Medical Engineering and Physics 37 (2015) 341–349

Contents lists available at ScienceDirect

Medical Engineering and Physics

journal homepage: www.elsevier.com/locate/medengphy

A mathematical model approach quantifying patients' response to changes in mechanical ventilation: Evaluation in volume support

S. Larraza[a,*], N. Dey[b], D.S. Karbing[a], J.B. Jensen[c], M. Nygaard[b], R. Winding[b], S.E. Rees[a]

[a] Respiratory and Critical Care Group (RCARE), Center for Model-based Medical Decision Support, Department of Health Science and Technology, Aalborg University, Fredrik Bajers Vej 7, E4-213, DK-9220 Aalborg, Denmark
[b] Department of Anaesthesia and Intensive Care, Regions Hospital Herning, Herning, Denmark
[c] Mermaid Care A/S, Nr. Sundby, Denmark

ARTICLE INFO

Article history:
Received 16 June 2014
Revised 14 November 2014
Accepted 28 December 2014

Keywords:
Chemoreflex respiratory control
Support ventilation modes
Ventilatory response to CO_2
Computer simulation
Mechanical ventilation

ABSTRACT

This paper presents a mathematical model-approach to describe and quantify patient-response to changes in ventilator support. The approach accounts for changes in metabolism ($\dot{V}O_2$, $\dot{V}CO_2$) and serial dead space (VD), and integrates six physiological models of: pulmonary gas-exchange; acid–base chemistry of blood, and cerebrospinal fluid; chemoreflex respiratory-drive; ventilation; and degree of patients' respiratory muscle-response.

The approach was evaluated with data from 12 patients on volume support ventilation mode. The models were tuned to baseline measurements of respiratory gases, ventilation, arterial acid–base status, and metabolism. Clinical measurements and model simulated values were compared at five ventilator support levels.

The models were shown to adequately describe data in all patients (χ^2, $p > 0.2$) accounting for changes in $\dot{V}CO_2$, VD and inadequate respiratory muscle-response. *F*-ratio tests showed that this approach provides a significantly better ($p < 0.001$) description of measured data than: (a) a similar model omitting the degree of respiratory muscle-response; and (b) a model of constant alveolar ventilation. The approach may help predict patients' response to changes in ventilator support at the bedside.

1. Introduction

Setting mechanical ventilation (MV) is difficult, with suboptimal settings increasing the risk of overloading the respiratory muscles, lung injury and organ system failure [1–3]. MV can be seen as a trade-off between conflicting goals [4], including the balance between: poor oxygenation and oxygen toxicity, ventilator induced lung injury and acidosis; and in support modes of ventilation, respiratory stress and effects of prolonged MV. Computer-based protocols have been developed to assist in setting the ventilator, encouraging reduction in support without overly stressing patients and keeping them within a comfort zone or maintaining minimal work of breathing [5–7]. These systems have shown to reduce weaning duration [8,9], and shown to reduce MV time and length of stay in the ICU [8]. These systems have a limited representation of patients' physiology and, hence cannot perform predictions of patient-response following changes in support.

Model-based description of patients' respiratory response may help in predicting the effects of changes in ventilator support. This is not trivial, as patients may respond in several different ways to changes in MV, often resulting in changes in respiratory frequency (fR), tidal volume (VT) and blood acid–base status [10–13]. Patients may compensate reduced support by breathing more deeply with a greater muscle generated negative pressure (Pmus) [12,14]. Alternatively, patients may breathe more often [10], resulting in rapid shallow breathing at the extreme. Patients may combine these effects, or if having inadequate muscle strength, may reduce ventilation, and increase arterial partial pressure of CO_2 ($PaCO_2$) [11,15]. Describing patient-response is complicated further, as changes in ventilator settings affect physiological conditions. Reducing support may increase respiratory effort, and CO_2 production ($\dot{V}CO_2$), requiring higher alveolar ventilation ($\dot{V}A$) to maintain acid–base status. Reducing VT may decrease the anatomical serial dead space (VD), and as the VD/VT ratio is relatively constant, therefore, $\dot{V}A$ can be achieved with less minute ventilation ($\dot{V}E$) [16].

A simple model-based approach describing patient-response to changes in ventilator support, therefore, requires to integrate models of pulmonary gas-exchange, lung mechanics, blood acid–base, and respiratory-drive. Integrating such models and evaluating their ability to simulate patient-response to changes in ventilator support, has not previously been performed. Previous modeling approaches have

* Corresponding author. Tel.: +45 9940 978.
E-mail address: larraza@hst.aau.dk, seb.larraza@gmail.com (S. Larraza).

http://dx.doi.org/10.1016/j.medengphy.2014.12.006
1350-4533/

either: (a) combined some or all of the necessary components, focused on the effects of changing inspired fraction of O_2 or/and CO_2 (FIO_2, and $FICO_2$) in healthy subjects [17–19]; (b) have performed simulations in relation to MV, but focused only on pulmonary gas-exchange or/and lung mechanics [20–24]; (c) have implemented black-box control system models with physiological components to simulate patients on MV [25,26]; or (d) have focus on understanding a specific physiological process in relation to changes in ventilation, such as cerebral blood flow [17,19], pulmonary blood perfusion [27], functional residual capacity [28], periodic breathing [29–31] or respiratory-drive during exercise [13,32].

Recently, we have formulated a simple model describing patient-response to changes in support ventilation [4,33]. The aim of this paper is to present and evaluate the application of this model to describe and quantify patient-response to changes in volume support ventilation. As this model enables simulation of patients' end tidal CO_2 ($FECO_2$), fR, and arterial pH (pHa) at different VT levels, it is evaluated whether these simulations adequately describe measured data.

2. Methods

This section presents a model-approach to describe and quantify patient-response to changes in support ventilation and a clinical protocol to evaluate this approach. The approach includes a set of mathematical models, and the following clinical measurements, which are required to identify model parameters: end tidal O_2 (FEO_2); $FECO_2$; oxygen uptake ($\dot{V}O_2$); $\dot{V}CO_2$; VT; fR; and a measurement of arterial blood gases (ABG). All of these measurements are available from routine data plus measurement of indirect calorimetry, available for certain monitoring systems and ventilators [34].

2.1. Model description and tuning at baseline conditions

Fig. 1 illustrates the set of mathematical models which are used to describe patients' current state, and simulate patient-response to changes in ventilator support. The relationship between each model's inputs and outputs along the chain of respiratory control is illustrated by the wide arrows in Fig. 1. The thin arrows indicate measured variables needed for tuning each model at baseline conditions for the individual patient. In order to summarize inputs and outputs, the following equations((1)–(5)) are mathematical functions describing each model. Further details of the models are given in the electronic appendix.

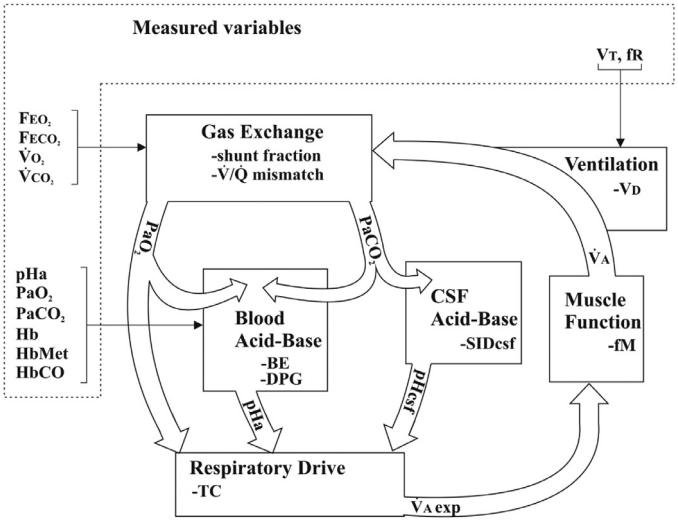

Fig. 1. Relationship between clinically available measurements and the set of models used to simulate patients' response to changes in mechanical ventilation. The models included are: pulmonary gas-exchange, acid–base chemistry of blood, acid–base chemistry of cerebrospinal fluid (CSF), chemoreflex respiratory-drive, muscle function and ventilation. Each model is calibrated to patient-specific conditions through the model parameters i.e. shunt fraction (fs), $\dot{V}/\dot{Q}$ mismatch, BE, DPG, SIDcsf, TC, fM and VD. The resulting variables from each model that link the models together, i.e. PaO_2, $PaCO_2$, pHa, pHcsf, $\dot{V}$Aexp and $\dot{V}$A, are illustrated inside arrows. The relationship between models and clinically available measurements (FEO_2, $FECO_2$, $\dot{V}O_2$, $\dot{V}CO_2$, pHa, PaO_2, $PaCO_2$, Hb, HbMet, HbCO, VT and fR) are illustrated with thin arrows.

Eq. (1) represents a model of pulmonary gas-exchange describing the relationship between FEO_2 and $FECO_2$ and the arterial partial pressure of O_2 (PaO_2) and $PaCO_2$ [35,36]. This model is tuned using: FEO_2; $FECO_2$; $\dot{V}O_2$; $\dot{V}CO_2$; PaO_2, and $PaCO_2$ from a single ABG; and three to five measurements of pulse oximetry (SpO_2) taken at three to five FIO_2 levels obtained from a 10–15 min procedure [37]. These data are required to estimate the pulmonary gas-exchange model parameters i.e. shunt fraction (fs), low and high ventilation-perfusion ($\dot{V}/\dot{Q}$) ratios. Parameter values have been shown to be uniquely identifiable from these measurements [35,36].

$$P_aO_2, PaCO_2 = \text{gas exchange}\,(FEO_2, FECO_2) \quad (1)$$

Eq. (2) represents a model of blood acid–base chemistry describing the relationship between PaO_2 and $PaCO_2$, oxygenation and acid–base variables [38–40]. This model is tuned using: pHa; PaO_2; $PaCO_2$; arterial oxygen saturation (SaO_2); bicarbonate concentration (HCO_3^-); and hemoglobin concentrations (Hb, HbMet, HbCO) taken from a single ABG; $\dot{V}O_2$; and $\dot{V}CO_2$. These data are required to estimate model parameters i.e. base excess (BE), describing blood acid–base status, and concentration of 2,3-diphosphoglycerate (DPG), describing the relationship between PaO_2 and SaO_2 on the oxygen dissociation curve. $\dot{V}O_2$ and $\dot{V}CO_2$ describe the effects of metabolism and respiration on oxygenation and blood acid–base at baseline [40]. BE and DPG are uniquely identifiable from a single ABG measurement as described previously [38,41].

$$\text{pHa}, SaO_2 = \text{blood acid base}\,(PaO_2,\ PaCO_2) \quad (2)$$

Eq. (3) represents a model of cerebrospinal fluid (CSF) acid–base chemistry describing the relationship between $PaCO_2$ and the acid–base status of CSF [42,43]. This model is tuned using $PaCO_2$ taken from a single ABG. $PaCO_2$ is used in the model to calculate: CSF partial pressure of CO_2 ($PcsfCO_2$); and the mixed venous bicarbonate concentration ($HCO_{3,0}^-$), which in turn is used to calculate the model parameter CSF strong ion difference (SIDcsf) [33] (see the electronic appendix). SIDcsf describes patients' respiratory-response corresponding to current metabolic state [44,45]. This is particularly relevant in COPD where high arterial BE and HCO_3^- increase SIDcsf and reduce chemoreflex respiratory-drive. SIDcsf is uniquely identifiable for a single value of $PaCO_2$.

$$\text{pHcsf} = \text{CSF acid base}\,(PaCO_2) \quad (3)$$

Eq. (4) represents a model of chemoreflex respiratory-drive describing the relationship between the net effects of acid–base and oxygenation in blood and CSF on the expected alveolar ventilation ($\dot{V}$Aexp) [17,18,42]. This model is tuned using: pHa taken from a single ABG, $\dot{V}O_2$, and $\dot{V}CO_2$. These data are required to estimate the model parameter Threshold of the Central chemoreflex respiratory-drive (TC), i.e. the CSF hydrogen ion concentration at which ventilation is increased due to the central respiratory-drive [33,42]. TC is estimated by a numerical optimization process which simultaneously solves Eqs. (1)–(4), with $\dot{V}O_2$, and $\dot{V}CO_2$, calculating pHa and minimizing the difference between simulated and measured values of pHa. TC is uniquely identifiable for single values of pHa and SIDcsf [33].

$$\dot{V}\text{Aexp} = \text{respiratory drive}(PaO_2, \text{pHa},\ \text{pHcsf}) \quad (4)$$

Eq. (5) represents a model of ventilation that describes the relationship between $\dot{V}$A, $\dot{V}$E, VD and fR. This model is tuned using: $\dot{V}CO_2$, $FECO_2$, $FICO_2$, VT and fR. These data are used to simultaneously solve