MATHEMATICAL MODEL OF OXYGEN TRANSPORT: A TEACHING AID FOR NORMAL PHYSIOLOGY ADAPTABLE TO EXTRACORPOREAL OXYGENATION CIRCUITS

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The ultimate aim of most intensive care therapies is to improve tissue oxygen delivery; consequently, a detailed knowledge of this area of physiology is important to a wide range of Critical Care Staff. We describe a simple mathematical model of oxygen transport that was initially written as a training aid for extracorporeal oxygenation training. The model has subsequently proved useful for explaining the determinants of oxygen transport to a broader audience. It is based on simple linear equations and is easily displayed with a standard computer spreadsheet. Apart from its teaching value, the model can also generate a graph of oxygen saturation vs. inspired oxygen fraction for different degrees of pulmonary shunt. This provides a noninvasive method for determining the magnitude of pulmonary venous admixture and may also prove to have some clinical value.

Key words: extracorporeal membrane oxygenation; isoshunt curves

Respiratory failure is the commonest reason for admission to a pediatric intensive care unit (ICU); consequently, a detailed knowledge of the determinants of O₂ transport is vital for staff involved in the care of critically ill children. We describe a mathematical model of O₂ transport that was initially designed for training courses in extracorporeal oxygenation therapy but has subsequently proved to be a useful teaching aid for normal physiological conditions.

Extracorporeal membrane oxygenation (ECMO) has a well-established place in the support of neonates with respiratory failure (13). The traditional circuit design has been venoarterial (VA-ECMO), where blood is drained from the right atrium, passed through an oxygenator, and returned to the aortic arch. More recently, a venovenous circuit design has gained popularity (VV-ECMO) (8). Venous access is usually achieved with a double-lumen catheter positioned in the right atrium, although single-lumen catheter access has been described (2).

Because of the use of venous cannulas, the advantages of VV-ECMO include preservation of the carotid artery, a decreased risk of arterial embolization (12), and greater circuit simplicity (7). The main drawbacks of VV-ECMO are the absence of circulatory support and a limited ability to meet elevated O₂ requirements. However, the practice of restricting VV-ECMO to patients with pure respiratory disease may be largely unnecessary, because recent work has shown that the technique can provide effective support in neonates with combined cardiorespiratory disease (3, 4). The disadvantages of systemic heparinization apply to both circuits.
Because gas exchange during W-ECMO occurs at two points in the circuit (the lung and the oxygenation membrane), the resulting gas transport is complex and is not as intuitively obvious as it is during VA-ECMO. Because of this, we developed a mathematical model of gas transport for use as a teaching aid during ECMO training programs. The model is based on linear equations and can be run on any standard personal computer spreadsheet. It has subsequently proved to be of wider value as an aid for teaching Critical Care Staff the interaction between variables involved in normal O₂ transport.

**METHODS**

**Normal O₂ transport.** Figure 1 is a flow diagram of O₂ transport in a child with a structurally normal heart and a fixed pulmonary shunt. The major determinants of O₂ transport in this circuit are: O₂ consumption (\(\dot{V}O_2\)), cardiac output (\(\dot{Q}_T\)), pulmonary shunt (\(Q_s\)), and the O₂ contents of arterial, mixed venous, and pulmonary capillary blood (\(Cao_2\), \(Cvo_2\), and \(CcO_2\), respectively).

The relationship between pulmonary shunt fraction (\(Q_s/\dot{Q}_T\)) and the blood O₂ contents at various points in the circuit (\(Cao_2\), \(Cvo_2\), and \(CcO_2\)) is described by the shunt equation (15)

\[
\frac{\dot{Q}_s}{\dot{Q}_T} = \frac{CcO_2 - Cao_2}{CcO_2 - Cvo_2} \quad (1)
\]

where O₂ content, in milliliters per liter, for arterial, venous, or capillary blood is calculated by the general equation (16)

\[
CxO_2 = 13.4 \cdot Hb \cdot SxO_2 + 0.03 \cdot PXO_2 \quad (2)
\]

The modifier “x” indicates that the equation may be used for arterial, venous, or pulmonary capillary blood values.

\(Cao_2\) is calculated by assuming that \(P_{O_2}\) is equal to the alveolar partial pressure of O₂ (\(P_{A_2}\)). \(P_{A_2}\) is derived from the alveolar gas equation, which expresses the relationship between barometric pres-
FIG. 2.
Sample spreadsheet for mathematical model of normal O₂ transport (Lotus Windows Release 4.0). Equations for derived variables such as arterial and venous O₂ contents (Cₐₒ₂, in Eq. 6 and Cᵥₒ₂, in Eq. 5) are displayed in column 3. These calculations are based on assumed variables inspired O₂ fraction (Fᵢₒ₂), respiratory quotient (RQ), arterial partial pressure of CO₂ (PaCO₂), alveolar partial pressure of O₂ (PₐO₂), hemoglobin (Hb), Qₜ, oxygen consumption (Vo₂), arterial and venous O₂ saturation (Sₐₒ₂, and Sᵥₒ₂), total O₂ delivery (Do₂), and O₂ extraction ratio (OER) entered in the appropriate rows. Predicted values including Sₐₒ₂ (94%) and Sᵥₒ₂ (59%) are provided in column 4 based on a hypothetical 20-kg child (Qₜ 2.5, Qₜ 1.6 l/min, Vo₂ 90 ml/min).

<table>
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<tr>
<th>LUNG</th>
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<tbody>
<tr>
<td>Fᵢₒ₂</td>
<td>fract</td>
<td>G₂</td>
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<tr>
<td>RQ</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PaCO₂</td>
<td>mm Hg</td>
<td>G₄</td>
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</tr>
<tr>
<td>PₐO₂</td>
<td>mm Hg</td>
<td>@SUM((710*G₂)-(G₄/G₃))</td>
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<td>fract</td>
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<td>Qₜ</td>
<td>L/min</td>
<td>G₁₀</td>
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<tr>
<td>Do₂</td>
<td>ml/min</td>
<td>G₁₁</td>
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</tr>
<tr>
<td>CO₂</td>
<td>ml/L</td>
<td>@SUM(G₁₂+(G₉<em>G₁₁</em>(G₁₀-G₄/G₃)))</td>
<td>170.12</td>
</tr>
<tr>
<td>Cᵥₒ₂</td>
<td>ml/L</td>
<td>@SUM(G₁₂+(G₁₀-G₄/G₃))</td>
<td>95.12</td>
</tr>
<tr>
<td>O₂</td>
<td>%</td>
<td>@SUM(G₁₃*(13.4*G₉)*100)</td>
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<tr>
<td>OER</td>
<td>%</td>
<td>@SUM(G₁₃*G₁₀)</td>
<td>37.16</td>
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</tbody>
</table>

Predicted values of Cₐₒ₂ and Cᵥₒ₂ can now be calculated for various defined values of Cₐₒ₂, Qₜ, Qₜ, and hemoglobin (Hb). Figure 2 outlines the steps involved in displaying these equations with a common computer spreadsheet (Lotus Windows Release 4.0, Lotus Development, Cambridge, MA).

For O₂ saturations below 100%, the term for dissolved O₂ in Eq. 2 can be ignored without significant loss of accuracy. O₂ content may then be converted to O₂ saturation, using the general equation

\[ Sₙₒ₂ = \frac{Cₙₒ₂}{13.4 \cdot Hb} \]  

and also for Cₐₒ₂

\[ Cₐₒ₂ = Cₐₒ₂ - \frac{Qₜ}{Qₜ} - \frac{Qₜ}{Qₜ} \]

\[ Cᵥₒ₂ = Cᵥₒ₂ - \frac{Qₜ}{Qₜ} - \frac{Qₜ}{Qₜ} \]  

**Equation numbers in bold face indicate the final forms of the predictive equations.**
Leaving final predicted results in terms of O₂ saturation rather than O₂ partial pressure has two advantages. First, O₂ saturation can be measured noninvasively, allowing model predictions to be checked clinically without use of arterial blood work. In addition, it avoids conversion errors due to the use of the O₂ dissociation curve, which changes position in response to a variety of factors, including temperature and pH.

Calculation of isoshunt lines. For most applications, our calculation of CcO₂ is based on the alveolar gas equation with \( F_iO₂ = 1.0 \). However, if \( F_iO₂ \) is varied, the predicted values of \( PaO₂ \) (Eq. 3) and, consequently, \( CcO₂ \) (Eq. 2) will change. Therefore, it is possible to predict how \( SaO₂ \) (or \( SaO₂^* \), with use of Eq. 7) will alter in response to \( F_iO₂ \) for given levels of pulmonary shunt. The result (Fig. 3) is similar to the isoshunt diagram of Benatar et al. (1) except that our results are presented in the more clinically useful term of O₂ saturation rather than partial pressure. By use of this graph and two noninvasive measurements (\( F_iO₂ \) and \( SaO₂ \)), it is possible to predict a patient’s degree of pulmonary shunt.

Flow diagram of a child with a fixed pulmonary shunt and a venovenous extracorporeal oxygenation circuit. \( Q_{EC} \), extracorporeal membrane oxygenation (ECMO) blood flow; \( C_{o2EC} \), ECMO O₂ content; \( C_{vo2EC} \), mixed venous O₂ content before ECMO circuit; \( C_{vo2EC} \), mixed venous O₂ content after ECMO circuit.
O₂ transport during VV-ECMO. The model can be expanded to calculate the effect on Cao₂ and CvO₂ of adding a VV-ECMO circuit. Figure 4 shows that there are now two shunts to consider: one through the lungs (Qₚ) and one through the ECMO circuit (Qₑ). Because blood flow rates can be defined at various points in the circuit (Qₑ, Qₛ, and Qₑₑₑ), and it can be assumed that ECMO blood flow (Qₑₑₑ) and unshunted pulmonary blood flow (Qₑₑₑ₋Qₛₑₑₑ) are both fully saturated, the subsequent saturation of mixed blood at any point in the circuit can be calculated using the law of conservation of mass.

On the first pass through the ECMO circuit, the O₂ content of mixed post-ECMO blood (CvO₂ₑₑₑ) is given by

$$C_{vO_2}^{EC} = \left(\frac{Q_{EC} \cdot Cc_{O_2}}{Q_T} + (Q_T - Q_{EC}) \cdot C_{vO_2}\right)$$

(8)

In the same way, the new arterial O₂ content (Cao₂ₑₑₑ) can be calculated by following this flow through the lungs

$$C_{ao2}^{EC} = \left(\frac{Q_S \cdot C_{vO_2}^{EC}}{Q_T} + (Q_T - Q_S) \cdot Cc_{O_2}\right)$$

(9)

The arterial blood now passes through the body and returns to the start of the ECMO circuit. The new mixed venous O₂ content can be calculated using the Fick equation, substituting the values of Vo₂ and Qₑ previously defined

$$C_{vO_2}^{EC} = C_{ao2}^{EC} - \frac{Vo_2}{Q_T}$$

(10)

If the computer makes three passes through the circuit, with updated O₂ contents for each run, the calculated values of Cao₂ₑₑₑ and CvO₂ₑₑₑ rise to a stable plateau.

The amount of O₂ added to the venous circulation during VV-ECMO is given by the ECMO flow rate multiplied by the O₂ content increase across the O₂ membrane

$$D_{O_2}^{EC} = Q_{EC} \cdot (C_{ao2} - C_{vo2})$$

(11)

Total O₂ delivery during ECMO is given by the cardiac output multiplied by arterial O₂ content

$$D_{O_2}^{EC} = Q_T \cdot C_{vo2}^{EC}$$

(12)

CO₂ clearance during ECMO. Removal of CO₂ by the extracorporeal membrane may be of greater physiological benefit than the addition of O₂ to the venous circuit. If CO₂ production (VCO₂) can be cleared by the ECMO circuit, it is possible to reduce the mechanical ventilator rate and rely on apneic oxygenation (6) with a consequent reduction in barotrauma. Although CO₂ transport is more complex than O₂ carriage, it is possible to calculate the ECMO blood flow required to clear total CO₂ production by use of some simple assumptions.

The amount of CO₂ transported through the ECMO circuit is the product of Qₑ and the venous CO₂ content (CvCO₂ₑₑₑ). If this flow of CO₂ were completely removed by the oxygenation membrane, then minute CO₂ clearance by the ECMO circuit could be given by the expression

$$Q_{EC} \cdot C_{vCO_2}^{EC}$$

At steady state, when CO₂ production is exactly matched by CO₂ clearance, the situation is described by the equation

$$VCO_2 = Q_{EC} \cdot C_{vCO_2}^{EC}$$

(13)

In our experience and the published experience of others (17), the membrane clears only about one-third of the CO₂ flowing through it. Consequently, the steady-state relationship is given by

$$VCO_2 = \frac{1}{3} \cdot Q_{EC} \cdot C_{vCO_2}^{EC}$$

(14)

The ECMO blood flow necessary to meet total CO₂...
production ($\dot{Q}_\text{ECmin}$) can now be expressed by rearranging Eq. 13

$$\dot{Q}_\text{ECmin} \approx \frac{3 \cdot \dot{V}_\text{CO}_2}{Cv\text{CO}_2, zt}. \quad (15)$$

On the basis of a standard CO$_2$ dissociation curve (10), the CO$_2$ content of whole blood at a partial pressure of 45 mmHg is 0.5 ml/min. Substituting this value into Eq. 15 gives

$$\dot{Q}_\text{ECmin} \approx 6 \cdot \dot{V}_\text{CO}_2 \quad (16)$$

**Errors and assumptions.** A complex physiological system cannot be perfectly described by simple linear equation; complete accuracy must be balanced against simplicity of use. However, our model is derived from four basic equations [the alveolar gas equation (9), the blood O$_2$ content equation (16), the Fick equation (14), and the shunt equation (15)], each of which has withstood many years of clinical scrutiny and is widely accepted as being an accurate biological representation.

Unfortunately, the same cannot be said for the measurement accuracy of individual components of the model, particularly for $Q_t$ and $RQ$, where errors of 20% are not unusual. Errors induced by variations in the O$_2$ dissociation curve have been avoided by leaving the final predictions in terms of O$_2$ saturation rather than partial pressure. We addressed the problem of cumulative measurement errors in a previous work (11). Briefly, the final predictive inaccuracies in $C_aO_2$ and $C_vO_2$ are difficult to quantify but are probably of sufficient magnitude to limit the model to a teaching role.

**RESULTS**

The predictive curves in Figs. 3, 5, and 6 are based on a hypothetical child of 20 kg with $Q_T$ of 80 ml·min$^{-1}$·kg$^{-1}$ (1.6 l/min), $\dot{V}_O_2$ of 4.5 ml·min$^{-1}$·kg$^{-1}$ (90 ml/min), $\dot{V}_CO_2$ of 3.5 ml·min$^{-1}$·kg$^{-1}$ (70 ml/min), Hb of 120 g/l, and $P_{aO_2}$ of 40 mmHg. These estimates are derived from our own study of cardiorespiratory variables in critically ill children (11) and are representative of a typical pediatric ICU patient.
Figure 3 contains a family of curves that predict how SaO₂ will vary in response to changes in Fin* at different levels of pulmonary shunt. Although alterations in the defined patient variables (Qs, Qt, Vo₂, and Hb) will change the absolute predicted values, the overall shapes of the curves and the subsequent conclusions remain the same.

Adding O₂ to the venous side of the circulation is an inefficient way to improve arterial O₂ delivery. Applying Eq. 16 to the same imaginary patient (VCO₂ of 70 ml/min, Q₁ of 1.6 l/min), the ECMO blood flow for complete clearance of CO₂ is six times VCO₂, that is, 420 ml/min. This represents 25–30% of Q₂. Figure 5 shows that VV-ECMO contributes 15–20% of Do₂T at this setting in a typical patient, depending on the value of Qs/Qt. As Q₁ and SvO₂ fall in a patient with a large pulmonary shunt, ECMO can contribute over 40% of Do₂T, but ECMO blood flow rates > 50% Qₜ are necessary to achieve this.

Similar information is displayed in Fig. 6, which shows how SaO₂ and SvO₂ respond to increasing QEC. Even with a pulmonary shunt of 50%, acceptable arterial saturations are possible at flows equal to \( Q_{EC\text{min}} \) (~30% Qₜ).

**DISCUSSION**

We describe a model of O₂ transport that has proved useful in our units mainly as a teaching tool, but the predicted isoshunt lines (Fig. 3) may have some clinical value. Figure 3 allows a noninvasive estimate to be made of pulmonary venous admixture; once O₂ saturation SaO₂ (pulse oximeter) and O₂ partial pressure Fin* (venturi mask) are known, the pulmonary shunt can be predicted. The original isoshunt curves of Benatar et al. (1) were calculated in terms of O₂ partial pressure, which can only be measured by sampling arterial blood. Our results are displayed in terms of O₂ saturation, because this number can be obtained noninvasively, although it limits the upper range of prediction to 100% saturation.

Adding O₂ to the venous side of the circulation is an inefficient way of supplying the body’s O₂ requirements. With the assumption of a two-compartment model of lung blood flow, O₂ added by venous ECMO will reach the arterial side by two routes: either through ventilated lung units or through the pulmonary shunt. For example, if Qs/Qt is 40%, then only 40% of Do₂T will pass directly to the arterial blood and be used to service Vo₂. The remaining 60% goes through ventilated lung, which produces fully saturated capillary blood irrespective of the initial venous saturation. O₂ added to this unshunted venous flow has no effect on the final arterial saturation.

The oxygenation efficiency of VV-ECMO is greatest when a very low SvO₂ is combined with a large pulmonary shunt. Under these circumstances, the circuit can provide up to 50% of normal O₂ requirements, but membrane blood flows > 50% Qₜ are necessary.

Although VV-ECMO provides no direct left ventricular assistance, several aspects of cardiac performance have been shown to improve during VV-ECMO (7), and the technique has been used to support children with significant cardiac disease (2). This effect may be due more to the reduction of mean intrathoracic pressure secondary to lower ventilator rates than to any modest improvement in arterial oxygenation. The reduction in ventilator rate is possible because of the efficient removal of CO₂ during ECMO. Our prediction that CO₂ production can be cleared by membrane blood flows of ~30% Qₜ (Eq. 14) corresponds well with our clinical experience and the reported observations of others in humans (12) and rabbits (5). Sufficient oxygenation can be achieved with ventilator rates of 5 breaths/min, with consequent reductions in mean airway pressure (1).

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Received 5 August 1994; accepted in final form 27 February 1995.

**REFERENCES**


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