7 L/min blood flow rate are 68.69 (2.68) and 61.67 (2.87), 195.22 (9.54) and 164 (7.48), 294.1 (9.9) and 243.33 (16.50), and 381.54 (7.95) and 315 (9.89) mL/min, respectively. Similarly, the predicted OTR and CTR means (sd) based on the aforementioned equations are at 1 , 3 , 5, and 7 L/min blood flow rate are 64.58 (1.53) and 81.41(2.33), 186.46 (7.39) and 151 (10.39), 269.58 (3.14), and 208.62 (6.11), and 344.4 (13.42) and 262.5 (18.53) mL/min, respectively. The Pearson correlation coefficients between experimental and predicted values are $R^2 > 0.99$ for both OTR and CTR. The relationship between OTR and CTR with the blood flow rate is shown in Figure 4.

Table 1. Inlet and outlet conditions for the oxygenator's performance evaluation. Gas flow rate through the oxygenator is same as the blood flow rate. Average hemoglobin concentration is 12.9 g/dL.

Blood Flow Rate (L/min)	Inlet		Outlet	
	pO_2 (mmHg)	pCO_2 (mmHg)	pO_2 (mmHg)	pCO_2 (mmHg)
1	36.05 (0.51)	43.8 (0.67)	518 (4.89)	29.53 (0.17)
3	35.83 (0.7)	43.63 (0.83)	367.73 (18.05)	34.27 (0.09)
5	37.7 (0.16)	46.97 (0.42)	210.33 (8.65)	38.53 (0.33)
7	37.81 (0.83)	45.97 (0.33)	122.04 (5.83)	38.47 (0.24)



(**a**) (**b**)

Figure 4. (**a**) Oxygen and (**b**) carbon dioxide transfer rates as a function of blood flow rate mean (sd) (n = 3).

4. Discussion

Kelman and Douglas equations for the calculation of the course of oxygen and carbon dioxide curves were evaluated using fresh porcine blood in an in vitro experimental study. For Kelman, $R^2 = 0.9964$, and for Douglas, $R^2 = 0.9905$, suggest that the significant portion of variance in the measured values is explained by the predicted values. However, the predicted value for oxygen saturation is consistently higher than the experimental results, as seen from the regression graph, which diminishes when the curve reaches near its 100% saturation. The bias in the calculation of oxygen saturation or carbon dioxide content is due to the shift in the oxygen and carbon dioxide dissociation in accordance with Bohr and Haldane effects [12], physiological difference between oxygen and carbon dioxide dissociation curve between human and porcine blood, and blood trauma during in vitro investigations.

A non-linear relationship between pH, pCO_2, and HCO_3^- was developed from the Hendersen–Hasselbalch equation and the non-bicarbonate buffer. Furthermore, the in vitro investigations demonstrate the linear relationship between pH and HCO_3^-, as represented by a buffer line, during extracorporeal carbon dioxide removal. From the Hendersen–Hasselbalch equation and the non-bicarbonate buffer, a non-linear relationship between pH, pCO_2, and HCO_3^- was developed that can be used to estimate pH from pCO_2, given the initial conditions for respiratory compensation via ECMO. However, due to metabolic compensation, such as adjustment of HCO_3^- in the renal system, this buffer line may shift; the slope of the buffer line remains the same. The extent of the influence of such metabolic compensation must be determined, along with the calculation of base excess, to develop a comprehensive model of acid–base balance.

Finally, the data from the oxygen and carbon dioxide dissociation curves were used to calculate the oxygen and carbon dioxide transfer rates of an oxygenator. Both OTR and CTR showed a linear relationship with the blood flow rate in both the experimental and predicted results. The predicted values were then compared with experimental data for blood flow rates of $1,\ 3,\ 5,$ and $7\ \mathrm{L/min}$. Maximum errors were observed at 7 and $1\ \mathrm{L/min}$ for average OTR and CTR, 10% and 32%, respectively. The high error in CTR calculation compared to OTR is due to the higher sensitivity of carbon dioxide concentration to blood pH and bicarbonate concentration. However, for both OTR and CTR, $R^2 > 0.99$ again suggests that a significant portion of variance in the measured values is explained by the predicted values.

5. Conclusions

The above results suggest that the presented empirical equations can be used in simulating cardiopulmonary systems with oxygenators as well as for extracorporeal lung support (ECLS) methods, e.g., ECMO, $ECCO_2R$, or others, for the desired operating condition by manipulating variables, such as the gas and blood flow rate values, including inlet venous blood gas data. In the future, this model will be developed for different configurations of the extracorporeal lung support systems, such as veno-venous or venoarterial, to predict oxygen and carbon dioxide transfer and acid–base status during such therapies. Furthermore, if needed, parameter optimization of the aforementioned equations for porcine blood can be conducted, in a large dataset with diverse inlet conditions, to minimize error in the overall prediction.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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