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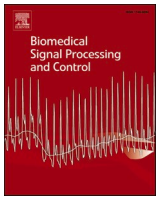

Prediction and estimation of pulmonary response and elastance evolution for volume-controlled and pressure-controlled ventilation

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ABSTRACT

Mechanical ventilation (MV) is a core treatment for patients suffering from respiratory disease and failure. However, MV settings are not standardized due to significant inter- and intra- patient variability in response to care, leading to variability in outcome. There is thus a need to personalize MV settings. This research significantly extends a single compartment lung mechanics model with physiologically relevant basis functions, and uses it to identify patient-specific lung mechanics and predict response to changes in MV settings. Nonlinear evolution of pulmonary elastance over positive end expiratory pressure (PEEP) is modelled by a newly proposed, physiologically relevant and simplified compensatory function to enable prediction of pulmonary response for both volume-controlled ventilation (VCV) and pressure-controlled ventilation (PCV), and identified as patient-specific using each patient's data at a baseline PEEP. Predictions at higher PEEP levels test the validity of the proposed models based on errors in predicted peak inspiratory pressure (PIP) in two VCV trials and volume (PIV) in one PCV trial. A total of 210 prediction cases over 36 patients (22 VCV; 14 PCV) yielded absolute predicted PIP errors within 1.0 cmH_2O (2.3%) and 3.3 cmH_2O (7.3%) for 90% cases in VCV, while predicted PIV errors are within 0.073 L (16.8%) for 85% cases in PCV. In conclusion, a novel deterministic virtual patient model is presented, able to offer accurate prediction of pulmonary response across a wide range of PEEP changes for the two main MV modes used clinically, enabling predictive decision support in real-time to safely personalize and optimize care.

1. Introduction

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) have detrimental impacts on lung stiffness and oxygenation resulting in high morbidity and mortality [1–4]. Mechanical ventilation (MV) is the core treatment for patients suffering from life-threatening respiratory failure in the intensive care unit (ICU). The primary goal of MV is to minimise the work of breathing, ensure adequate gas exchange, and recruit and hold open lung volume to enable recovery [5–9]. However, suboptimal MV settings can lead to over-distension and ventilator induced lung injury (VILI), both of which increase morbidity and mortality [1,6,8–12]. To avoid these harmful effects, protective MV settings have been proposed [1,4,13–15].

Low tidal volume is clinically well-accepted in MV to mitigate VILI, but can lead to alveolar de-recruitment [16–18]. Thus, a protective 'open lung' approach uses positive end-expiratory pressure (PEEP) during breathing to prevent alveolar collapse combined with low tidal volume ventilation, thus maintaining an open lung at the end of expiration to ensure sufficient oxygenation and pressure support [6,8,9,18–21]. Staircase recruitment maneuvres (RMs), comprising a series of incremental and decremental PEEP steps, have been used as one important component in clinical care for recruiting lung volume for lung

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protective strategies and assessing the choice of PEEP [6,15,22–24].

RMs with subsequent PEEP changes can be effective in improving oxygenation, while minimising harm [20,25–27]. However, optimal RM and PEEP settings remain patient-specific, time-varying, and thus not standardized [11,12,18,28–31]. The 'best' setting can be different between patients, as well as varying over different conditions and time [5,14,32–35]. An suboptimal PEEP setting can lead to excessive or insufficient support for patients, inducing VILI and leading to higher morbidity and mortality [36,37]. Thus, it is critical to to provide clinicians with better information to monitor patient-specific pulmonary state and forecast the influence of new PEEP settings on pulmonary response for each patient, to improve and personalize care, minimize risk, and maximize care and safety [8,19,34,35]. Therefore, accurate, predictive and patient-specific MV strategies are a major need in advancing care and minimising MV-associated injury [5,19,34].

Furthermore, two different MV modes are both widely used, volume controlled ventilation (VCV) and pressure controlled ventilation (PCV) [38–40]. VCV allows clinicians to control tidal volume directly, eliminating volutrauma, but they need to be alert to the resulting peak inspiratory pressure (PIP) and barotrauma. Conversely, PCV controls pressure, but risks volutrauma from too large a peak inspiratory volume (PIV) [38]. Both limitations may lead to unexpected VILI [39,41]. To date, no noticeable clinical outcome differences have been seen comparing VCV and PCV [42,43]. Thus, the decision on MV strategies relies on clinician preference, patient characteristics, or patient comfort [38,39]. Therefore, accurate, model-based, and patient-specific pulmonary response prediction is necessary.

In the last two decades, several complex models have been proposed and can effectively capture a large range of nonlinear pulmonary dynamics [34,44–51]. However, their complexity means they suffer poor or non-identifiability [34,52], or are too complex to identify or apply at the bedside [53–59], thus limiting or eliminating their potential for clinical application. Far simpler black box models can be created, but require large amounts of data to train and may lack the ability to capture or describe all physiological features in various situations [58,60,61]. In addition, physiological relevance is important because it supports clinical confidence and use and provides further insight to clinical end-users [52,62], but such black-box models cannot offer physiological relevance. Finally, some models of all types capture lung mechanics well with good personalization of parameters, but are poor in predicting the response to changes in care [63–65], lacking the means to offer guidance to clinicians, and suggesting the identified parameters may not be correct. However, accurate prediction is a major need in guiding and improving the safety and efficacy of clinical MV treatment [66–68]. Thus, there is a need for simpler, identifiable, physiologically relevant models which can offer accurate prediction to changes in care by capturing the evolution of lung mechanics as MV parameters change [34,52].

Currently, while several models can identify data [9,11,44,69–71], the authors are aware of only one approach able to accurately predict outcomes from changes in MV care for resulted airway pressure for VCV and tidal volume for PCV[8,19,72]. These approaches use physiologically relevant basis functions to define respiratory mechanics over all possible pressures and volumes seen in MV, which is uncommon [35,58]. However, while they predict well, the basis functions proposed are independent of known PEEP levels and changes, creating complexity in understanding and implementation, especially for PCV predictions. Thus, if accurate prediction can be obtained with a simpler model where elastance evolution as PEEP changes is captured as a function of PEEP, it could provide an easier, more intuitive, and clinically applicable approach in clinical use.

This research presents physiologically relevant, simpler, basis functions to estimate elastance and resistance evolution as MV parameters change using the same clinically validated single compartment lung mechanics model as previous studies [59,73]. It is validated by assessing prediction error when made patient specific using data from one single PEEP level to predict pressure and flow at higher PEEP levels. Such a predictive model would offer the ability to quantify the trade-off or compromise between increasing basis function simplicity and improving clinical utility.

2. Methods

2.1. Patient data

Pressure and flow data from 36 mechanically ventilated ICU patients (4 from the CURE pilot trial [74], 18 from the McREM pilot trial [19,75], and 14 from the Maastricht pilot trial) were used to validate the method developed in this study.

2.1.1. VCV trials

In the CURE and McREM trials, all 22 patients were fully sedated and intubated under invasive volume-controlled ventilation , with tidal volume set to 6–8 ml/kg in CURE [76,77] and 8 $\pm$ 2 ml/kg in McREM (both based on ideal body weight). The two studies had consistent inclusion criteria of $PaO_2/FiO_2 < 300$ mmHg and $PaO_2/FiO_2 < 298$ mmHg for CURE and McREM, respectively, which is part of ARDS severity scoring system [2].

2.1.1.1. CURE trial. The CURE trial was conducted on 4 patients at Christchurch Hospital ICU in August 2016 (ANZTR number: ACTRN12613001006730) [74,76]. Demographics are shown in Table 1. Pressure and flow data in this study were sampled at 50 Hz [76].

Spontaneous breathing was prevented using sedation with muscle relaxants during RMs, to minimise asynchrony [44,78–80]. Two staircase RMs were applied to each patient with increments and decrements of 4 cmH_2O, consisting of 2 sets, Set 1 and Set 3, with increasing PEEP levels and 2 sets with decreasing PEEP levels, as shown in Fig. 1 (a) [77]. Every set had six increasing or decreasing PEEP levels, while only five PEEP levels were used in Set 1 of Patient 1 by clinical choice. In this study, only sets with increasing PEEP levels are studied. Thus, there are a total of 47 steps across 8 sets for 4 patients, from which 8 cases are used for identifying the model at the lowest PEEP level. The remaining 39 cases are used for prediction and model validation across increasingly large PEEP intervals up to 20 cmH_2O.

2.1.1.2. McREM trial. The McREM trial was conducted across eight ICUs from September 2000 to February 2002. Data were sampled at 125 Hz [75]. Demographics are shown in Table 2.

A total of 18 patients from a total of 28 in the McREM trial were selected as they underwent one complete increasing staircase RM where PEEP was set to increase at increments of 2 cmH_2O, as shown in Fig. 1 (b). During the protocol, an end-inspiratory hold of 0.2 s was set for all 18 patients [75]. In this study, the identification procedure is applied at PEEP = 10 cmH_2O instead of ZEEP (zero end-expiratory pressure) because starting at PEEP = 10 cmH_2O creates a clear and equal comparison with the other trial datasets in this study. Overall, this trial yields 100 cases, from which 18 cases are used for identification and the remaining 82 cases are used for prediction and model validation, with increasing PEEP intervals up to 16 cmH_2O.

Table 1
Patients and clinical trial demographics in the CURE pilot trial [74]

Patient No	Sex	Age (years)	Length of MV (days)	Clinical Diagnostic
1	Male	33	23	Peritonitis
2	Male	77	24	Legionella pneumonia
3	Male	61	23	Staphylococcus Aureus pneumonia
4	Female	73	2	Streptococcus pneumonia

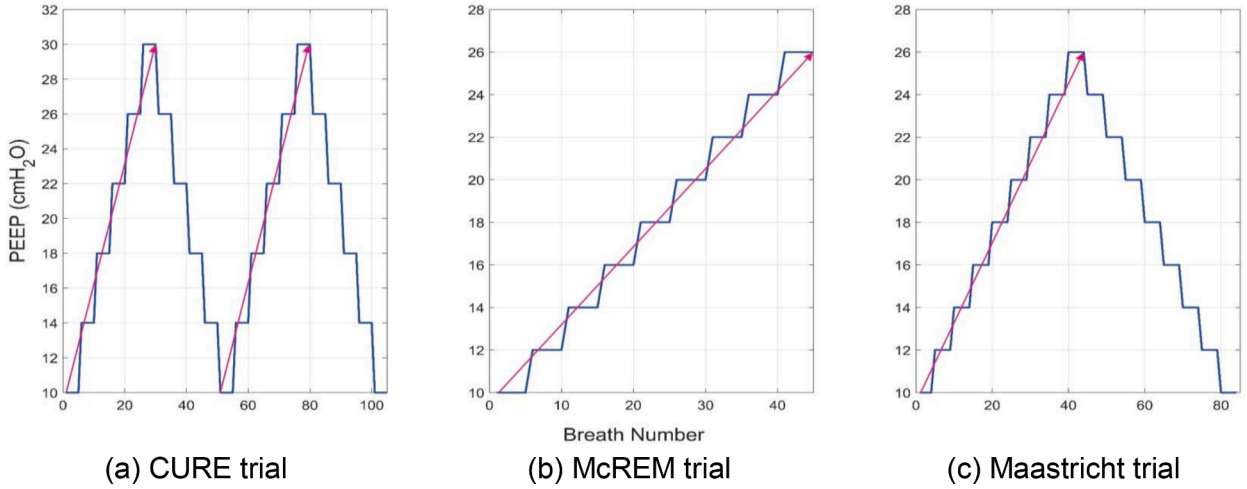


Fig. 1. Example of RMs used in the CURE trial (a), the McREM trial (b), and the Maastricht trial (c). The values are schematic and varies with patients.

Table 2
Patients and clinical trial demographics in the McREM pilot trial [75]

Patient No	Sex	Age (years)	Length of MV (days)	Clinical Diagnostic
1	Male	37	10	Pneumonia
2	Male	39	2	Traumatic aortic dissection, lung contusion
3	Female	50	8	Pancreatitis, pneumonia
4	Female	30	8	Peritonitis, sepsis
5	Female	49	3	Pneumonia
6	Male	34	10	Traumatic open brain injury
7	Male	67	4	Post resuscitation
8	Male	39	10	Perf. sigma, peritonitis
9	Male	42	9	Pneumonia, pancreatitis
10	Male	51	5	Traumatic brain injury, pneumonia
11	Male	77	6	Pneumonia
12	Male	74	10	Subarachnoid and subdural hemorrhage
13	Male	41	16	Peritonitis
14	Male	62	2	Subarachnoid hemorrhage
15	Male	39	7	Traumatic brain injury, pneumonia
16	Male	74	9	S/P coronary artery bypass grafting, pneumonia
17	Male	59	19	ARDS
18	Male	45	8	Blunt abdominal trauma, pneumonia

2.1.2. PCV trial

Data from the Maastricht trial was conducted on 14 patients from November 2017 to February 2018 in Maastricht, Netherlands (METC 17–4–053). Ventilator pressure and flow data was recorded directly from the ventilator. Typical ventilators use hot wire anemometers to measure flow with accuracy to 1 ml/s or less. Volume was integrated for each breath separately from the flow data. All 14 patients are treated with Bi-level Positive Airway Pressure pressure-controlled ventilation. Demographics are shown in Table 3.

Each patient was treated with one full staircase RM with 2 cmH_2O increments or decrements in PEEP, as shown in Fig. 1 (c). Only the RM arm with incremental PEEP levels is studied for all 14 patients, with model identification starting at 10 cmH_2O to be consistent with the two VCV trials. Thus, it yields 103 cases,while 14 cases for model identification and the remaining 89 cases are for prediction and validation, with a maximum 16 cmH_2O PEEP interval.

Table 3
Patients and clinical trial demographics in the Maastricht pilot trial. CABG = Coronary Artery Bypass Grafting, AVR = Aortic Valve Replacement

Patient No	Sex	Age (years)	PaO_2/FiO_2	Clinical Diagnostic
1	Male	77	255	CABG
2	Female	85	308	CABG
3	Male	57	323	CABG
4	Male	47	233	CABG
5	Male	73	150	AVR
6	Male	75	383	CABG
7	Female	71	443	AVR
8	Male	76	398	CABG
9	Female	64	255	Subarachnoid Haemorrhage
10	Female	68	428	Pneumonia
11	Female	78	143	Pneumonia
12	Female	18	83	Mitral and Tricuspid Valve Replacement
13	Female	71	443	Pneumonia
14	Male	36	158	CABG

2.2. Model definition, identification, and prediction

2.2.1. Lung mechanics model

The proposed method is based on a well-validated single compartment lung mechanics model [73]:

$$P(t) = E^*V(t) + R^*Q(t) + PEEP\# \tag{1}$$

where $P(t)$ is airway pressure (cmH_2O), $V(t)$ is the tidal volume delivered (L), $Q(t)$ is the flow (L/s), and PEEP is the positive end-expiratory pressure (cmH_2O). Pulmonary elastance (cmH_2O/L) and pulmonary resistance (cmH_2O*s/L) are defined as E and R , respectively.

2.2.2. Identification

At baseline PEEP, for all VCV and PCV trials, pressure and flow data are used to identify nonlinear evolution of elastance and resistance for each patient and any single breath. These basis functions for elastance, $E_i(t)$, and resistance, $R_i(t)$, are defined:

$$E_i(t) = e1 + e2^*P_i(t), i = 1\# \tag{2}$$

$$R_i(t) = r1 + r2^*Q_i(t), i = 1\# \tag{3}$$

where $P_i(t)$ and $Q_i(t)$ $(i = 1)$ are the measured pressure and flow data. The values of $e1$, $e2$, $r1$, and $r2$ are the patient-specific, constant coefficients to be identified for each patient. They can be identified from any single breath, and are identified at the baseline PEEP level for each

patient in this study.

The elastance basis function, Equation (2), is significantly simplified from the one used in [8,19,35], which defines $E = f(P(t), V(t))$. The functions in Equation (2)-(3) remain constant for all further PEEP levels using coefficient values identified at a given PEEP level for each patient. The accuracy of this choice of coefficients across all clinically realistic ranges of pressure and flow is tested in the accuracy of prediction results using the identified model.

PIP error using the identified model parameters is defined:

$$PIP_{fit_{error}} = \frac{fittedPIP - clinicalPIP}{clinicalPIP}\# \tag{4}$$

Thus, in this step, $e1$, $e2$, $r1$, and $r2$ are identified, while the resulting E_i and R_i at $i = 1$, and $PIP_{fit_{error}}$ can be calculated with known or identified data and values.

2.2.3. Prediction

In this approach, a subscript, i , is used to indicate PEEP level, where $PEEP_1$ ($i = 1$) is the baseline PEEP level to which the model is identified, and $PEEP_i$ is the i^{th} applied PEEP level. In the three studied pilot trials, the maximum is $i = 6$ in the CURE trial, $i = 9$ in the McREM trial, and $i = 8$ in the Maastricht trial, where the McREM and Maastricht trials used smaller ΔPEEP steps.

2.2.3.1. Elastance and resistance prediction. In the modelling approach presented here, a compensatory coefficient, Φ_i , is proposed aiming to capture the nonlinear evolution of elastance over PEEP for all three trials and calculated as a unit-less value. For $PEEP_i$ levels ($i > 1$), the function of Φ_i is defined with a clinically selected $PEEP_{max} = 24$ cmH_2O:

$$\Phi_i = \begin{cases} \left(1 + PIP_{fit_{error}}\right)^{-1}, & i = 2 \\ \vartheta 1 * \Delta PEEP, & if\ i > 2\ and\ PEEP_i \le PEEP_{max} \\ \vartheta 1 * \Delta PEEP - \vartheta 2 * \left(PEEP_i - \dfrac{PEEP_{max}}{\Delta PEEP}\right)^2, & if\ i > 2\ and\ PEEP_i > PEEP_{max} \end{cases} \tag{5}$$

while $\vartheta 1 = 0.0174$ in the CURE trial and $= 0.0087$ in both the McREM and Maastricht trials, and $\vartheta 2 = \left|PIP_{fit_{err}}\right| - 0.0123$ for all trials. $\Delta PEEP = PEEP_i - PEEP_{i-1}$, where $PEEP_i$ is the currently applied PEEP level. The values for $\vartheta 1$ and $\vartheta 2$ were optimized parametrically by line search. In the CURE trial, $\Delta PEEP$ is 4 cmH_2O clinically, while in the McREM trial and the Maastricht trial it is 2 cmH_2O. Thus, $\vartheta 1$ is reasonably decreased to half the value used for the CURE trial ($\vartheta 1 = 0.0174 \rightarrow 0.0087$), while $\vartheta 2$ and $PEEP_{max}$ remain the same. Hence, the parameters are general over all three trials and two MV modes.

Thus, elastance is predicted for $PEEP_i$ levels ($i = 2, 3, 4, \ldots$) using:

$$E_i(t) = e1 * \sum_{j=2}^{j=i} \Phi_j + e2 * P_1(t) * \sum_{j=2}^{j=2} \Phi_j * \sum_{j=2}^{j=3} \Phi_j * \cdots * \sum_{j=2}^{j=i} \Phi_j \tag{6}$$

Resistance is assumed to be constant over all PEEP levels for each patient as identified at $PEEP_1 (i = 1)$ [19,35,72], yielding:

$$R_i(t) = r1 + r2 * Q_1(t)\# \tag{7}$$

2.2.3.2. Pressure prediction for VCV. For VCV, the CURE trial and the McREM trial, predicted airway pressure is the independent output variable. Pressure prediction from $PEEP_1$ to a new $PEEP_i$ level can be calculated with predicted elastance and resistance:

$$P_i(t) = E_i(t) * V_1(t) + R_i(t) * Q_1(t) + PEEP_i\# \tag{8}$$

where $E_i(t)$ and $R_i(t)$ are obtained from Equations (6) – (7).

2.2.3.3. Volume and flow prediction for PCV. For PCV, the Maastricht trial, since pressure is the known input, instead of tidal volume and flow, tidal volume is the predicted variable, using:

$$V_i(t) = \frac{P_1(t) - PEEP_1 - R_i(t) * Q_1(t)}{E_i(t)}\# \tag{9}$$

where $E_i(t)$ and $R_i(t)$ are obtained from Equations (6) – (7).

A flowchart presenting the entire identification ($i = 1$) and prediction ($i > 1$) procedure is shown in Fig. 2.

2.3. Validation and error analysis

In this study, the same error metrics are used to describe the results for both identification and prediction. PIP is the critical clinical indicator in VCV, as it is related to ventilator induced lung injury (VILI) due to pulmonary barotrauma [6,81,82]. Equally, PIV is the key indicator during PCV [39]. Errors are presented as absolute difference (cmH_2O and L). Root-mean-square (RMS) error is also used to show prediction error in pressure and reproducibility of the $P(t)$ trajectory over an entire breath in VCV trials, and volume prediction errors and the reproducibility of $V(t)$ trajectory in PCV trial.

2.4. Sensitivity analysis

Equation (5) relies on fixed values for $\vartheta 1$, $\vartheta 2$, and $PEEP_{max}$. While $PEEP_{max}$ is clinically justified, the $\vartheta 1$ and $\vartheta 2$ values are tested across a range of ± 5%, ± 10%, and ± 15% individually and jointly in a sensitivity analysis to quantify robustness in addition to the three independent data sets and different MV modes used in validation. Mixed changes, such as + 15% for one variable and −15% for the other, are also run, although changes of the same sign are expected to produce the largest errors based on Equation (5). Thus, a total of 48 combinations of $\vartheta 1$ and $\vartheta 2$ are analysed in this approach. The same error metrics are reported to assess model robustness to these parameter value choices.

3. Results

3.1. VCV trials prediction

3.1.1. Elastance evolution and prediction

Fig. 3 (a) shows an example of elastance evolution for the CURE trial Patient 4, Set 1 across 6 PEEP levels, identified at PEEP = 11 cmH_2O and predicting response at higher PEEP levels. Fig. 3 (b) shows an example for Patient 15 across 6 PEEP levels in the McREM trial, identified at PEEP = 10 cmH_2O and then predicting response, where T_0 is the time when inspiration ends and reaching maximum tidal volume. Typical prediction cases are shown in Fig. 4, with low absolute median pressure predicted error of 0.25 cmH_2O, 0.46 cmH_2O and PIP error of 0.23 cmH_2O, 0.58 cmH_2O for Patient 1, Set 3 in CURE and Patient 14 in McREM, respectively.

3.1.2. Pressure prediction

Prediction uses the first PEEP level to identify patient-specific model parameters and then predicts the response at higher PEEP levels. Absolute prediction errors (cmH_2O) of PIP and RMS with median pressure error over the whole breath and interquartile range (IQR) for both two VCV trials are shown in Table 4. Cumulative distribution functions (CDFs) and boxplots for prediction error as a function of ΔPEEP interval showing absolute predicted PIP error (cmH_2O) are given in Fig. 5 for the CURE trial and Fig. 6 for the McREM trial. For both two VCV trials, the predicted error is slightly larger with larger ΔPEEP, which is reasonable and expected. It is worth noting with larger ΔPEEP, the clinical PIP is also increasing, and thus the percentage errors of PIP prediction do not have noticeable relationship with ΔPEEP. Finally, Fig. 7 (a) shows the correlation of predicted and measured PIP values with $R^2 = 0.99$ for CURE and $R^2 = 0.88$ for McREM showing a high level of prediction accuracy ($R^2 = 0.94$ overall).

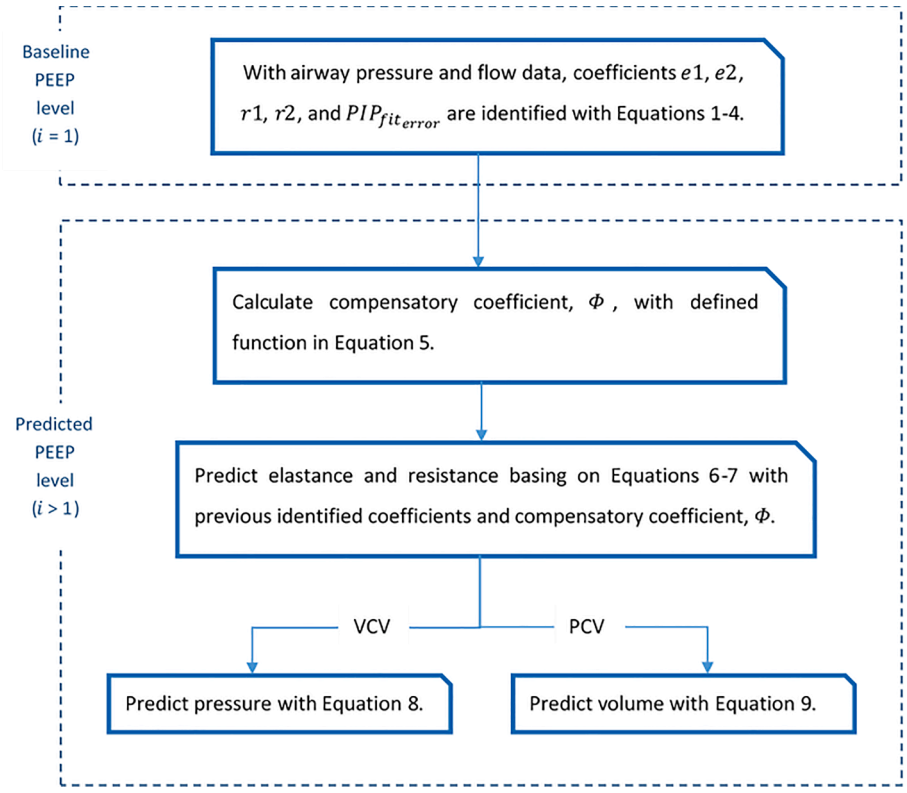


Fig. 2. Flowchart of the entire identification ($i = 1$) and prediction ($i > 1$) procedure.

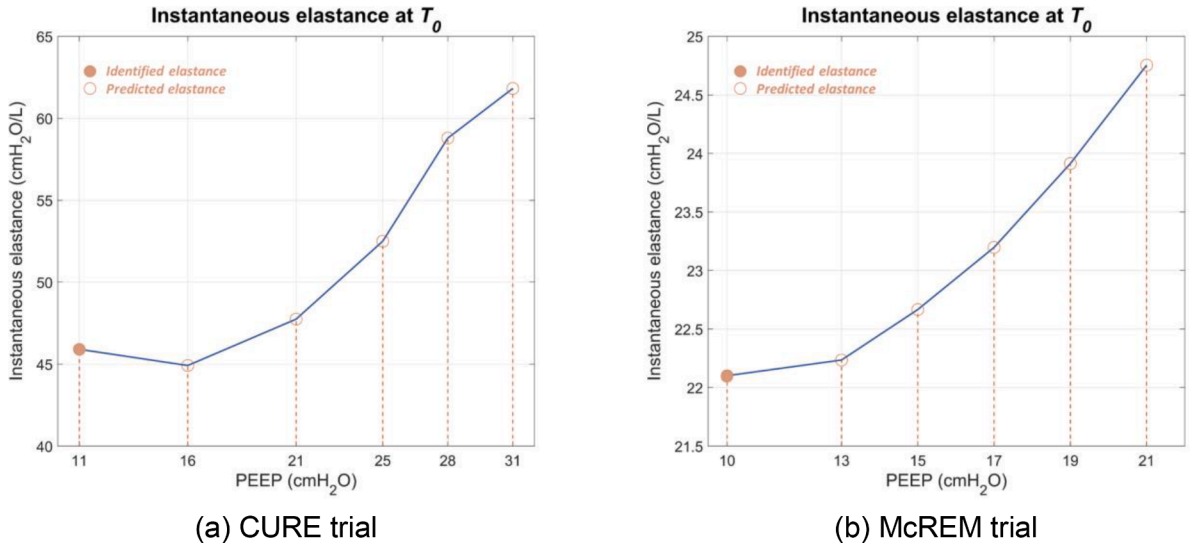


Fig. 3. Examples of elastance evolution at end of inspiration, T_0 , over PEEP in Set 1 of Patient 4 for CURE (a) and Patient 15 for McREM (b). It is identified (filled circle) at PEEP = 11 cmH_2O in CURE and 10 cmH_2O in McREM, and predicted (empty circle) to higher PEEP levels using Equations (5) - (6).

3.2. PCV trial prediction

Prediction outcome of volume in PCV basing on base PEEP level, absolute prediction errors of PIV (L) and RMS errors (L), are shown with median prediction error and IQR in Table 5. Correlation for predicted and measured PIV is shown in Fig. 7 (b) with $R^2 = 0.74$. It is clinically acceptable, and 74% of predictions are greater than the clinical value, which can lead to a more conservative treatment choice and thus lower the risk of volutrauma. A typical prediction case for predicted volume in PCV is shown in Fig. 8, with median predicted volume error of 0.018 L over the whole breath trajectory and PIV error of 0.027 L.

3.3. Sensitivity analysis

The values of $\vartheta 1$ and $\vartheta 2$ were optimised parametrically by line search. To quantify the impact of this choice of values and decision to used fixed values, $\vartheta 1 \text{and} \vartheta 2$ are modified ± 5%, ± 10%, and ± 15% individually and jointly. These changes yield further 48 analyses. The maximum changes of predicted PIP error (cmH_2O), PIV error (L), and RMS error (cmH_2O, L) are recorded and compared with those form the initial values of $\vartheta 1 \text{and} \vartheta 2$, as shown in Table 6 for VCV trials and the PCV trial.

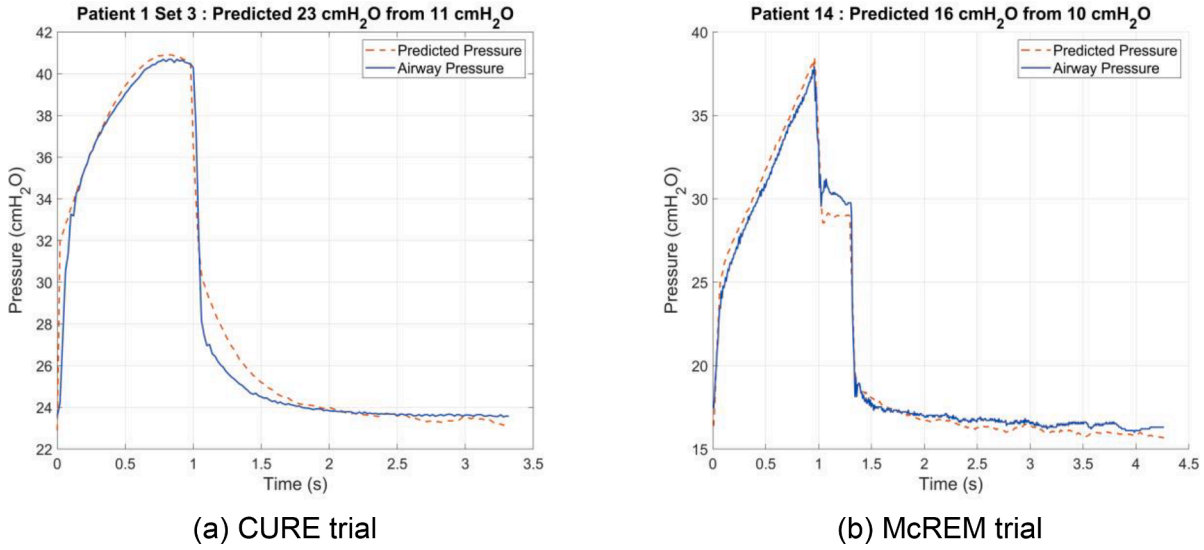


Fig. 4. Typical predicting case in Set 3 of Patient 1, from 11 to 23 cmH_2O ($\Delta PEEP = 12$ cmH_2O) in CURE (a) and in Patient 14, from 10 cmH_2O to 16 cmH_2O ($\Delta PEEP = 6$ cmH_2O) in McREM (b).

Table 4
Prediction outcome for VCV trials with PIP error (cmH_2O) and RMS error (cmH_2O)

Prediction outcome for VCV trials		CURE trial	McREM trial
Prediction cases		39 cases	82 cases
Maximum ΔPEEP		20 cmH_2O	16 cmH_2O
PIP error(cmH_2O)	median	0.43	1.04
	[IQR]	[0.21, 0.79]	[0.46, 2.18]
RMS error(cmH_2O)	median	0.97	1.11
	[IQR]	[0.81, 1.12]	[0.81, 1.48]

3.4. Model identification quality

Prediction accuracy is dependent on a good identification at the base PEEP level. For VCV trials, identification difference (cmH_2O) for first PEEP level of 22 identification cases are presented in Table 7. Fig. 9 (a) shows the correlations of model identification, identified PIP and measured PIP, are $R^2 = 0.87$ in CURE, $R^2 = 0.96$ in McREM, and $R^2 = 0.98$ overall. For the PCV trial, identification outcomes for tidal volume (L) is also provided in Table 7, while the correlation of model identification is shown in Fig. 9 (b) with $R^2 = 0.99$.

4. Discussion

The personalized, predictive virtual patient model presented uses only data from the first clinically relevant PEEP level to predict the respiratory mechanics and response at higher PEEP, where ΔPEEP can be up to 20 cmH_2O, a clinically unrealistically change used only to validate the model. Changing PEEP is a key setting to optimise MV care and outcomes [6,12,31]. This overall outcome is achieved using a relatively simple first order single compartment lung mechanics model and physiologically relevant basis functions for elastance and resistance. It is simplified from more complex, and potentially less intuitive, virtual patient models with equally accurate prediction [8,19,35].

Similar to Morton et al [8,19,35,72], resistance is assumed constant across all PEEP levels, as identified at the first PEEP level. Given the relatively low prediction errors, assessing any evolution in resistance would add complexity for minimal gain. Morton et al treated elastance

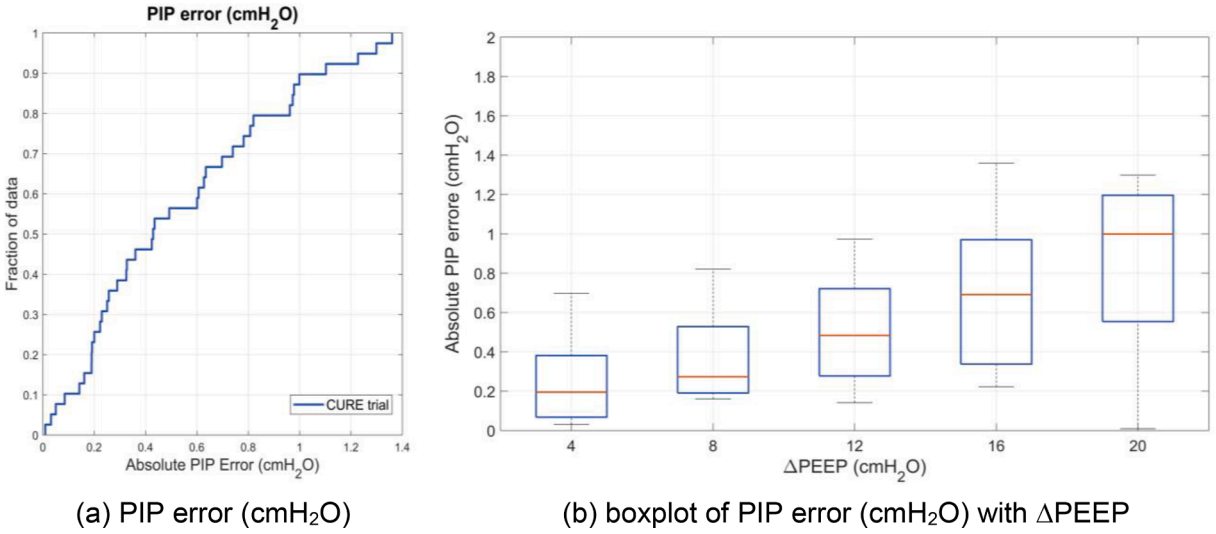


Fig. 5. CDFs plots of predicted absolute PIP error (cmH_2O) for all 39 prediction cases (a) and boxplot of absolute PIP error (cmH_2O) with ΔPEEP (b) for the CURE trial.

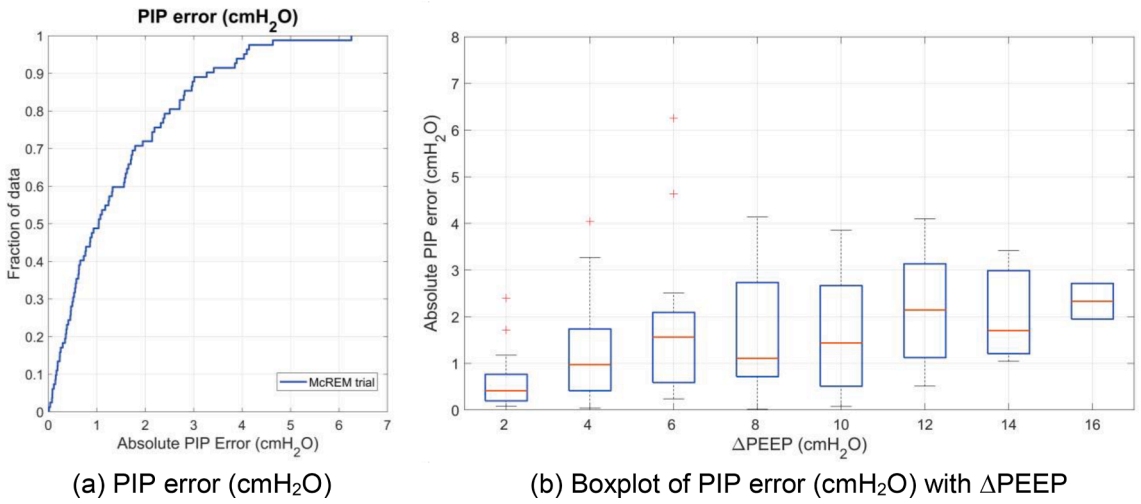


Fig. 6. CDFs plots of predicted absolute PIP error (cmH_2O) for all 82 prediction cases (a) and boxplot of absolute PIP error (cmH_2O) with ΔPEEP (b) for the McREM trial.

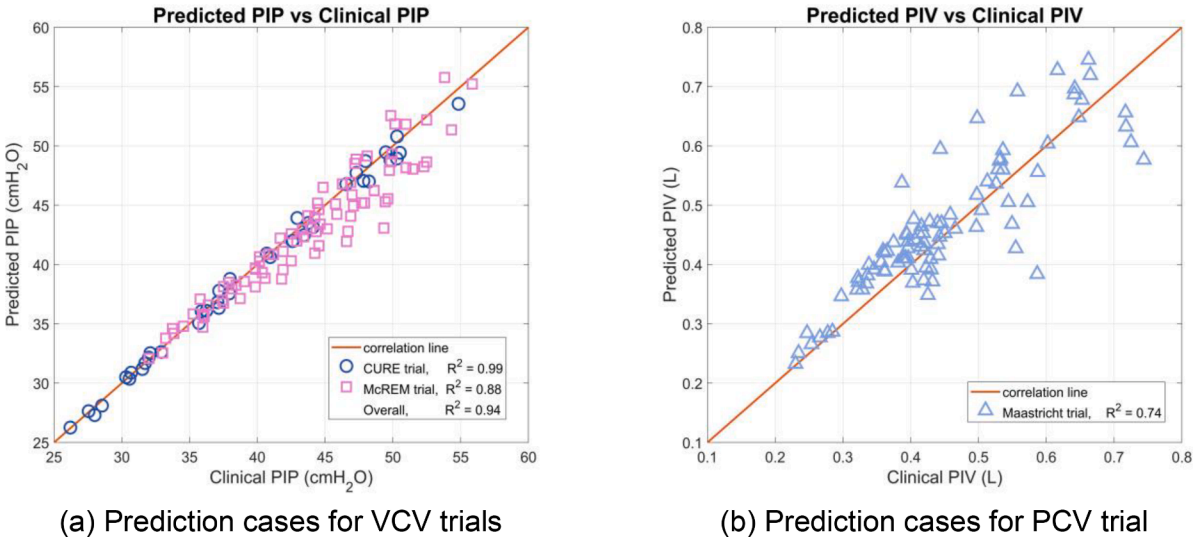


Fig. 7. (a) Predicted PIP vs Clinical PIP ($R^2 = 0.99$ in CURE, $R^2 = 0.88$ in McREM, and $R^2 = 0.94$ overall); (B) Predicted PIV vs Clinical PIV ($R^2 = 0.74$ in Maastricht).

Table 5
Prediction outcome for PCV trial with absolute error (L) and RMS error (L)

Prediction outcome for PCV trial		Maastricht trial
Prediction cases		89 cases
Maximum ΔPEEP		16 cmH_2O
PIV error (L)	median	0.037
	[IQR]	[0.020, 0.058]
RMS error (L)	median	0.043
	[IQR]	[0.034, 0.063]

and its evolution as a more complex function of both volume and pressure. It yielded very good results, but was much higher in complexity, and had some higher prediction errors. Moreover, the proposed approach also yields clinically acceptable results in PCV, which is more difficult to simulate than VCV trials because the two unknown variables of flow and volume are changing simultaneously. Hence, the greater simplicity in the model presented could offer a better approach given to similar to improved prediction performance for both VCV and PCV pilot trials.

The cost of this model simplification is a loss of physiological information, which may concern some clinicians. While effective, it does not have the physiological and clinical relevance of the residual volume (V_{frc}) calculation calculated and predicted by Morton et al [8,19,35,72]. V_{frc} volume is the volume captured by ΔPEEP holding more of the lung open at the end of expiration. Thus, this model is effective and generalizes well across MV modes and patients, but may not meet some clinicians requirements or provide greater physiological or clinical insight. This outcome is expected, and occurs in many modelling areas.

In particular, considering the nonlinear evolution of elastance, a compensatory equation is proposed in Equation (5). It successfully estimates elastance other approaches did not capture as well [8,19]. The compensatory equation is a function of the known ΔPEEP, applied PEEP level, identification error of base PEEP, and an assumed general $PEEP_{max}$. $PEEP_{max}$ is suggested as an internal factor in the nonlinear evolution of elastance, set as 24 cmH_2O in this approach, which is clinically typical and justified maximum PEEP level and worked well for all 210 predictions. Fig. 3 presents the clear nonlinear relationship between PEEP and elastance, while the turning points vary with patients and data sets. This performance matches clinically observed evolution in [1,32,69]. However, despite being a personalized approach, it relies on correlation and set values for $PEEP_{max}$, $\vartheta 1$ and $\vartheta 2$, which may not generalize in

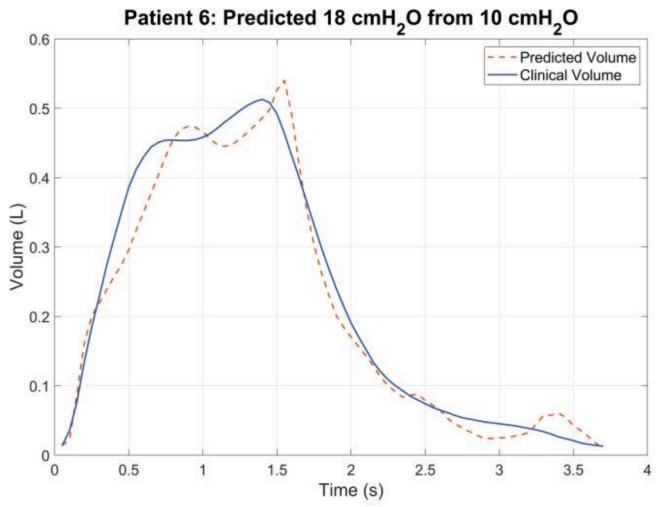


Fig. 8. Typical prediction for volume in Patient 6, from 10 cmH_2O to 18 cmH_2O ($\Delta PEEP = 8$ cmH_2O) in the Maastricht trial cohort, showing the model prediction (dashed) and clinically measured volume (solid) at this higher PEEP level.

Table 6
Comparison of median and average predicted PIP/PIV (cmH_2O, L) and RMS error (cmH_2O, L) between initial set and tested analyses of ϑ_1 and ϑ_2 for VCV trials and PCV trials respectively

Errors changes in VCV and PCV trials with tested analyses of ϑ 1 and ϑ 2		Maximum error change		
		VCV trials		PCV trial
		CURE trial	McREM trial	Maastricht trial
PIP/PIV error(cmH_2O, L)	median	0.22	0.07	0.004
	average	0.34	0.04	0.003
RMS error(cmH_2O, L)	median	0.04	0.04	0.002
	average	0.11	0.03	0.002

Table 7
Identification outcome for VCV and PCV trials with PIP/PIV error (cmH_2O, L) and RMS error (cmH_2O, L).

Identification outcome for VCV and PCV trials		VCV trials		PCV trial
		CURE trial	McREM trial	Maastricht trial
Identification cases	8 cases	18 cases	14 cases	
PIP/PIV error (cmH_2O, L)	Median	0.49	0.60	0.010
	[IQR]	[0.15, 0.61]	[0.19, 1.01]	[0.004, 0.012]
RMS error (cmH_2O, L)	median [IQR]	0.85 [0.73, 0.96]	0.64 [0.56, 0.77]	0.016 [0.015, 0.023]

larger data sets or studies. In contrast, the robustness of prediction performance across independent data sets and MV modes shows it generalized well enough over the studied data sets. Overall, these simplifications and choices represent a loss of physiological information, and a potentially too simple model for broad clinical use, where this study needs more clinical data for a more complete validation.

Similar to this approach, Vicario et al [83] used an added physiological constraint which is estimated for respiratory muscle pressure to help illustrate and estimate the nonlinear behaviour of the lungs. These results offer an effective way to estimate the pulmonary elastance and resistance. However, due to its time-varying physiological constraint equation, the results may have more instability and also lack generality and mechanical or physiological relevance. However, this independent study result still indicates the impact of such assumptions and constraints on lung mechanics and response, which is also seen in this study. In this case, the physiological compensatory equation employed will be the same constant during each PEEP level. Thus, it is more stable than the one used in Vicario et al.

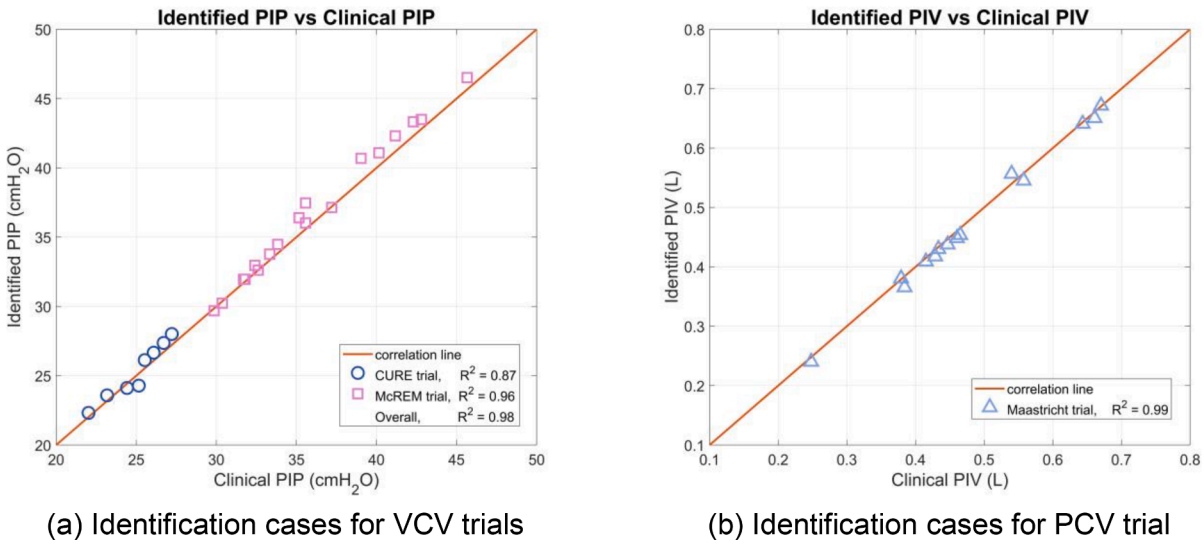
In predicted pressure for VCV trials, for all 39 cases of CURE, the highest absolute predicted PIP error is 1.36 cmH_2O difference, where 35 cases are within 1 cmH_2O PIP error. In the McREM trial, a total of 82 cases, the highest predicted PIP error is 6.26 cmH_2O. However, except for this worst prediction case, all the other predicted PIP errors are within 4.7 cmH_2O, while 59 cases are within 2 cmH_2O and 40 cases are within 1 cmH_2O. Overall, 90% of predictions are within 5.7% prediction error. Table 4 indicates reproducibility for overall pressure trajectory with 0.97 cmH_2O and 1.11 cmH_2O median RMS error in the CURE trial and the McREM trial, respectively, compared to other modelling studies, which only identify models and make no prediction [32,69,83–85], where prediction is the clinically useful impact.

In predicting tidal volume and airway flow for the PCV trial, the performance between volume prediction and flow prediction is not consistent. Considering the very good prediction outcomes in VCV trials, a median PIV prediction error with 0.037 L is acceptable, while biased errors to higher PIV could lead to a clinically preferable conservative decision. This result is achieved with a simple calculation, which means convergence problems are avoided with a low computational cost. Finally, it is important to note these sets of results predict pulmonary response for changing MV inputs (PEEP), where only Morton et al [8,19,35,72] have provided such results previously. Thus, comparison of prediction errors is favourable in comparing to model-identified errors and to prior work by Morton et al.

A sensitivity analysis of the values of $\vartheta 1$ and $\vartheta 2$ is shown in Table 6. Among the 48 analysed sets, the median predicted absolute median PIP error in CURE trial increases 0.22 cmH_2O from the initial baseline value choice, while $\vartheta 1$ and $\vartheta 2$ are both 15% smaller, which also yielded a largest median PIP error increasing of 0.07 cmH_2O in the McREM trial. In the Maastricht trial, the median PIV prediction error increases with a 0.004 L difference under same set and 0.002 L for RMS error. Thus, this approach is robust to these parameter choices.

This study is tested with three independent data sets including two VCV trials and one PCV trial covering a total of 36 patients under various diagnostic and situations. Generalization is reasonably demonstrated, and more data with different PEEP settings, tidal volume decisions, and MV strategies need to be analysed to ensure more widespread generality to more completely quantify the impact of the simplifying choices made. These studies require more data than available for this proof-of-concept validation, although the initial results presented here show significant promise.

Overall, the proposed model provides accurate and robust predictions even with a clinically unrealistic Δ PEEP up to 20 cmH_2O and 16 cmH_2O for VCV and PCV trials, respectively, avoiding complicated procedures or iterative calculation seen in limited prior works [19,35,72]. It is computationally efficient to identify the required parameters for following prediction without any training or updating in black box models, thus minimizing computation, identifiability, and generalisation issues seen in these other approaches and more complex models. Finally, despite simplification, nonlinear elastance evolution is effectively captured and yields accurate predictions across 3 clinical trials (2 VCV, 1 PCV), while offering new insight into the required level of complexity for a virtual patient model for clinical use in MV. Clinically, defining the elastance evolution as a function of the key changing MV parameter, PEEP, ensures the model is more intuitive and easy to understand as evolution is solely a function of the input parameter being changed. All these outcomes significantly extend prior works and offer new insight into modelling of pulmonary mechanics and the potential use of such models to guide clinical care.



(a) Identification cases for VCV trials (b) Identification cases for PCV trial

Fig. 9. (a) Model identified PIP vs Clinical PIP ($R^2 = 0.87$ in CURE, $R^2 = 0.96$ in McREM, and $R^2 = 0.98$ overall); (b) Model identified PIV vs Clinical PIV ($R^2 = 0.99$ in Maastricht).

5. Conclusion

This paper presents a predictive model with a novel, simpler model to capture nonlinear lung elastance and its evolution. In particular, this newly proposed compensatory function is validated in use to predict the pulmonary response in pressure during VCV and volume during PCV, where prediction accuracy is the key element in creating model-based control and validating these virtual patient models before clinical testing. All fixed parameter choices were checked for robustness using a sensitivity test to ensure there was no hidden dependence on these choices. The overall model showed results accurate enough for it to be clinically tested in prospective clinical studies to demonstrate its potential safety, efficacy, and ability to improve care and outcomes.

CRediT authorship contribution statement

Qianhui Sun: Methodology, Software, Validation, Formal analysis, Writing – original draft. **J. Geoffrey Chase:** Conceptualization, Writing – review & editing, Supervision. **Cong Zhou:** Conceptualization, Writing – review & editing, Supervision. **Merryn H. Tawhai:** Conceptualization. **Jennifer L. Knopp:** Conceptualization. **Knut Möller:** Conceptualization. **Serge J Heines:** Data curation. **Dennis C. Bergmans:** Data curation. **Geoffrey M. Shaw:** Conceptualization, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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