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Estimating the Measuring Effort for Using a Two-Parameter Gas Exchange Model in Clinical Practice

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Abstract: Mathematical models of human gas exchange may support clinicians in interpreting a patient's respiratory state during mechanical ventilation. Patient-specific parameters based on measured data under different clinical settings, e.g. various combinations of inspired oxygen fraction (FiO_2) and minute ventilation (MV), enable these models to predict clinically relevant parameters such as arterial partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$). Accuracy of predictions depends on parameter identification which in turn is influenced by measuring precision and data quality. In consequence, erroneous or noisy measurements may lead to wrong clinical decisions. Therefore it is investigated how measurement effort for identification of a two-parameter model of pulmonary gas exchange can be minimized to allow an efficient use in clinical practice. Simulated patient data was corrupted with artificial noise to investigate its influence on parameter identification and model prediction of PaO_2 and $PaCO_2$. Analysis was conducted with data representing lung conditions of different severity of lung failure. Results show that model prediction of PaO_2 and $PaCO_2$ is possible with a deviation below clinical relevance using only two blood gas data sets at different FiO_2-levels. The effort necessary for robust parameter identification varies with the patient's health state i.e. the degree of lung failure.

Keywords: Mathematical models, parameter identification, model-based control, initial states, gas exchange, noise analysis.

1. INTRODUCTION

As a routinely applied therapy in the intensive care unit, mechanical ventilation ensures patient's oxygen (O_2) supply and removal of carbon dioxide (CO_2) in acute lung failure. Clinicians are confronted with the task of finding appropriate ventilator settings based on a variety of patient monitoring data. Inadequate ventilator settings involve the risk of ventilator induced lung injuries (VILI) as well as O_2 and CO_2 toxicity. Currently, research is driven by the need for a decision support system being able to assist the clinicians with this dilemma.

Besides knowledge-based approaches to achieve suggestions for appropriate ventilator settings, also mathematical models simulating human gas exchange may support the clinician in achieving a desired ventilation goal (Allerod et al. 2008). Model-based decision support allows a patient-specific interpretation of measurements and the calculation of individual parameters, providing further diagnostic insight in the patient's respiratory state. To identify those patient-specific parameters (parameter identification process — PIP), both patient monitoring data and blood gas measurements are required. Model parameters are tuned such that simulation results fit the observed patient reactions. Consequently individualized models may be used as basis to calculate optimized settings for inspired oxygen fraction (FiO_2) and minute ventilation (MV) to achieve targeted arterial partial pressures of O_2 (PaO_2) and CO_2 ($PaCO_2$).

The accuracy of model simulation and reproduction of data usually rises with model complexity. Simple one-parameter models can be identified using minimal measuring effort but are not able to reproduce both patient's O_2 and CO_2 data simultaneously (Karbing et al. 2011). Therefore, the usage of trivial models is only sufficient in patients without obstructions in gas exchange. To describe gas exchange of patients with lung disease, more complex models involving multiple parameters considering both O_2 and CO_2 blood gases are necessary. Our work deals with a two-parameter model of pulmonary gas exchange assuming constant flow and steady state conditions. The model comprises a shunt as well as two alveolar compartments with different ventilation and perfusion ratios. The latter allows simulation of $\dot{V}/Q$-mismatch in the patient. Former work shows promising results for a robust identification of this model in patients with acute respiratory distress syndrome (ARDS) using blood gas data at four different FiO_2 steps and appropriate parameter initialization (Riedlinger et al. 2013). Model based decision support requires an accurate prediction of PaO_2 and $PaCO_2$, which depends on both the model that is used for prediction and a robust identification of its parameters. Robust identification requires patient data acquired during certain ventilation maneuvers. This again contradicts clinical practice, where models should be identifiable with minimal data and without additional effort by the clinician. The work at hand thus investigates how PIP of a two-parameter gas exchange model with $\dot{V}/Q$-mismatch and shunt could be established with a minimum of measuring effort.

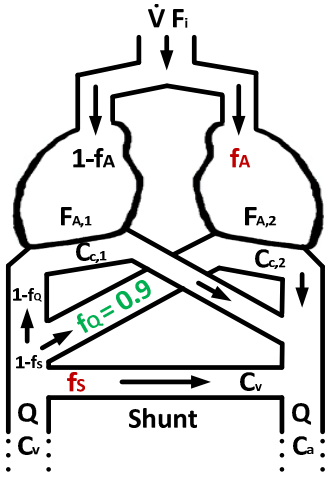

Fig. 1. Model structure: Model parameters to identify are shunt fraction f_S and ventilation distribution f_A. Perfusion distribution f_Q is fixed. Symbols are F – gas fraction, C – gas concentration, V̇ – ventilation, Q – perfusion, i – inspired, A – alveolar, a – arterial, v – venous.

2. MATERIALS AND METHODS

2.1 Model

The analyzed gas exchange model is based on a model concept assuming continuous flow and steady state conditions (Vidal Melo et al. 1993, Karbing et al. 2011). It acts on the assumption of two alveolar compartments with a different distribution of ventilation (V̇) and perfusion (Q) as well as a shunt compartment. The shunt fraction f_S defines the amount of blood that is not participating in gas exchange. Parameters f_A and f_Q describe the fractions of alveolar ventilation and perfusion respectively in one of the two lung compartments. Parameter f_Q is set to a fixed value (f_Q = 0.9) (Kjaergaard et al. 2001) to reduce the number of free parameters. V̇/Q-mismatch then is defined through parameter f_A representing the fraction of ventilation in the compartment that receives 90% of the non-shunted blood flow. Model structure and model parameters are depicted in Fig. 1. Model inputs are inspired and end-tidal gas fractions (FiO_2, $FiCO_2$, $FetO_2$, and FetCO2) as well as V̇ and Q.

Model equations (1) to (11) are taken from Karbing et al. (2011) and describe arterial concentrations of both blood gases O_2 and CO_2 for certain inspired and end-tidal fractions (Fi_x, Fet_x), where x is either O_2 or CO_2, respectively. Alveolar ventilation $\dot{V}_A$ depends on respiratory frequency f_R, the tidal volume V_{tid} and the anatomic dead space volume V_{ds}:

$$\dot{V}_A = f_R\,(V_{tid} - V_{ds}) \quad (1)$$

End tidal gas fractions Fet_x are composed of alveolar gas fractions (FA_x) in the two lung compartments:

$$F_{et,x} = (1 - f_A)\,F_{A,x,1} + f_A\,F_{A,x,2}\,. \quad (2)$$

Oxygen uptake ($\dot{V}O_2$) for both compartments results from compartmental alveolar flow and the difference between inspired and alveolar oxygen fraction:

$$\dot{V}_{O2,1} = (1 - f_A)\,\dot{V}_A\,(F_{i,O2} - F_{A,O2,1}) \quad (3)$$

$$\dot{V}_{O2,2} = f_A\,\dot{V}_A\,(F_{i,O2} - F_{A,O2,2}) \quad (4)$$

As inspired fraction of CO_2 is supposed to be zero, carbon dioxide removal ($\dot{V}CO_2$) can be calculated using (5) and (6).

$$\dot{V}_{CO2,1} = (1 - f_A)\,\dot{V}_A\,F_{A,CO2,1} \quad (5)$$

$$\dot{V}_{CO2,2} = f_A\,\dot{V}_A\,F_{A,CO2,2} \quad (6)$$

Venous blood gas concentrations separated in both compartments then are given by (7) to (10).

$$C_{v,O2,1} = C_{c,O2,1} - \dot{V}_{O2,1}/(Q\,(1 - f_s)\,\cdot 0.1) \quad (7)$$

$$C_{v,O2,2} = C_{c,O2,2} - \dot{V}_{O2,2}/(Q\,(1 - f_s)\,\cdot 0.9) \quad (8)$$

$$C_{v,CO2,1} = C_{c,CO2,1} + \dot{V}_{CO2,1}/(Q\,(1 - f_s)\,\cdot 0.1) \quad (9)$$

$$C_{v,CO2,2} = C_{c,CO2,2} + \dot{V}_{CO2,2}/(Q\,(1 - f_s)\,\cdot\,0.9) \quad (10)$$

Equilibrium between gases in capillary blood and alveoli is assumed. Capillary partial gas pressures Pc_x then is calculated multiplying alveolar gas fractions FA_x by the difference between barometric pressure and saturated water vapor pressure at body temperature. Capillary blood gas concentrations Cc_x is derived from Pc_x with the help of O_2 and CO_2 dissociation curves (Kelman 1966; Meade 1972).

Equations (1) to (10) are used to estimate $FA_{x,1}$ and $FA_{x,2}$ numerically by satisfying the condition $Cv_{x,1}$=$Cv_{x,2}$. Finally, adding Cc_x (non-shunted blood) and concentration in shunted blood (Cv_x) leads to arterial blood gas concentrations

$$C_{a,x} = C_{c,x,1}\,(1 - f_s)\,0.1 + C_{c,x,2}\,(1 - f_s)\,0.9 + C_{v,x}\,f_s\,. \quad (11)$$

2.2 Analysis with simulated data

Patient data for model analysis was acquired in silico, i.e. simulated using the presented gas exchange model and standard values for an adult man. Different values were chosen for parameters f_S and f_A according to the desired lung status as specified in Table 1. PaO_2 and $PaCO_2$ were calculated at various levels of FiO_2 (FiO_2 = 21%, 40%, 60%, 80%, 100%) applying the inversed dissociation curves on the simulated CaO_2 and $CaCO_2$. The use of synthetic data allowed direct comparison of adjusted and identified parameter values. These data (Pa_x) served as input data for PIP. Identification was conducted by minimizing the sum of squared error (SSE) function between Pa_x and modelled partial pressures of oxygen and carbon dioxide (Pm_x) by changing values of model parameters f_s and f_A:

$$SSE = \sum_i \left(P_{m,O2} - P_{a,O2}\right)^2 + \sum_i \left(P_{m,CO2} - P_{a,CO2}\right)^2. \quad (12)$$

Carbon dioxide data in blood depend on the ventilation rate which was held constant for the simulation at 12 breaths per minute. Focus of this analysis lies on prediction of oxygen blood data. Initially, only one FiO_2 value and therefore one single data set from the artificial patient data was used for parameter identification. To analyse sensitivity and robustness of the PIP using one single FiO_2 data value only, a fixed offset (plus 5% of the original value) was added to artificial PaO_2 and $PaCO_2$. PmO_2 was then predicted with the model that was fitted to the modified data.

Table 1. Model parameters for simulation

Lung condition	f_S	f_A
Healthy	0.02	0.9
Mild ARDS	0.1	0.7
Severe ARDS	0.3	0.5

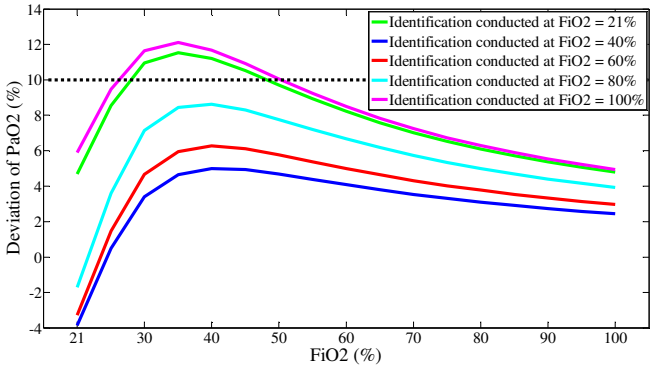

Fig. 2. Deviations of simulated to exact PaO_2 at different levels of FiO_2 with one data set used for identification assuming healthy patient parameter conditions ($f_S = 0.02$ and $f_A = 0.9$) and fixed offset of +5% for PaO_2 and $PaCO_2$ data points . Dashed line shows maximum acceptable deviation (10%).

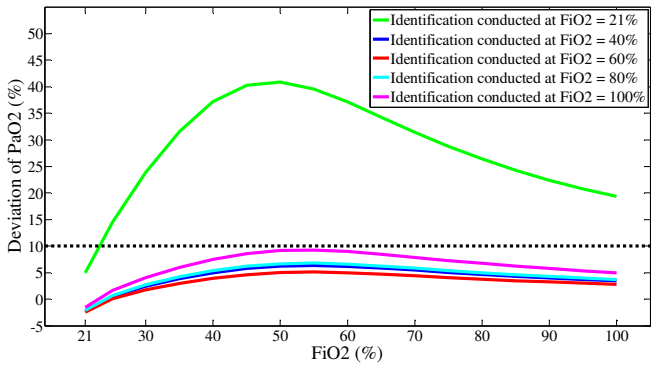

Fig. 3. Deviations of simulated to exact PaO_2 at different levels of FiO_2 with one data set used for identification assuming mild ARDS parameter conditions ($f_S = 0.1$ and $f_A = 0.7$) and fixed offset of +5% for all PaO_2 and $PaCO_2$ data points. Dashed line shows maximum acceptable deviation (10%).

Subsequently, the number of FiO_2 steps was increased stepwise from 1 to 5 to give information about the number of data sets required for robust PIP and adequate PaO_2 prediction at different pulmonary patient states. Here, Pa_x data were uniformly distributed randomly with a range of 10%. Prediction curves for both PaO_2 plus $PaCO_2$ were compared to exact curves resulting from the calculation with the adjusted model parameters.

3. RESULTS

When simulating patient data under healthy lung conditions ($f_S = 0.02$, $f_A = 0.9$), parameter identification led to prediction curves for PaO_2 with deviation to the exact curve slightly above the acceptable range of ±10% when only data at one single FiO_2 value were fitted and a fixed measuring offset of +5% was applied. Fig. 2 shows that identification with FiO_2 = 100% and with FiO_2 = 21% then leads to higher deviation in the lower areas of FiO_2 where linearity is absent due to shunt. The added offset in PaO_2 led to false shunt estimations ($fs \approx 0$). Analysing prediction of PaO_2 for mild ARDS data using one single FiO_2 value and fixed offset of 5% is shown in Fig. 3. When identifying at low FiO_2 = 21%, there was a deviation from the predicted to the exact curve clearly above the clinically acceptable deviation of 10%. Maximum deviation of the prediction curve for identification at FiO_2 = 100% was 9.2%, i.e. slightly below the acceptable range. Smallest deviation was found for identification at FiO_2 = 60%.

Fig. 4 shows PaO_2 prediction curves depending on different numbers of data sets used for parameter identification for severe ARDS patient data. Again, using only one data point with low FiO_2 led to high deviation compared to the exact curve of PaO_2 for high FiO_2. When using two data points with one of them being in the upper FiO_2 range, the prediction shows clear convergence to the simulated exact course of PaO_2.

Table 2 summarizes fitted parameters and deviation in predicted Pa_x for the three different lung states when one single FiO_2 value was used for identification and a fixed offset of +5% was applied to the data. In all lung conditions both parameters f_s and f_A were underestimated.

Results show that small shunt fractions of 2% in healthy lung conditions were compensated by $\dot{V}/Q$-mismatch ($f_A \neq 0.9$). Maximum deviation for PaO_2 of 10% was exceeded when fitting at FiO_2 of 21% and 100%. Under mild ARDS lung conditions, the offset led to high maximum deviation of 40.9% between predicted and exact PaO_2 data when fitting at FiO_2 = 21%. Best prediction results were reached for identification at FiO_2 = 60%. In severe ARDS lung condition, PaO_2 prediction was inside the acceptable range for PIP at FiO_2 of 80% and 100%. Identification at FiO_2 of 21% led to a maximum deviation of 256.3%.

$PaCO_2$ data could be fitted to the offset data with high accuracy for all parameter combinations tested in this work leading to a maximum deviation to exact $PaCO_2$ of 5% depending on the applied level of offset and random noise. $PaCO_2$ is only changing negligibly with increasing FiO_2.

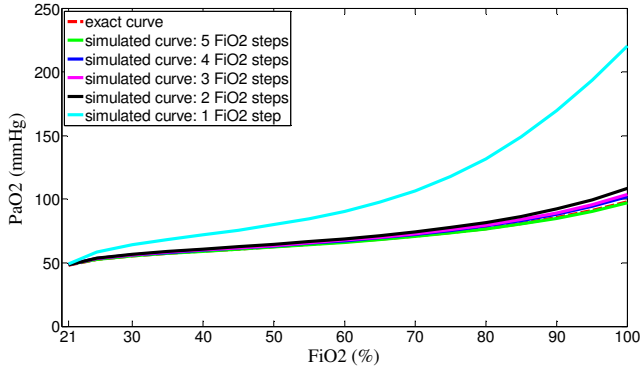

Fig. 4. Simulated PaO_2 at different levels of FiO_2 with different numbers of data sets used for identification assuming severe ARDS parameter conditions ($f_S = 0.3$, $f_A = 0.5$) and random noise of ±5% for all PaO_2 and $PaCO_2$ data points. Identification using one data set was conducted at FiO_2 = 21%. For each further step, next higher FiO_2 level was used additionally (40%, 60%, 80%, 100%).

Table 2. Parameters and resulting maximal prediction deviations using one identification time of measurement and data offset of +5%.

FiO_2	Healthy lung condition				Mild ARDS lung condition				Severe ARDS lung condition			
	f_S	f_A	Max. dev. PaO_2 (%)	Max. dev. $PaCO_2$ (%)	f_S	f_A	Max. dev. PaO_2 (%)	Max. dev. $PaCO_2$ (%)	f_S	f_A	Max. dev. PaO_2 (%)	Max. dev. $PaCO_2$ (%)
21%	0.00	0.80	11.5	1.0	0.05	0.60	40.9	5.0	0.15	0.42	256.3	2.1
40%	0.01	0.71	5.0	5.0	0.09	0.61	6.4	5.0	0.27	0.45	21.7	5.0
60%	0.00	0.70	6.3	5.0	0.09	0.62	5.1	5.0	0.28	0.45	14.0	5.0
80%	0.00	0.71	8.6	4.7	0.09	0.61	6.8	5.0	0.29	0.45	8.7	5.0
100%	0.00	0.83	12.1	0.4	0.08	0.61	9.2	5.0	0.29	0.45	5.0	5.0

4. DISCUSSION

The effort that is necessary for robust parameter identification and an adequate model prediction of PaO_2 and $PaCO_2$ at different levels of FiO_2 was analysed using simulated data. Accurateness of model prediction depends on the quality of the measurement data available for parameter identification. For the presented two-parameter model, blood gas measurements drawn at one single FiO_2 level are sufficient for identification. However, with one dataset only measurement errors or noise in the data cannot be compensated. Using data at low FiO_2 may lead to erroneous model prediction of PaO_2 even if only small measuring errors of <5% occur. $PaCO_2$ data could be predicted accurately.

Fig. 5 shows resulting PaO_2 curves for different shunt fractions f_S. Parameter f_A was set to 0.9 indicating that there is no $\dot{V}/Q$-mismatch. Without shunt, PaO_2 rises linearly with increasing FiO_2. For higher shunt fractions, the curve becomes nonlinear in areas of low FiO_2. For this reason, PaO_2 curves for different shunt fractions are difficult to distinguish at low FiO2. Small measuring errors therefore potentially lead to erroneous shunt fraction identification when using PaO_2 measurements at small FiO_2. Best prediction results with one single FiO_2 value are reached using data for PIP in the nonlinear area of the PaO_2 course. With rising f_S, this area shifts to higher FiO_2 regions.

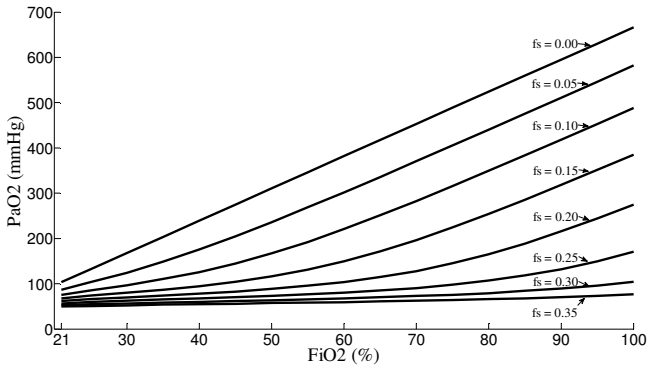

Fig. 5. Model simulated PaO_2 at different levels of FiO_2 with different shunt fraction f_S. $\dot{V}/Q$-mismatch was not considered ($f_A = f_Q = 0.9$). For shunt fraction larger than 35% there is only marginal change in PaO_2 with increasing FiO_2.

Using data at multiple FiO_2 steps improves the model prediction accuracy of PaO_2 as shown in Fig. 4. Noise in identification data can be partially compensated. Parameter identification with two FiO_2 steps may lead to accurate prediction of PaO_2 in healthy lung condition. Obviously, robustness of PIP strongly depends on the level of FiO_2 set at data acquisition. A detailed analysis using statistical evaluation based on Monte Carlo methods and real patient data is necessary to gain further insight to PIP of this model. However, our analysis raises confidence that the pulmonary gas exchange model may proof applicable in clinical practice with reasonable required identification effort.

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