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Computer model of oxygenation in neonates

A demonstration of utility

Abstract: Maintaining a prescribed peripheral oxygen saturation (SpO_2) target during routine care of neonates is challenging and inspired fraction of oxygen (FiO_2) titration practices differ among caregivers and centers. Algorithms for automatic feedback control of SpO_2 are being developed and tested, that would adapt to the changing neonatal organism and better maintain the required SpO_2 target range. While clinical data is necessary to validate differences in the titration strategies, a continuous physiological model of oxygenation in neonates would facilitate baseline testing of different approaches, manual or automated. The objective of our study was to enhance a mathematical model of oxygenation of the neonate and to compare the performance of the model with available clinical data. We have implemented the diffusion resistance into the model as well as a variable oxyhemoglobin dissociation relationship and the bias between arterial and peripheral oxygen saturation. Values of model parameters were scaled to fit preterm infant scenarios. The comparison of the clinical data and computer simulations suggest that the model can reliably simulate episodes of oxygen desaturation and describe the relation between ventilation, FiO_2 and SpO_2 . It appears that the model may be an effective tool to test manual and automatic FiO_2 titration strategies.

Keywords: Automated control, computer model, oxygen, peripheral saturation, preterm infant.

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1 Introduction

Maintaining a prescribed peripheral oxygen saturation (SpO_2) target range during routine care of neonates is challenging, having a nominal success of 50% and wide differences within and between centers [1]. Failure to maintain the desired SpO_2 range increases the risk of tissue and organ damage due to hypoxemia, but also the risk of oxidative damage due to hyperoxemia. These issues are a result of variation in cardiorespiratory stability of patients, as well as differing inspired fraction of oxygen (FiO_2) titration practices among caregivers and centers [2]. Therefore, algorithms for automatic feedback control of SpO_2 are being developed and tested, that would adapt to the changing neonatal organism and better maintain the required SpO_2 target range [3]. There is a paucity of clinical data describing the relative effectiveness of different FiO_2 titration strategies [2]. While clinical data is necessary to validate differences in the titration strategies, a continuous physiological model of oxygenation in neonates would facilitate baseline testing of different approaches, manual or automated [4]. Morozoff et al. presented a complex computer model of oxygen transport in a neonate [5]. The lumped-parameter model was divided into the respiratory part and the circulatory part, bounded by the oxyhemoglobin dissociation curve (ODC). Breathing activity and FiO_2 were inputs of the model, and SpO_2 was the output of the model.

The objective of our work was to enhance the mathematical model of oxygenation of the neonate and to compare the performance of the enhanced model with available clinical data. We aimed to build a flexible model that could reliably simulate an SpO_2 response to changes in breathing effort and in set FiO_2 under the condition of physiological acceptance of the model parameter values.

2 Methods

We have enhanced the original model in several ways: We introduced alveolar-capillary diffusion resistance (R_{diff}) [6–8] that replaces perfusion limited diffusion, i. e. $P_c O_2 = P_A O_2 - R_{\text{diff}} \dot{V} O_2$ instead of $P_c O_2 = P_A O_2$, where $P_c O_2$ is pulmonary capillary oxygen partial pressure, $P_A O_2$ is alveolar oxygen

partial pressure and $\dot{V}O_2$ is oxygen flow across the alveolar-capillary membrane. A range of static ODCs was replaced by a model of ODC by Siggaard-Andersen that, among other parameters, explicitly depends on the percentage of fetal hemoglobin (HbF) of total hemoglobin and on the concentration of 2,3-diphosphoglycerate (2,3-DPG) in red blood cells [9]. Oxygen consumption in tissues was treated as constant, independent of a momentary oxygen saturation. The bias between arterial and peripheral oxygen saturation, typical for neonates, was added [10, 11]. Blood volume in the circulatory part was scaled according to the weight of a neonate [12]. The model was implemented in Matlab–Simulink programming and simulating environment (MathWorks, Natick, USA)

2.1 Simulations

Performance of the enhanced model was tested on available clinical data of a premature male infant, 27 days old, weighing 1,019 grams (provided by Economedtrix, from their database). The neonatal patient was supported by AVEA mechanical ventilator (Vyaire Medical Inc., Mettawa, IL, USA) in the Volume Assist/Control mode with set tidal volume of 25 mL, ventilation rate 25 min⁻¹ and PEEP level 8 cm H₂O. Automatic FiO₂ control was not activated. Expiratory tidal volume (V_{Te}), FiO₂ and SpO₂ were recorded with sampling period 5 s. We identified three episodes of a significant decline in the SpO₂ signal with apparent time correlation between the oxygen desaturation and the reduction in the respiratory effort (i.e., disordered breathing marked by tidal volume of zero) that was preceded by regular ventilation. We limited each of the desaturation episodes (marked as Event 1, 2 and 3) to a time segment of 2 minutes before and 4 minutes after the first point of zero V_{Te} .

An optimizing computer program was written in Matlab utilizing the *fminsearch* built-in procedure that finds the minimum of a multivariable function using the simplex search method. The program searched for an optimal set of selected model parameters that minimized the sum of squared error (SSE) between the model SpO₂ output and patient SpO₂ record. Only the last 330 s of the event recording was evaluated, allowing internal state variables of the model to stabilize. Recorded FiO₂ signal was used as the simulation input. Breathing activity set in the model followed the recorded V_{Te} pattern.

The optimization procedure worked in two modes, designated as single-event simulations and all-event simulations. In single-event simulations, the model parameters were adjusted to fit the model output solely to the output data of a particular Event 1–3. In all-event simulations, the program

searched for a single set of parameters that would minimize the total SSE of the three events together. Besides the SSE, the model fit to the clinical data was assessed by the coefficient of determination (R^2).

The model parameters selected for the optimization were: oxygen capacity of blood, cardiac output, oxygen consumption in tissues, pulmonary blood shunt, the concentration of 2,3-DPG in red blood cells, percentage of HbF of total hemoglobin, measurement delay of SpO₂ and R_{diff} . Table 1 presents the initial values of optimized parameters and the lower and upper limits of parameter values. Values of physiological parameters were based on typical values or typical intervals reported in neonatal literature [13–16] with respect to the age and weight of a patient. We relaxed the upper bounds of cardiac output and HbF and both the lower and upper bounds of O₂ consumption. The measurement delay of SpO₂ was estimated from the averaging period of 8 s, but we did not set an upper limit for the parameter. Also, we did not set an upper limit for R_{diff} . Following the single-event simulations, initial values of parameters for the all-event simulations were set as median values of the optimal parameter values found for the single-event simulations. The lower and upper bounds for the all-event simulations were set within the range of values found for the single-event simulations, with an exception of cardiac output.

Table 1: Typical values of parameters and their limits used for the optimization of model performance.

Parameter	Initial	Lower Limit	Upper Limit
O ₂ Capacity (mL O ₂ /mL)	0.123	0.097	0.149
Cardiac Output (mL/s)	3.75	2.50	6.00
O ₂ Consumption (mL O ₂ /s)	0.133	0.100	0.200
Pulmonary Shunt (%)	17.5	5.0	30.0
2,3-DPG (mmol/L of RBCs)	6.095	1.933	10.257
HbF (% of Total Hb)	85.2	80.6	99.0
SpO ₂ Meas. Delay (s)	6	4	–
Diffusion Resistance (mmHg·s/mL O ₂)	100	1	–

3 Results

The parameter values that provided the best fit of the model output to measured SpO_2 during three events of oxygen desaturation are summarized in Table 2. Results of single-event simulations, in which the model parameters were adjusted only according to the clinical data of a particular Event 1, 2 or 3, are compared with results of all-events simulations, where a single set of parameters was used for all three events.

Table 2: Optimal values of model parameters and the assessment of goodness-of-fit of the model output (SpO_2) when compared to clinical data.

Parameter	Event 1	Event 2	Event 3	All Events
O_2 Capacity of (mL O_2 /mL)	0.127	0.120	0.107	0.127
Cardiac Output (mL/s)	4.97	4.00	5.97	2.52
O_2 Consumption (mL O_2 /s)	0.153	0.106	0.165	0.130
Pulmonary Shunt (%)	24.9	23.8	20.4	23.3
2,3-DPG (mmol/L of RBCs)	8.672	6.744	5.025	6.034
HbF (% of Total Hb)	90.7	98.2	99.0	91.6
SpO_2 Meas. Delay (s)	13.1	20.1	16.6	20.0
Diffusion Resistance (mmHg·s/mL O_2)	784	1897	1062	1007
SSE	57	55	87	2209
R^2 (Single-event)	0.971	0.961	0.957	
R^2 (All-events)	0.753	0.728	0.336	

The results show a successful fit of the model output to clinical data in case of single-event simulations, with R^2 bigger than 0.95. The optimal parameter values were found within ± 2 standard deviations from the typical value for O_2 capacity of blood and for the concentration of 2,3-DPG in red blood cells. The optimization program estimated high HbF, related to the left shift of the ODC curve. The pulmonary shunt was estimated consistently in the range of 20–25%. In case of the all-event parameter set, the model provided a good approximation of Event 1 and Event 2 with R^2 bigger than 0.7 but failed to approximate Event 3 (R^2 less than 0.4). For

Figure 1: Model performance illustrated on a single episode of desaturation (Event 1). At the bottom panel, peripheral oxygen saturation measured on a neonatal patient (black) is followed by the model output during a single-event simulation (blue, $R^2=0.97$) and an all-event simulation (red, $R^2=0.75$). Model inputs were the measured oxygen fraction (top panel) and expiratory tidal volume (middle panel).

simulations with single-event parameter sets, the total SSE of the three events is about 11-times lower than total SSE of simulations with the all-event parameter set.

An example of the model fit (SpO_2 waveforms) is presented in Figure 1, which compares the clinical recording, the output of a simulation with the specific single-event parameter set and the output of a simulation with the all-event parameter set.

4 Discussion

The comparison of the clinical data and computer simulations suggests that our model can reliably simulate single episodes of oxygen desaturation and describe the relation between ventilation, input oxygen fraction and peripheral oxygen saturation. The parameters of the model provide sufficient flexibility to adhere to clinical data while their values remain within physiologically acceptable limits.

However, in our bench test we had difficulties to find a single set of parameters that would satisfactorily explain all

the desaturation events identified within the patient. This might be partly due to the instability of the neonate, but more likely due to the low sampling rate of the clinical recordings, that provided rather trend data on ventilation; erroneous or incomplete input in Event 3 may have resulted in the poor performance of the all-event fit. A wide range of identified values of some parameters among the events could also reflect the sensitivity of the model performance to some parameters and the existence of various local minima in the high-dimensional optimization problem.

The biggest limitation of our study is the low number of episodes suitable for simulations. We selected only the desaturation episodes with an obvious correlation between desaturation and diminished respiratory effort and did not include, for example, events with poor SpO₂ signal (indicated by poor pulse index value). A bigger set of clinical data, with more detailed recordings on ventilation, would allow us to estimate and fix the parameters of the model that are unlikely to change over the data collection period, conclusively decide on the importance and effect of various parameters and validate the model thoroughly.

5 Conclusion

We enhanced a mathematical model of oxygenation of the neonate and evaluated its performance on available clinical data of a premature infant. The model can reliably simulate single episodes of oxygen desaturation and could be an effective tool to test FiO₂ titration strategies.

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