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Evaluation of a mathematical model to predict intrapulmonary shunt non-invasively

Purpose: We have previously published a mathematical model of oxygen transport. Using several physiological assumptions, the model provides a non-invasive estimate of intrapulmonary shunt. During a larger study of lung injury in a pig model, we had the opportunity to check the validity of our assumptions and the accuracy of the model's predictions.

Methods: We used six female pigs, average weight 12.8 kg. Following general anesthesia, tracheostomy and insertion of pulmonary venous and arterial lines, lung injury was induced by repeated saline lung lavage. Using hemodynamic measurements made at different levels of inspired oxygen, intrapulmonary shunt was calculated both by the traditional shunt equation and also by our mathematical model based on non-invasive measurements of F_iO_2 and SaO_2 .

Results: There was good agreement between the two methods of shunt calculation. Using linear regression the correlation coefficient was 0.95. Bland and Altman analysis showed a bias of -0.8 and precision of 12%.

Conclusion: In a controlled setting, intrapulmonary shunt can be estimated from non-invasive measurements to a reasonable degree of accuracy. However, the calculation requires too many assumptions to be of general clinical value. The equations used provide a validated physiological model that acts as a useful tool for teaching cardiorespiratory physiology.

Objectif : Nous avons publié déjà un modèle mathématique de transport d'oxygène qui, en utilisant certaines hypothèses physiologiques, fournit une estimation non effractive du shunt intrapulmonaire. Lors d'une étude plus importante de la lésion pulmonaire avec un modèle porc, nous avons pu vérifier la validité de nos hypothèses et l'exactitude des prédictions modélisées.

Méthode : Nous avons utilisé six porcs femelles dont le poids moyen était de 12,8 kg. Après l'anesthésie générale, la trachéotomie et l'insertion de cathéters artériel et veineux pulmonaires, la lésion du poumon a été provoquée par un lavage du poumon avec une solution salée. Le shunt intrapulmonaire a été calculé, à partir de mesures hémodynamiques réalisées à différents niveaux d'oxygène inspiré, selon l'équation de shunt habituelle et aussi selon notre modèle mathématique basé sur les mesures non effractives de F_iO_2 and SaO_2 .

Résultats : Il y avait une bonne correspondance entre les résultats des deux méthodes de calcul de shunt. Selon la courbe de régression linéaire, le coefficient de corrélation était de 0,95. L'analyse de Bland et Altman a montré un biais de -0,8 et une précision de 12 %.

Conclusion: Dans une situation contrôlée, le shunt intrapulmonaire peut être évalué avec une précision acceptable à partir de mesures non effractives. Cependant, le calcul nécessite beaucoup trop de suppositions pour avoir une valeur clinique générale. Les équations utilisées fournissent un modèle physiologique validé qui peut servir d'outil d'enseignement de la physiologie cardiorespiratoire.

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ACCURATE assessment of the efficiency of oxygen transfer from inspired gas to arterial blood is an important part of the management of any critically ill child. The simplest estimates of oxygen transfer are based on the difference in partial pressures between alveolar oxygen (P_AO_2) calculated by the alveolar gas equation¹ and measured arterial oxygen (PaO_2). Whether the relationship between these variables is expressed as a gradient ($P_AO_2 - PaO_2$), a ratio (PaO_2/P_AO_2) or an index ($(P_AO_2 - PaO_2)/PaO_2$), the results have been shown to be unreliable indicators of the actual percentage of pulmonary venous flow that is shunted through unventilated alveoli.² This quantity is best estimated by the shunt equation:³

Equation 1

$$\frac{Q_s}{Q_t} = \frac{(C_c O_2 - C_a O_2)}{(C_c O_2 - C_v O_2)}$$

where Q_s is shunt flow, Q_t is cardiac output and $C_c O_2$, $C_a O_2$ and $C_v O_2$ are end capillary, arterial and mixed venous oxygen contents. Unfortunately, the terminology of pulmonary shunt varies. At 100% inspired oxygen, this equation predicts the true shunt. At lower levels of $F_I O_2$, the calculated value includes a component due to ventilation/perfusion mismatch and is often referred to as venous admixture (Q_{av}). Throughout this paper, the term Q_s refers to the calculated shunt at any level of $F_I O_2$.

Clinical application of the shunt equation is limited by the requirement for a mixed venous blood sample. Two methods have been used to estimate $C_v O_2$ without the need for a pulmonary artery catheter. A vena caval blood sample can be substituted with fair accuracy⁴ but it still requires the use of a central line. Alternatively, an estimated shunt can be calculated using an assumed arterial-venous oxygen content difference⁵ ($C_{(a-v)} O_2$). Although $C_{(a-v)} O_2$ can vary widely⁶ with critical illness, this technique has been updated⁷ and used clinically.⁸

We previously published a mathematical model of oxygen transport that did not require a term for $C_v O_2$ ⁹ so allowing us to calculate Q_s non-invasively. The model is easily displayed on a standard computer spreadsheet and has proved to be a useful teaching tool but, until recently, we had no opportunity to test its physiological validity.

The main aim of this study was to examine the accuracy of our predictions by comparing predicted values of Q_s with calculated values measured during a larger study of acute lung injury in pigs. We also wished to test the validity of the assumptions that have

to be made in order to use the model.

Methods

Mathematical model

We have previously described a mathematical model of oxygen transport.⁹ Its derivation depends on the resolution of the shunt equation and the Fick equation. The shunt equation (eq 1) describes the relationship between pulmonary shunt fraction (Q_s/Q_t) and the blood oxygen contents at various points in the pulmonary circuit ($C_a O_2$, $C_v O_2$ and $C_c O_2$). The Fick equation¹⁰ describes the relationship between oxygen consumption (V_{O_2}), cardiac output (Q_t) and the arterial-venous oxygen content difference.

Equation 2

$$Q_t = \frac{V_{O_2}}{C_a O_2 - C_v O_2}$$

At equilibrium, equations 1 and 2 can be considered as simultaneous. They can be rearranged to solve for Q_s after substituting for $C_v O_2$.

Equation 3

$$Q_s = \frac{Q_t(C_c O_2 - C_a O_2)}{C_c O_2 - C_a O_2 + \frac{V_{O_2}}{Q_t}}$$

The result is a predictive model for Q_s that does not require the calculation of $C_v O_2$. However, the list of unknown variables is long. Apart from Q_t and V_{O_2} , the calculation of $C_c O_2$ and $C_a O_2$ requires the following: barometric pressure (P_B), saturated water vapour pressure (P_{swv}), SAO_2 , $F_I O_2$, PaO_2 , hemoglobin (Hb), respiratory quotient (RQ) and $PaCO_2$. Several of these variables can be measured with minimal invasion ($F_I O_2$, SAO_2 , $PaCO_2$, P_B , Hb). PaO_2 can be derived from SAO_2 using Thomas' algorithm.¹¹ Based on another study of cardiorespiratory variables in critically ill children,¹² we found that the remaining unknown variables remain surprisingly constant in paralysed children ($V_{O_2} = 4.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $V_{CO_2} = 3.5 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$, $Q_t = 80 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$, Hb = 120 g·L⁻¹). Substituting these values into equation 3, it is possible to construct an iso-shunt diagram (Figure 1). Using this graph, Q_s can be predicted based on non-invasive measurements of $S_a O_2$ and $F_I O_2$. The reliability of the prediction clearly depends on the validity of the underlying assumptions.

Animal preparation

Our investigation was part of a larger study designed to investigate the management of acute lung injury. The study was approved by the Hospital Ethics Committee and the University of British Columbia Animal Care Committee. Six pigs with an average weight 12.8 kg were studied. Following premedication ($0.02 \text{ mg}\cdot\text{kg}^{-1}$ atropine, $20 \text{ mg}\cdot\text{kg}^{-1}$ ketamine, $0.2 \text{ mg}\cdot\text{kg}^{-1}$ midazolam *im*), anesthesia was induced with inhaled halothane and oxygen and then maintained with a thiopental infusion ($3.3 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$) and pancuronium boluses ($0.1 \text{ mg}\cdot\text{kg}^{-1}$) to maintain muscle relaxation. The lungs were intubated and ventilated at a rate of 25 bpm, tidal volume $10 \text{ ml}\cdot\text{kg}^{-1}$ and end expiratory pressure of $5 \text{ cm H}_2\text{O}$.

Study design

Following preparation of the animal, acute lung injury was induced by recurrent lung lavage with warm saline until $P_a\text{O}_2$ was less than 100 mm Hg at $F_{\text{I}}\text{O}_2$ of 1.0. The inspired oxygen was reduced from 1.0 to 0.21 in five steps followed by an equilibration period of 30 min. At each level, simultaneous samples of systemic and pulmonary arterial bloods were taken and analysed immediately to obtain the following data: Hb, SaO_2 , PaO_2 , PaCO_2 , SvO_2 , PvO_2 . Heart rate and cardiac output were also measured. Subsequently, two independent observers calculated Q_s : one using the classical shunt equation (eq 1) and the other using only non-invasive measurements of $F_{\text{I}}\text{O}_2$ and SaO_2 to estimate Q_s using the iso-shunt diagram (Figure 1).

Statistical analysis

The estimates of Q_s were compared using two techniques. The first was linear regression using the method of least squares analysis. The degree of agreement was expressed as a correlation coefficient. Comparisons were also made using the Bland and Altman statistical method.¹³ Briefly, this method involves first a graphic representation of the plot of the difference between the paired results against their mean value. The agreement between the two measurements can then be summarised by calculating the bias (mean of the paired differences) and the precision, or limits of agreement, represented by the standard deviation of the mean difference. If the differences are normally distributed, one can expect 95% of the values to lie between these limits.

Results

We found it more difficult to induce lung injury in the pigs than previous reports had suggested.¹⁴ In addition, once injury was established, it did not remain

FIGURE 1 The effect of varying inspired O_2 fraction ($F_{\text{I}}\text{O}_2$) upon arterial O_2 saturation (SaO_2) predicted for levels of pulmonary shunt fraction (Q_s/Q_t) from 10% to 60%. Calculations are based on a hypothetical child, $Q_t = 80 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$, $V_{\text{O}_2} = 4.5 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$, $V_{\text{CO}_2} = 3.5 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$, $\text{Hb} = 120 \text{ g}\cdot\text{L}^{-1}$.

FIGURE 2 Measured shunt fraction (Q_s/Q_t) compared with predicted values using the technique of Bland and Altman. The difference is plotted against their mean value. Bias = 0.8% , precision = 12.2% .

stable over the four hours of the experiment; four animals worsened while two improved.

Thirty-two paired measurements of Q_s were made in six animals. The correlation coefficient (r), calculated by the method of least squares was 0.95 . The predicted values of Q_s based on our assumed values of Q_t , V_{O_2} , V_{CO_2} and Hb were generally lower than the calculated measurements. This becomes clear when comparison is made using the method of Bland and

Altman¹³ (Figure 2). It can be seen that the majority of points fall below the line. A few positive outliers above the line balance this trend so the calculated bias is only 0.8%. The precision was 12.2%.

The initial assumptions of Q_t , V_{O_2} , V_{CO_2} and Hb required for the prediction of iso-shunt curves for children (Figure 1) appeared to be reasonable. Mean values measured in pigs were all slightly higher ($Q_t = 92$ vs 80 ml·min⁻¹·kg⁻¹, $V_{O_2} = 5.1$ vs 4.5 ml·min⁻¹·kg⁻¹, $V_{CO_2} = 3.9$ vs 3.5 ml·min⁻¹·kg⁻¹, Hb = 125 vs 120 g·L⁻¹). The effect of an increased V_{O_2} was balanced by a higher Q_t so that the predicted values of Q_s did not change.

Discussion

We calculated intrapulmonary shunt using a non-invasive technique and compared it to an invasive "gold standard" in an animal model of acute lung injury. Although the correlation coefficient between the two measurements was 0.95, the scatter of results demonstrated by the Bland and Altman plot (Figure 2) shows that the non-invasive prediction can only be viewed as an approximation to the true value. Our results are comparable with other non-invasive techniques for estimating Q_s/Q_t . Calculations based on substituting a vena caval blood sample generated a correlation coefficient of 0.97⁴ which compares well with our coefficient of 0.95. Similarly, Hope's¹⁵ updated validation of Benatar's "virtual shunt" based on an assumed $C_{(a-v)}O_2$ ⁵ produced a bias of 0.7% and a precision of 15.8% which, again, compares well with our measurements of 0.8% and 12.2% respectively.

There is a limit to the approximations that any mathematical equation will tolerate. The various attempts to estimate Q_s/Q_t without the need for a pulmonary arterial blood sample are no exception. Small improvements in accuracy are possible by substituting measured values for some of the assumed variables¹⁵ but the final result is still only a prediction. The assumptions underlying our mathematical model are based on extensive experience with critically ill children¹² but clearly cannot be expected to sum up every single patient. Once a reliable idea of the hemodynamic variables of a particular population is obtained, it would be possible to "tune" the iso-shunt lines for that group. For instance, it would be possible to remove the small bias noted in the Bland and Altman plot by changing some of the assumed variables. However, the small improvement in accuracy would hardly justify the extra work.

The recent debate concerning the value of pulmonary artery catheters¹⁶ reflects the trend (particularly in pediatrics) towards non-invasive monitoring. A balance has to be found between the information

derived from invasive catheters and the potential risk of side effects. At a time when non-invasive techniques are increasing in sophistication, it is probable that the necessity to derive Q_s - by whatever means - will decrease, making it unlikely that iso-shunt lines will have much clinical value. However, a detailed understanding of cardiopulmonary physiology will always be essential. This study has shown that our predictive equation provides a realistic model that gives a useful tool for teaching the physiology of oxygen transport.

References

- 1 Nunn J. *Applied Respiratory Physiology*, 4th ed. Oxford: Butterworth Press, 1993: 195-6.
- 2 Cane RD, Shapiro BA, Templin R, Walther K. Unreliability of oxygen tension-based indices in reflecting intrapulmonary shunting in critically ill patients. *Crit Care Med* 1998; 16: 1243-5.
- 3 Nunn J. *Applied Respiratory Physiology*, 4th ed. Oxford: Butterworth Press, 1993: 178-9.
- 4 Reinhart K, Rudolph T, Bredle DL, Hannemann L, Cain SM. Comparison of central-venous to mixed-venous oxygen saturation during changes in oxygen supply/demand. *Chest* 1989; 95: 1216-21.
- 5 Benatar S, Hewlett A, Nunn J. The use of iso-shunt lines for control of oxygen therapy. *Br J Anaesth* 1973; 45: 711-8.
- 6 Harrison RA, Davison R, Shapiro BA. Reassessment of the assumed A-V oxygen content difference in the shunt equation. *Anesth Analg* 1975; 54: 198-202.
- 7 Roe PG, Jones JG. Analysis of factors which affect the relationship between inspired oxygen partial pressure and arterial oxygen saturation. *Br J Anaesth* 1993; 71: 488-94.
- 8 Dingley J, Hope DA, Vaughan RS. The use of a non-invasive method to measure intrapulmonary shunt during one-lung anaesthesia. *Anaesthesia* 1996; 51: 654-7.
- 9 Secar M, Anderson B, Hall R, Hui H. Mathematical model of oxygen transport: a teaching aid for normal physiology adaptable to extracorporeal oxygenation circuits. *Am J Physiol (Adv Physiol Educ)* 1995; 268: S32-9.
- 10 Nunn J. *Applied Respiratory Physiology*, 4th ed. Oxford: Butterworth Press, 1993: 152.
- 11 Thomas LJ Jr. Algorithms for selected blood acid-base and blood gas calculations. *J Appl Physiol* 1972; 33: 154-8.
- 12 Secar M, Wensley D, MacNab A. Oxygen consumption-oxygen delivery relationship in children. *J Pediatr* 1993; 123: 208-14.
- 13 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1: 307-10.

- 14 *Nielsen JB, Sjöstrand UH, Edgren EL, Lichtwarck-Aschoff M, Svensson BA.* An experimental study of different ventilatory modes in piglets in severe respiratory distress induced by surfactant depletion. *Intensive Care Med* 1991; 17: 225–33.
- 15 *Hope DA, Jenkins BJ, Willis N, Maddock H, Mapleson WW.* Non-invasive estimation of venous admixture; validation of a new formula. *Br J Anaesth* 1995; 74: 538–43.
- 16 *Connors AF Jr, Speroff T, Dawson NV, et al.* The effectiveness of right heart catheterization in the initial care of critically ill patients. *JAMA* 1996; 276: 889–97.