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A simple gas exchange model predicting arterial oxygen content for various FiO_2 levels

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Abstract — **The application of mechanical ventilation is a life-saving routine therapy that allows the patient to overcome the physiological impact of surgeries, trauma or critical illness by ensuring vital oxygenation and carbon dioxide removal. Above a certain level of minute ventilation (usually set to ensure acceptable carbon dioxide removal and oxygenation) oxygenation is only marginally affected by a further increase in minute ventilation. Thus, oxygenation is predominantly influenced by inspiratory oxygen fraction (FiO_2) Usually, finding the appropriate setting is a trial-and-error procedure, as the clinician is unaware of the exact value that needs to be set in order to reach the desired arterial oxygen partial pressures (PaO_2) in the patient.**

Mathematical models of physiological processes in the human body may be used to predict patient reactions towards alterations in the therapy regime. These predictions can be exploited by Medical Decision Support Systems to find optimal therapy settings. A simple mathematical model is presented, that allows calculation of a patient's shunt fraction, i.e. the percentage of blood that is not participating in lung gas exchange. On this basis, it predicts PaO_2 at various FiO_2-levels and thus allows reaching desired PaO_2 in just one step. Due to its simple design it does not require complicated - and possibly error-prone - parameter identification procedures, thus allowing its application at the bedside.

Retrospective analysis of oxygenation data from a patient data management system showed that the presented model predicted PaO_2 with less than 10% deviation in 23 out of 29 measurements, proving the practical applicability of the presented model approach.

I. Introduction

The application of mechanical ventilation is a well established procedure that is routinely used in intensive care medicine. Mechanical ventilation often is a lifesaving therapy, providing oxygenation and carbon dioxide elimination in critical illness. When adjusting ventilator settings, the clinician's primary goal is to find appropriate settings to allow sufficient oxygenation and carbon dioxide removal. The fastest and most important way of providing vital oxygenation for the patient is by ensuring sufficient minute ventilation and by optimizing inspired oxygen fraction (FiO_2). However, above a certain level of minute ventilation, arterial oxygen partial pressure (PaO_2) is only minimally affected by a further increase in minute ventilation. Thus, with minute ventilation adjusted to ensure acceptable levels of carbon dioxide in the blood, FiO_2 is the most important parameter determining PaO_2. The adjustment of FiO_2 to achieve the desired PaO_2 in an individual patient usually is trial-and-error based, i.e. the clinician is unaware of the exact value of FiO_2 that needs to be set in order to reach the desired oxygenation in the patient. To avoid exposing the patient to hypoxia or hyperoxia, FiO_2-changes are usually performed in small steps and blood gas analysis is done frequently after changes in FiO_2. On the average, between two and three of these steps are needed by the clinician to reach the desired PaO_2. Enabling the clinician to reach the desired PaO_2 in just one step would therefore lead to achieving normoxia in the patient after a shorter time span, eliminating most of the required blood gas analysis and thus decreasing the number of blood samples that need to be drawn from the patient. It would therefore decrease therapy costs due to smaller number of necessary blood gas tests and shorter observation time needed by the clinician.

Mathematical models can aid in the understanding of the human body and its physiological processes as well as in optimizing the applied therapeutic strategy. The application of such models in medical decision support may lead to optimization of ventilation quality. Simple models of gas exchange might thus allow the clinician to gain information about the patient's underlying physiology and enable the prediction of the patient's reaction to changes in the ventilator settings.

Mathematical models need to be adapted to the individual patient to be able to represent its reaction to the therapeutic setting. However, the parameter identification of complex models is difficult in situations where monitoring is minimal. Yet a robust parameter identification is mandatory for practical use of mathematical modeling in a clinical environment. Therefore, models should always be kept as simple as possible to capture the present disease.

Below, a simple model of gas exchange is proposed, that allows calculation of the shunt fraction of an individual patient as well as predicts arterial oxygen partial pressures for specific FiO_2 levels.

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II. Materials and Methods

A. Mathematical model

The proposed model is related to the model presented by Riley [1]. However, it divides the lungs into just two compartments. One compartment is well perfused and ventilated; the other compartment is perfused but not ventilated. Its magnitude is depicted by the shunt parameter, i.e. the fraction of blood that does not participate in gas exchange. Thus, air enters the ventilated compartment, where oxygen gets dissolved in blood and carbon dioxide is eliminated from the blood. End-capillary blood then mixes with the shunted venous blood to become the arterial blood stream. The model does not contain separate inspiration/expiration-phases, i.e. alveolar gas flow and alveolar volume are constant. Figure 1 shows a schematic description of the proposed model. Here, P denotes partial gas pressure, C is blood gas concentration, V is air volume and $\dot{V}$ is air flow. Q describes the cardiac output and fs is the shunted fraction of blood. Indices are I (Inspiratory), A (Alveolar), e (end-capillary), v (venous) and a (arterial).

Alveolar partial pressure of oxygen (PAO2) can be calculated using the alveolar gas equation [2] assuming that alveolar carbon dioxide partial pressure is equal to the partial pressure found in arterial blood:

$$P_{A,O2} = F_{i,O2} \cdot (P_{atm} - P_{H2O}) - \frac{P_{a,CO2} \cdot \left[1 - F_{i,O2} \cdot (1 - RQ)\right]}{RQ} \quad (1)$$

Here, FiO_2 is the inspired oxygen fraction, P_{atm} is atmospheric pressure, P_{H2O} is water vapor pressure, $PaCO_2$ is arterial partial pressure of carbon dioxide and RQ is the respiratory quotient. Under the assumption that alveolar gas partial pressure is equal to end-capillary partial pressure, $C_{e,O2}$ can be calculated as in (2).

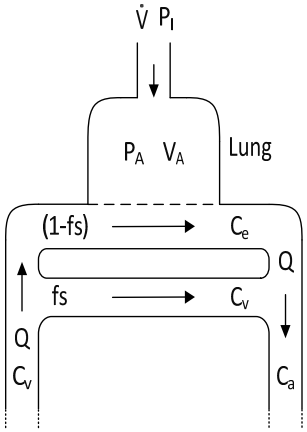

Fig. 1. Schematic representation of the two-compartment model of lung gas exchange. P denotes partial gas pressure, C is blood gas concentration, V is air volume and $\dot{V}$ is air flow. Q describes the cardiac output and fs is the shunted fraction of blood. Indices are I – Inspiratory, A – Alveolar, e – end-capillary, v – venous and a – arterial.

$$C_{O2} = k_1 \cdot Hb \cdot S_{O2} + k_2 \cdot P_{O2} \quad [3] \quad (2)$$

Here, k_1 and k_2 are constants ($k_1 = 1.312 \cdot 10^{-3}$ [l/g], $k_2 = 3.03 \cdot 10^{-5}$[$mmHg^{-1}$]), Hb is the Haemoglobin concentration, S_{O2} is the oxygen saturation. S_{O2} is calculated using Kelman's equations describing the oxygen dissociation curve [4], where S_{O2} is a function of PaO_2, $PaCO_2$, pH and body temperature. Arterial oxygen gas content (CaO_2) can be calculated from arterial oxygen partial pressure (PaO_2) using (2). PaO_2 is measurable by blood gas analysis. Finally, CvO_2 can be calculated assuming a constant arterial-venous oxygen difference (standard value: 5 [ml/dl]) [2]:

$$C_{v,O2} = C_{a,O2} - a/\bar{v}\, Diff \quad (3)$$

Shunt fraction fs is then defined as [5]:

$$fs = \frac{\left(C_{e,O2} - C_{a,O2}\right)}{\left(C_{e,O2} - C_{v,O2}\right)} \quad (4)$$

Thus, shunt fraction of an individual patient can be calculated using measurements from just one blood gas analysis providing Hb, $PaCO_2$ and PaO_2. Assuming that shunt fraction is not altered with different inspired oxygen fractions, resulting PaO_2 can be predicted for arbitrary FiO_2. To this extend, (1) and (2) are used to calculate PAO_2 and CeO_2. CaO_2 can then be calculated by combining (3) and (4):

$$C_{a,O2} = C_{e,O2} - \frac{fs \cdot a/\bar{v}\, Diff}{(1 - fs)} \quad (5)$$

PaO_2 is obtained by inversing (2). Due to its implementation, the equation describing the oxygen dissociation curve cannot be inversed directly. Thus, PaO_2 is calculated iteratively employing the Nelder-Mead Simplex-Search method [6].

B. Graphical user interface

The proposed model is intended for direct use at the bedside. The clinician should be able to use its calculations to get information about the patients health status and predict the outcome of applied inspired oxygen content. Both should be possible without the implementation of the model in a medical decision support system. Thus, a graphical user interface was designed in MATLAB® (R2012a, The Mathworks™, Natick, USA), that allows clinicians to apply model calculations without further knowledge or technical frameworks. Figure 2 shows an illustration of the graphical user interface. It allows entering required data from one blood gas analysis. After calculation of the patient's shunt, the clinician can use the GUI to predict PaO_2 for arbitrary FiO_2 as well as calculate required FiO_2 for a desired PaO_2 outcome. All information is displayed both in numbers and graphically in an iso-shunt diagram [5].

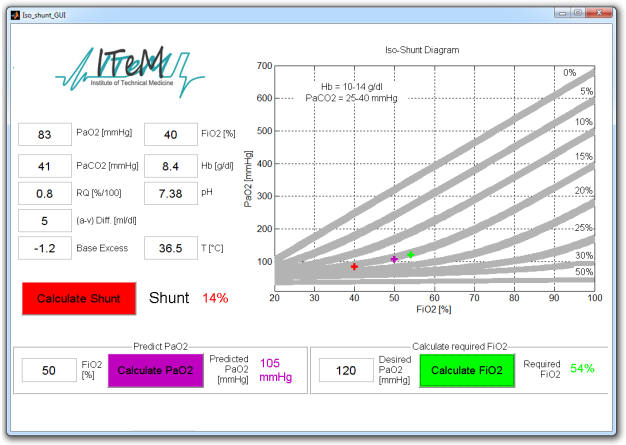

Fig. 2. Graphical user interface for straightforward use of the proposed model to calculate shunt, required FiO_2 and predict PaO_2 at the bedside. The clinician is able to enter data from one blood gas analysis. After calculation of shunt, PaO_2 can be predicted for arbitrary FiO_2 and required FiO_2 for desired PaO_2 can be calculated.

C. *Patient data*

Anonymized blood gas analysis results taken from a patient data management system (PDMS) were used to evaluate the proposed model. Only patient data with more than two blood gas results were used for evaluation. Selection of patients was not limited to healthy patients; also severely ill patients were included into the evaluation. The recorded FiO_2 levels in the data have been applied on a therapeutic basis, not in the context of a clinical trial. All patients were ventilated with a minute ventilation that ensures acceptable levels of carbon dioxide content in the blood. In total, data from 10 patients was used for evaluation.

D. *Evaluation*

In clinical practice, titration usually starts at high levels of FiO_2 to avoid hypoxia. Thus, in each patient, PaO_2 measured at the highest applied FiO_2 was used to calculate shunt fraction. Remaining PaO_2-measurements were used for evaluation, i.e. a total of 29 data points were available for testing. Temperature and blood gas measurements (pH, Base excess, $PaCO_2$) were fixed to the values found in the first PaO_2 measurement, i.e. at the highest applied FiO_2. Figure 3 shows the evaluation process.

III. Results

Results show a maximum difference of 18% between measured and predicted PaO_2. Mean difference was 6.3% with a standard deviation of 4.8%. 6 of the 29 predicted PaO_2 values showed a deviation greater than 10%, where the mean difference was 13.3% with a standard deviation of 2.5%. The remaining 23 values were all predicted with less than 10% difference; here, mean error was 4.5% with a standard deviation of 3.3%.

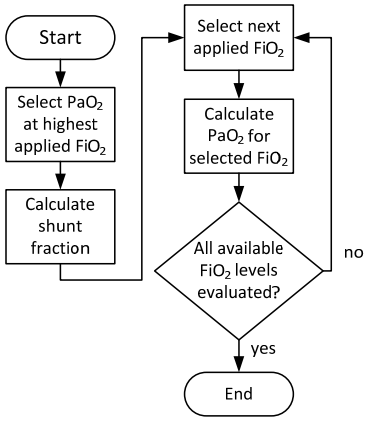

Fig. 3. Flow chart of the evaluation process. In every patient data set, highest applied FiO_2 is used to calculate shunt fraction. Based on the assumption that shunt value is constant for all FiO_2 levels, PaO_2 can be calculated for all applied inspiratory oxygen fractions.

Figure 4 shows a comparison of measured and predicted PaO_2 values. Here, solid line depicts 0% error between measured and predicted values, dotted lines show +/-10% error bounds. Calculated shunts for all patients show a mean value of 17.5% with a standard deviation of 7.7%.

IV. Discussion

Clinicians selecting ventilator settings for individual patients both lack from deeper insights into the patient's physiology as well as the ability to predict the outcome of a certain therapeutic setting. The proposed model provides knowledge about the patient's disease state through calculation of shunt fraction as well as enables prediction of PaO_2 for various FiO_2 levels. Predictions of PaO_2 show to be mostly within a 10% error range. Deviations greater than 10% were all found to be caused by interventions by the clinician which altered oxygenation in the patient (suction of respiratory tract, repositioning). Predictions of PaO_2 within the 10% range did not have preceding interventions. For the sake of evaluating the proposed model under circumstances close to reality however both data with and without interventions was used.

Wang et al. proposed a model of gas exchange that allows prediction of patient's reaction to changes in the ventilator settings as well as enables optimization of ventilation therapy [7]. The model consists of five compartments (alveolar, pulmonary, arterial, tissue and venous) and comprises five parameters, that need to be identified (shunt, dead space volume, oxygen consumption, carbon dioxide production and cardiac output). Validation using PDMS data from 46 patients showed a mean deviation of 13.9% between measured and predicted PaO_2. Bigeleisen presents model calculations also based on Riley's propositions and the iso-shunt diagrams presented by Benatar [8]. However, the proposed model is either depended on pulmonary catheterization to receive the necessary measurements or is

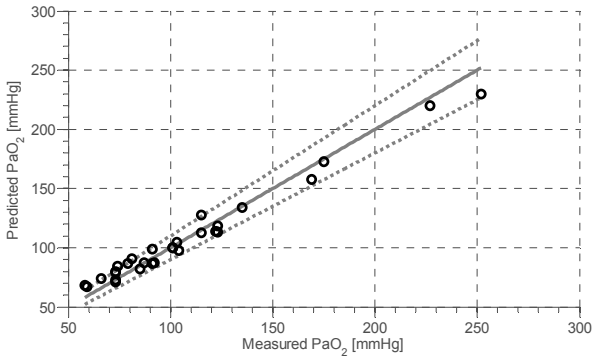

Fig. 4. Comparison between measured and predicted PaO_2 at different applied FiO_2 levels for all evaluated patients. Solid line depicts 0% error between measured and predicted values, dotted lines show +/- 10% error bounds. Mean difference was found to be 6.3% with a standard deviation of 4.8%. 23 out of the total 29 measurements were predicted with less than 10% error.

limited to the use in conditions, where both PaO_2 and PAO_2 lie along the flat part of the oxygen dissociation curve.

The simple design of the model comprising only one parameter to be adapted to the patient allows direct calculation of shunt fraction from just one blood gas analysis without the need for complicated - and possibly error-prone - parameter identification procedures. Still, the evaluated patient group showed a mean difference of just 6.3% between measured and predicted PaO_2. The proposed model includes a number of assumptions for the sake of simplicity. These are - among others - the exclusion of ventilation/perfusion-mismatches, inspiration/expiration, diffusion limitations and changes in oxygen consumption and carbon dioxide production. Thus, the use of this model is limited to patients with a constant disease state. Rapid changes in oxygenation, that might be caused by suctioning or repositioning of the patient, cannot be predicted by the model. However, deviant PaO_2 predictions might be exploited as an indicator for changes in the patient's disease state.

Moreover, the calculation of shunt and the prediction of PaO_2 does not consider changes in minute ventilation. Therefore, it is only applicable in patients, where minute ventilation is set to ensure adequate oxygen and carbon dioxide levels. However, in most patients in the ICU minute ventilation is set accordingly. The model assumes a constant arterial-venous oxygen difference set to a standard value found in literature. The quality of the shunt estimation is greatly affected by the correctness of the arterial-venous oxygen difference. The prediction of PaO_2 is also based on this parameter but is not affected by any estimation errors. The a/v-difference is used in both the calculation of shunt and the prediction of PaO_2, eliminating the influence of any estimation error in the prediction process. Thus, even if the calculated shunt should show to be incorrect due to a false a/v-difference, PaO_2 prediction is still correct. To achieve a more precise prediction of actual shunt, arterial-venous oxygen difference may be calculated by taking arterial and mixed-venous blood samples at the same time or by measuring cardiac output. The evaluation of shunt values calculated by the model should therefore be focused on in further research.

The presented user interface allows the straightforward bedside use of the model calculations allowing the clinician to set FiO_2 to the correct value in just one step.

Information gained by the model can be helpful in parameter identification of more complex models. Schranz et al. presented a hierarchical approach for robust identification in models of lung mechanics [9]. It is based on the idea that parameters of simple models that can be calculated directly from patient data may be exploited to find suitable initial guesses in the identification of more complex models. The presented model would enable the same approach in a hierarchical model of gas exchange.

V. Conclusion

The presented simple model of gas exchange allows the prediction of the FiO_2 level that is necessary to achieve a clinically desired PaO_2, eliminating the need for trial-and-error based FiO_2-step maneuvers. A future extension of the presented technique should be to include information gained by additional blood gas analyses.

If arterial-venous oxygen difference is known, it also allows the calculation of a patient's shunt and thus provides the clinician with further knowledge about the patient's disease state.

The presented graphical user interface allows the use of model calculations at the bedside without further technical knowledge by the clinician. An Android based app for display of the model calculations on tablets or smartphones is currently in development.

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