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A mathematical model approach quantifying patients' response to changes in mechanical ventilation: Evaluation in pressure support☆,☆☆,★

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ABSTRACT

Purpose: This article evaluates how mathematical models of gas exchange, blood acid-base status, chemical respiratory drive, and muscle function can describe the respiratory response of spontaneously breathing patients to different levels of pressure support.
Methods: The models were evaluated with data from 12 patients ventilated in pressure support ventilation. Models were tuned with clinical data (arterial blood gas measurement, ventilation, and respiratory gas fractions of O_2 and CO_2) to describe each patient at the clinical level of pressure support. Patients were ventilated up to 5 different pressure support levels, for 15 minutes at each level to achieve steady-state conditions. Model-simulated values of respiratory frequency (fR), arterial pH (pHa), and end-tidal CO_2 ($FeCO_2$) were compared to measured values at each pressure support level.
Results: Model simulations compared well to measured data with Bland-Altman bias and limits of agreement of fR of 0.7 ± 2.2 per minute, pHa of -0.0007 ± 0.019, and $FeCO_2$ of -0.001 ± 0.003.
Conclusion: The models describe patients' fR, pHa, and $FeCO_2$ response to changes in pressure support with low bias and narrow limits of agreement.

1. Introduction

Setting the appropriate level of support in patients receiving mechanical ventilation (MV) can be difficult. In pressure support ventilation (PSV), it is challenging to predict how patients might respond to reducing or increasing pressure support (PS) levels [1-5]. On reducing PS, patients may respond positively or negatively: positively by increasing muscle activity without substantial extra work of breathing (WOB), effectively compensating for the reduction in support [3,6], and negatively either by failing to increase muscle activity, resulting in inadequate ventilation and changes in blood acid-base status, or by substantially increasing WOB perhaps resulting in a stressful breathing pattern and discomfort [1,7]. Conversely, increasing PS may give positive response if respiratory muscles are unloaded, relaxing the stressed patient and improving ventilation, or a negative response if respiratory muscles are completely unloaded, as this may lead to muscle atrophy, alveolar expansion, air trapping, asynchrony, and ineffective triggering [5,7,8].

Part of the difficulty in understanding or predicting how patients might respond lies in the interrelationship between different physiological systems involved in patients' response to changes in ventilation [2,9-12]. For instance, at a particular PS level, ventilation depends upon lung mechanics and patients' effort and ability to breathe spontaneously. Patients' effort and ability to breathe spontaneously depend upon both chemical respiratory drive (CRD) and muscle response. The degree of CRD depends upon blood and cerebrospinal fluid (CSF) acid-base status [10,12,13] and patients' level of sedation [14], with blood acid-base status being dependent on factors including pulmonary gas exchange and metabolic production of CO_2 ($\dot{V}CO_2$) [15-19]. The degree of muscular response depends upon patients' CRD, strength, and endurance of respiratory muscles [3,9,20].

Describing physiological systems through mathematical models may be a useful way to combine all these effects and to describe individual patient responses to changes in ventilator support. Previously, a set

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★ Ethical approval: The clinical protocol (reference no. 1-10-72-231-13) was approved by the Ethics Committee of Mid-Jutland. Data from all of the enrolled patients were collected with informed written and oral consent from the patient or relatives and, in case of the latter, the patient's general practitioner, as required by Danish law.
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of mathematical models including all the aforementioned physiological systems but lung mechanics was evaluated in a clinical study to describe individual patient response to changes in tidal volume (Vt) [21]. The model approach was shown to adequately describe patients' changes in respiratory frequency (fR), arterial pH (pHa), and end-tidal fraction of CO_2 ($FeCO_2$) to step changes in Vt. The previous study was limited to patients ventilated in assist volume-control ventilation (ACV). This limitation represented a reasonable initial evaluation of the models, as in ACV, Vt is not dependent upon lung mechanics or patient effort [2], meaning that the required model complexity was reduced. However, most patients ventilated in support ventilation modes are in PSV [5,6]. During PSV, Vt is not fixed and depends upon both lung mechanics and patient effort [2,6,22]. The aim of this study was to evaluate the ability of the previous set of models, including a description of lung mechanics, to describe patients' response to changes in PS. For that purpose, patients were subjected to up to 5 step changes in PS, and it was evaluated whether the models provide a good description of measured values of fR, pHa, and $FeCO_2$ at each PS level.

2. Methods

The study was designed to measure patients' response to reduction or/and increase of PS and to evaluate the models' ability to describe changes in fR, pHa, and $FeCO_2$. This section describes the clinical protocol, the set of models, and statistics used to evaluate the models' description of patients' response to changes in PS.

2.1. Clinical protocol

Data from 15 patients ventilated on PSV were collected with ethical approval from the Ethics Committee of Mid-Jutland, Denmark. Informed written and oral consent was obtained from patients or relatives and, in the case of the latter, patients' general practitioner.

All patients were older than 18 years, intubated, and ventilated in PSV. Patients were excluded if, at the time of inclusion, dynamic lung compliance was less than 30 mL/cm H_2O, positive end-expiratory pressure greater than or equal to 10 cm H_2O, systolic blood pressure less than 90 mm Hg with vasopressor, or $Paco_2$ greater than 8.5 kPa or if previously diagnosed with chronic obstructive pulmonary disease (COPD) or in absence of arterial catheter. Patients were sedated with propofol and fentanyl. According to the intensive care unit standard practice, sedatives were titrated to achieve a Richmond Agitation-Sedation Scale (RASS) score between 0 and −2, depending upon patients' conditions.

Patients were ventilated using continuous positive airway pressure–assisted spontaneous breathing ventilation mode (Evita XL; Dräger Medical, Lübeck, Germany). This mode is pressure controlled, flow cycled, patient triggered, and pressure supported [23]. Trigger sensitivity was set to 5 L/min, ramp time was adjusted to achieve an inspiratory flow less than 60 L/min, cycling off criterion was set to 25% of the peak inspiratory flow, apnea ventilation frequency was set to 5 per minute, and automatic tube compensation was turned off. Baseline PS was the current clinical PS level. Pressure and flow profiles and airway concentration of O_2 and CO_2 were measured continuously (CARESCAPE; GE Healthcare, Helsinki, Finland). These data were used to determine breath-by-breath values of PS, end-tidal fraction of O_2, and $FeCO_2$. The flow profile was integrated to determine Vt and used to calculate fR. Effective compliance (Ceff) was calculated as the ratio between measured Vt and PS. Oxygen intake ($\dot{V}O_2$) and $\dot{V}CO_2$ were calculated by synchronizing flow and gas concentration profiles and integrating their product. A time window of 1 minute was used to calculate average values for Vt, fR, $FeCO_2$, Ceff, $\dot{V}O_2$, and $\dot{V}CO_2$. Serial dead space (Vds) was calculated with an equation describing CO_2 mass conservation, as described previously [21], that is,

$$Vds = Vt - \frac{\dot{V}\,CO_2}{fR * (FeCO_2 - FiCO_2)} \quad (1)$$

Fifteen minutes after setting baseline ventilator settings, measurements were taken of arterial blood gases (ABG) (ABL Flex 800; Radiometer, Brønshøj, Denmark) and pulmonary gas exchange (ALPE Integrated; Mermaid Care A/S, Nørresundby, Denmark).

Patients were subjected to a maximum of 5 PS step changes of 2 cm H_2O each, beginning with reduction of PS from baseline. After each PS reduction, 15 minutes was waited to allow steady state followed by measurement of ABG. Pressure support was further reduced only if pHa greater than 7.3 and fR less than 30 per minute, if less than 5 PS steps were performed, and if PS greater than 0 cm H_2O. In case of completing the 5 PS step modifications solely with PS reduction, the protocol concluded with a measurement of ABG taken 15 minutes after resetting the ventilator to baseline. Otherwise, PS was increased to the baseline level and subsequently by 2 cm H_2O step increases. After each PS increase, 15 minutes was waited to allow steady state, followed by measurement of ABG. Pressure support was further increased only if Vt less than 8 mL/kg, if peak inspiratory pressure (PIP) less than 30 cm H_2O, and if less than 5 PS step changes were performed. After completion of the 5 PS step changes or if it was not possible to further increase PS, the protocol concluded with a measurement of ABG taken 15 minutes after resetting the ventilator to baseline.

2.2. Mathematical models

Fig. 1 illustrates the set of mathematical models used to describe patients' response to changes in PS. A detailed description of the models is provided in the supplementary material. The panel of the left hand side illustrates with thick line arrows, which models require measured inputs to perform simulations. Measured inputs are listed inside the corresponding arrow. The panel on the right hand side illustrates the mathematical models with boxes, and the relationships between them, with thin line arrows. Model parameters are listed inside the corresponding box, and variables linking models as inputs and outputs are listed inside the linking arrows. In this context, the word “parameter” is used to specify model constants, which are not measured directly but can be estimated by fitting or “tuning” the models for individual patients, so that simulated values match measured data at a single PS level. This tuning process is described in the supplementary material. It is, however, important to note that there are 2 types of model parameters, depending upon whether their values change on modifying PS. Model parameters, which are independent of PS, describe pulmonary gas exchange, that is, shunt fraction (fs) and low and high ventilation perfusion ratios ($\dot{V}/\dot{Q}$); blood acid-base status, that is base excess (BE) and 2,3-diphosphoglycerate; and CRD, that is, CSF strong ion difference (SIDcsf) and central chemoreflex threshold (TC). Model parameters, which depend upon PS and, therefore, estimated at each PS level, are Vds, Ceff, and muscle function (fM).

After estimating values of model parameters describing individual patients' data, the set of models can be used to simulate fR, pHa, and $FeCO_2$ on changing PS. This simulation process can be understood by following the chain of respiratory control illustrated in Fig. 1. For instance, starting with the lung mechanics model, this model is used to calculate Vt from PS. Tidal volume is then input to the pulmonary gas exchange model along with alveolar minute ventilation ($\dot{V}A$) and inspired oxygen fraction (Fio_2) to calculate fR, $FeCO_2$, and $Paco_2$. Values of $Paco_2$, $\dot{V}O_2$, and $\dot{V}CO_2$ are input to the model of blood acid-base status to calculate pHa. Model calculated values of pHa and $Paco_2$ are input into the CRD model to calculate expected alveolar minute ventilation ($\dot{V}A$exp). Expected alveolar minute ventilation is then input to the model of fM to calculate $\dot{V}A$. This value of $\dot{V}A$ ought to be equivalent to the input into the pulmonary gas exchange model, hence completing the chain of respiratory control.