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Minimal Lung Mechanics Basis-functions for a Mechanical Ventilation Virtual Patient

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Abstract: Mechanical ventilation (MV) is used in the intensive care unit (ICU) to treat patients with respiratory failure. However, MV settings are not standardized due to significant inter- and intra- patient variability in response to care, leading to variability in care, outcome, and cost. There is thus a need to personalize MV. This research extends a single compartment lung mechanics model with physiologically relevant basis functions, to identify patient-specific lung mechanics and predict response to changes in MV care. The nonlinear evolution of pulmonary elastance as positive-end-expiratory pressure (PEEP) changes is captured by a physiologically relevant, simplified compensatory equation as a function of PEEP and pressure identification error at the baseline PEEP level. It allows both patient-specific and general prediction of lung elastance of higher PEEP. The prediction outcome is validated with data from two volume-controlled ventilation (VCV) trials and one pressure-controlled ventilation (PCV) trial, where the biggest PEEP prediction interval is a clinically unrealistic 20cmH_2O, comprising 210 prediction cases over 36 patients (22 VCV; 14 PCV). Predicted absolute peak inspiratory pressure (PIP) errors are within 1.0cmH_2O and 3.3cmH_2O for 90% cases in the two VCV trials, while predicted peak inspiratory tidal volume (PIV) errors are within 0.073L for 85% cases in studied PCV trial. The model presented provides a highly accurate, predictive virtual patient model across multiple MV modes and delivery methods, and over clinically unrealistically large changes. Low computational cost, and fast, easy parameterization enable model-based, predictive decision support in real-time to safely personalize and optimize MV care.

Keywords: Mechanical ventilation; PEEP; Respiratory mechanics; Elastance; Prediction; VILI; Basis function; System identification; Virtual patient.

1. INTRODUCTION

Mechanical ventilation (MV) is the core treatment for patients suffering life-threatening respiratory failure in the intensive care unit (ICU). The primary goal to enable recovery is to minimise work of breathing, ensure adequate gas exchange, and recruit and hold open lung volume. However, suboptimal MV settings can lead to over-distension and ventilator induced lung injury (VILI), which increase morbidity and mortality (Major et al., 2018). To avoid these harmful effects, protective MV settings have been proposed (Amini et al., 2017).

Recruitment maneuvers optimising positive-end-expiratory pressure (PEEP) are a clinically effective lung protective MV strategy, and effective in improving oxygenation and minimising harm. However, the optimal PEEP setting itself remains patient-specific, time-varying, and thus not standardized (Amato et al., 2015). Hence, it is critical to enable clinicians to monitor and forecast patient-specific pulmonary response for new PEEP settings, to improve personalize care and minimize risk. Therefore, accurate, predictive and patient-specific MV strategies are a major need in advancing care and minimising MV-associated injury (Chase et al., 2018).

The two main MV modes are volume-controlled ventilation (VCV) and pressure-controlled ventilation (PCV). VCV allows clinicians to control tidal volume, eliminating volutrauma, the resulting peak inspiratory pressure (PIP) can cause barotrauma. Conversely, PCV controls the delivered airway pressure, but risks volutrauma from too large a peak

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inspiratory volume (PIV). Thus, both may lead to unexpected VILI (Garnero et al., 2013). To date, no noticeable clinical outcome differences have been seen comparing VCV and PCV (Rittayamai et al., 2015). Thus, the decision on MV strategy relies on clinician preference, patient characteristics, or patient comfort. Hence, accurate, model-based, and patient-specific pulmonary response prediction is necessary for both VCV and PCV to improve patient care and outcomes.

Complex models can capture a large range of dynamics (Chase et al., 2018, Tawhai et al., 2011), but may suffer poor or non-identifiability (Chase et al., 2018, Docherty et al., 2011, Schranz et al., 2012) limiting bedside use. Simpler black box models can require large amounts of data to train and can lack the ability to capture or describe all physiological features (Langdon et al., 2017, Sun et al., 2020), where physiological relevance is important because it supports clinical confidence and use (Chase et al., 2016). Finally, some models capture lung mechanics well, with good personalization of parameters, but can be poor in predicting the response to changes in care, meaning they do not generalize well enough. Thus, relevant deterministic mechanics are advantageous (Chase et al., 2018).

This research presents physiologically relevant, simpler basis functions to estimate elastance and resistance using the well validated single compartment lung mechanics model (Bates, 2009). A compensatory equation captures nonlinear evolution of elastance over PEEP, where there is currently no effective way to use it to predict elastance changes with PEEP (Chiew et al., 2011). Using MV data at one single PEEP level, pulmonary mechanics response (PIP/PIV) can be predicted over PEEP increases up to a clinically unrealistic 20cmH_2O for both VCV and PCV. The goal is to quantify the trade-off between increasing basis function simplicity and improving clinical utility via predictive accuracy.

2. METHODS

2.1 Model Definition

The proposed method is based on a well-validated single compartment lung mechanics model (Bates, 2009):

$$P(t) = E * V(t) + R * Q(t) + PEEP \quad (1)$$

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.

Identification: At baseline PEEP ($i = 1$), pressure and flow data are used to identify patient-specific elastance and resistance using basis functions defined:

$$E_i(t) = e_1 + e_2 * P_i(t), \quad i = 1 \quad (2)$$
$$R_i(t) = r_1 + r_2 * Q_i(t), \quad i = 1 \quad (3)$$

where E_i and R_i (i = 1) are the identified elastance and resistance by $P_i(t)$ and $Q_i(t)$ (i = 1), the measured pressure and flow data. The values of e_1, e_2, r_1, and r_2 are the constant coefficients to be identified. The elastance basis function is significantly simplified from the one used in (Morton et al., 2018, Morton et al., 2019a), which defines $E = f\big(P(t), V(t)\big)$.

After identification, the PIP fitting error, α, can be calculated:

$$\alpha = \frac{fitted\ PIP - clinical\ PIP}{clinical\ PIP} \quad (4)$$

Thus, in this step, e_1, e_2, r_1, and r_2 are identified and remain constant, while the resulting E_i and R_i at i = 1, and α can be identified/calculated.

$E_i(t)$ and $R_i(t)$ prediction: For prediction ($i > 1$), a compensatory coefficient, Φ_i, captures elastance evolution over PEEP. For $PEEP_i$ levels ($i > 1$), Φ_i is defined:

$$\Phi_i = \begin{cases} (1+\alpha)^{-1} & , \quad i = 2 \\ \vartheta_1 * \Delta PEEP & , \quad i > 2 \end{cases} \quad (5)$$

Specifically, for $i > 2$ and $PEEP_i$ > 24cmH_2O, Φ_i is defined with a clinically selected $PEEP_{max}$ = 24cmH_2O:

$$\Phi_i = \vartheta_1 * \Delta PEEP - \vartheta_2 * \left(PEEP_i - \frac{PEEP_{max}}{\Delta PEEP}\right)^2 \quad (6)$$

where ϑ_1 = 0.0174 in the CURE trial and = 0.0087 in both the McREM and Maastricht trials, and $\vartheta_2 = |\alpha| - 0.0123$ for all trials. $\Delta PEEP = PEEP_i - PEEP_{i-1}$, where $PEEP_i$ is the currently applied PEEP level. The values for ϑ_1 and ϑ_2 were optimized parametrically by line search. In the CURE trial, the ΔPEEP step is 4cmH_2O, and is 2cmH_2O in McREM and Maastricht. Thus, ϑ_1 is reasonably decreased to half the value used for the CURE trial (ϑ_1 = 0.0174→0.0087), while ϑ_2 and $PEEP_{max}$ remain the same. Hence, the parameters are general over all three trials and two MV modes.

Elastance is predicted for $PEEP_i$ levels (i = 2, 3, 4, …) using:

$$E_i(t) = e_1 * \sum_{j=2}^{j=i} \Phi_j + e_2 * P_1(t) * \sum_{j=2}^{j=2} \Phi_j * \ldots * \sum_{j=2}^{j=i} \Phi_j \quad (7)$$

Resistance is assumed constant over all PEEP levels for each patient, as identified at baseline $PEEP_1$, using:

$$R_i(t) = R_1(t) = r_1 + r_2 * Q_1(t) \quad (8)$$

Pressure and volume prediction: With predicted $E_i(t)$ and $R_i(t)$, for VCV patients, airway pressure is predicted as the independent output variable from baseline PEEP to $PEEP_i$ ($i > 1$):

$$P_i(t) = E_i(t) * V_1(t) + R_i(t) * Q_1(t) + PEEP_i \quad (9)$$

For PCV patients, since pressure is the known input instead of tidal volume and flow, tidal volume is predicted using:

$$V_i(t) = \frac{P_1(t) - PEEP_1 - R_i(t) * Q_1(t)}{E_i(t)} \quad (10)$$

2.2 Sensitivity analysis

Equation (5) relies on fixed, constant values for ϑ_1, ϑ_2, and $PEEP_{max}$. While $PEEP_{max}$ is clinically justified, the ϑ_1 and ϑ_2 values are tested across hybrid changes of ±5%, ±10%,

and ±15% in a sensitivity analysis to quantify robustness in addition to the three independent data sets used in validation, yielding a total of 48 combinations of ϑ_1 and ϑ_2 analysed.

2.3 Patient data

Pressure and flow data from 36 mechanically ventilated ICU patients (4 from the CURE pilot trial (Chiew et al., 2015), 18 from the McREM pilot trial (Stahl et al., 2006), and 14 from the Maastricht pilot trial) were used to validate the method developed in this study. For consistency, the baseline PEEP level is 10cmH_2O for all 3 trials. Demographics are presented for VCV patients in Table 1 and for PCV patients in Table 2.

Table 1 - Patients and clinical trial demographics for VCV patients in CURE (N=4) and in McREM (N=18). TBI = Traumatic Brain Injury, SDH = Subarachnoid Hemorrhage, SAH = Subarachnoid and Subdural Hemorrhage.

No.	Sex	Age	P/F	Clinical Diagnostic
the CURE trial				
1	M	33	177	Peritonitis
2	M	77	209	Legionella pneumonia
3	M	61	109	Staphylococcus Aureus pneumonia
4	F	73	155	Streptococcus pneumonia
the McREM trial				
1	M	37	163	Pneumonia
2	M	39	170	Traumatic aortic dissection, lung contusion
3	F	50	202	Pancreatitis, pneumonia
4	F	30	162	Peritonitis, sepsis
5	F	49	289	Pneumonia
6	M	34	192	Open TBI
7	M	67	234	Post resuscitation
8	M	39	188	Perf. sigma, peritonitis
9	M	42	235	Pneumonia, pancreatitis
10	M	51	230	TBI, pneumonia
11	M	77	225	Pneumonia
12	M	74	298	SAH, SDH
13	M	41	178	Peritonitis
14	M	62	288	SDH
15	M	39	143	TBI, pneumonia
16	M	74	271	S/P coronary artery bypass grafting, pneumonia
17	M	59	75	ARDS
18	M	45	173	Blunt abdominal trauma, pneumonia

VCV patients from the CURE and McREM trials were fully sedated and invasively intubated. In the CURE trial, 4 patients are underwent two staircases RMs with increments and decrements of 4cmH_2O. While only incremental RM arms (Set 1 and Set 3) are studied, yielding 47 cases across 4 patients in total (8 for identification and 39 for prediction), with a maximum 20cmH_2O PEEP interval. McREM includes 18 patients with 2cmH_2O/step incremental staircase RMs starting at 0cmH_2O. The prediction procedure is applied for higher PEEP levels ($i = 2, \dots, 7$) after identification at baseline PEEP ($i = 1$), yielding a maximum 12cmH_2O PEEP interval. Detailed clinical RM settings can be found in (Sun et al., 2020) for CURE and in (Morton et al., 2019a) for McREM.

Data from the Maastricht trial included 14 patients with Bi-level Positive Airway Pressure PCV (METC 17–4-053). Each patient received a full staircase RM with 2cmH_2O PEEP steps. Only incremental PEEP steps are studied, yielding 103 cases in total, with 14 cases for model identification and 89 cases for prediction validation over maximum 16cmH_2O PEEP interval.

Table 2 - Patients and clinical trial demographics for PCV patients in Maastricht (N=14). CABG = Coronary Artery Bypass Grafting, AVR = Aortic Valve Replacement.

No.	Sex	Age	P/F	Clinical Diagnostic
1	M	77	255	CABG
2	F	85	308	CABG
3	M	57	323	CABG
4	M	47	233	CABG
5	M	73	150	AVR
6	M	75	383	CABG
7	F	71	443	AVR
8	M	76	398	CABG
9	F	64	255	SDH
10	F	68	428	Pneumonia
11	F	78	143	Pneumonia
12	F	18	83	Mitral and Tricuspid Valve Replacement
13	F	71	443	Pneumonia
14	M	36	158	CABG

3. RESULTS

3.1 Elastance evolution and prediction

Since elastance is defined to be constant over time for each PEEP level, basing on (2), an example of elastance evolution during inspiration is shown in Figure 1 (a) for Patient 4 Set 1 in CURE across 6 PEEP levels, identified at PEEP = 11cmH_2O and predicting response at higher PEEP levels. The instantaneous elastance at T_0 over PEEP is also provided in Figure 1 (b), where T_0 is the time when inspiration ends and reaches maximum tidal volume (PIV).

3.2 Pressure prediction for VCV patients

Absolute prediction errors 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 3. The correlation between predicted and clinical PIP is shown in Figure 2 (a) 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) while 1:1 is the perfect match line.

3.3 Volume prediction for PCV patients

Absolute prediction errors of PIV and RMS are shown with median and IQR errors in Table 4. Correlation for predicted

and clinical PIV is shown in Figure 2 (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.

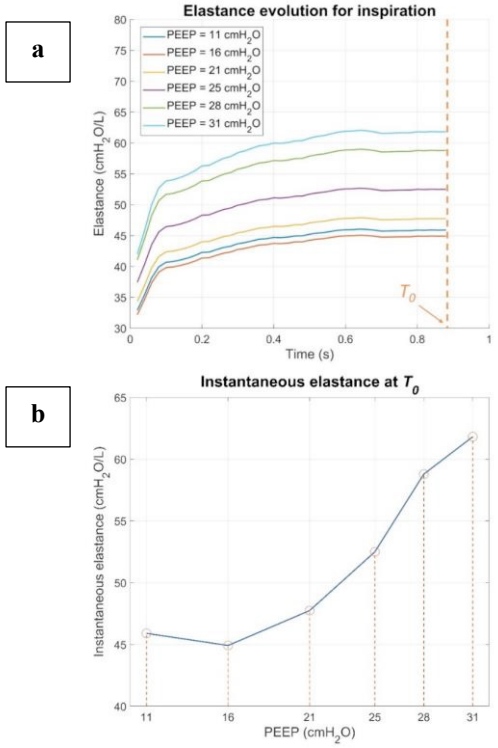

Figure 1 - Examples of elastance evolution during inspiration (a) and instantaneous value at end of inspiration, T_0, over PEEP (b) of Set 1 for Patient 4 in CURE, identified at PEEP = 11cmH₂O.

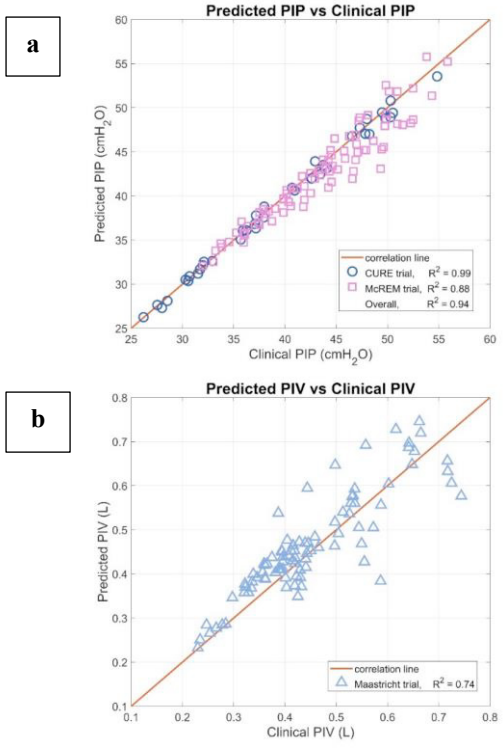

Figure 2 - (a) Predicted PIP vs Clinical PIP ($R^2 = 0.99$ in CURE, $R^2 = 0.88$ in McREM, and $R^2 = 0.94$ overall); (b) Predicted PIV vs Clinical PIV ($R^2 = 0.74$ in Maastricht).

Table 3 - Pressure prediction outcome for VCV trials in absolute PIP and RMS error (cmH₂O).

Pressure prediction		CURE trial	McREM trial
Prediction cases		39 cases	82 cases
Maximum ΔPEEP		20cmH₂O	16cmH₂O
PIP error (cmH₂O)	median	0.43	1.04
	[IQR]	[0.21, 0.79]	[0.46, 2.18]
RMS error (cmH₂O)	median	0.97	1.11
	[IQR]	[0.81, 1.12]	[0.81, 1.48]

Table 4 - Prediction outcome for PCV trial with absolute PIV and RMS error (L).

Volume prediction		Maastricht trial
Prediction cases		89 cases
Maximum ΔPEEP		16cmH₂O
PIV error (L)	median	0.037
	[IQR]	[0.020, 0.058]
RMS error (L)	median	0.043
	[IQR]	[0.034, 0.063]

3.4 Sensitivity analysis

The values of ϑ_1 and ϑ_2 were optimised by line search. To quantify the impact of this choice of values and decision to used fixed values, ϑ_1 and ϑ_2 are modified $\pm 5\%$, $\pm 10\%$, and $\pm 15\%$ individually and jointly. The changes of predicted PIP error (cmH₂O), PIV error (L), and RMS error (cmH₂O, L) are recorded and compared with those form the initial values of ϑ_1 and ϑ_2, as shown in Table 5 for VCV trials and the PCV trial.

Table 5 - Comparison of median and average predicted PIP/PIV (cmH₂O/L) and RMS error (cmH₂O/L) between initial set and tested analyses of ϑ_1 and ϑ_2.

Maximum error changes with tested analysis of ϑ_1 and ϑ_2		VCV trials		PCV trial
		CURE	McREM	Maastricht
PIP/PIV error (cmH₂O/L)	median	0.22	0.07	0.004
	average	0.34	0.04	0.003
RMS error (cmH₂O/L)	median	0.04	0.04	0.002
	average	0.11	0.03	0.002

4. DISCUSSION

This approach presents a predictive and personalized virtual patient model which uses only data from a single baseline PEEP level to predict the respiratory mechanics at higher PEEP level (maximum $\Delta PEEP$ = 20cmH₂O). PEEP iteration is a key setting to optimise MV care and outcomes (Amato et al., 2015, Major et al., 2018). 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 (Morton et al., 2018, Morton et al., 2019a, Zhou et al., 2021a).

Resistance is assumed constant across all PEEP levels, as identified at the baseline PEEP level. Given the relatively low prediction errors, assessing any evolution in resistance would add complexity for minimal gain. Morton et al treated elastance 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 due to the two unknown, coupled variables, flow and volume. Hence, 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.

In particular, considering the nonlinear evolution of elastance, a compensatory equation is proposed in (5)-(6). It successfully estimates elastance other approaches did not capture as well (Morton et al., 2019a). It is a function of ΔPEEP, predicted $PEEP_i$, PIP identification error of baseline PEEP, and an assumed general $PEEP_{max}$. $PEEP_{max}$ is an internal, clinically set factor in nonlinear elastance evolution, and set at 24cmH_2O here, which is a clinically typical and justified maximum PEEP level. This choice worked well for all 210 predictions and both MV modes.

Figure 1 presents the clear nonlinear relationship between PEEP and elastance, where the shape varies between patients and data sets. This performance matches clinically observed evolution in (Amini et al., 2017, Chiew et al., 2011, Sundaresan et al., 2011). However, despite being a personalized approach, it relies on correlation and set values for $PEEP_{max}$, ϑ_1, and ϑ_2, which may not generalize in larger data sets or studies. In contrast, the robustness of prediction performance across independent data sets and MV modes shows it generalized well enough with these values over data sets and modes, as seen in the sensitivity analysis in Table 5.

In predicting PIP for VCV trials, for the CURE trial, the highest absolute predicted PIP error is 1.36cmH_2O among 39 prediction cases, while the errors for 35 cases are within 1cmH_2O. In the 82 McREM trial cases, the highest predicted PIP error is 6.26cmH_2O. However, except for this worst prediction case, all the other predicted PIP errors are within 4.70cmH_2O, while 59 cases are within 2cmH_2O and 40 cases are within 1cmH_2O. Table 3 indicates reproducibility for overall pressure trajectory with 0.97cmH_2O and 1.11cmH_2O median RMS error in the CURE trial and the McREM trial, respectively, compared to other studies, which identify models and make no prediction (Chiew et al., 2011, Sundaresan et al., 2011), where prediction is the clinically useful impact.

Considering the very good prediction outcomes in VCV trials, a median PIV prediction error with 0.037L is acceptable for PCV patients, while biased errors to higher PIV (69 out of 89 predictions) could lead to a clinically preferable conservative decision. Note the overall PIV and RMS errors can be improved to 0.026L and 0.029L from 0.037L and 0.043L, respectively, with an iteration loop added, similar to (Morton et al., 2020). However, it may leads to a convergence problem and a lower positive prediction bias, for 36 out of 89 cases. Thus, the prediction outcome for PCV patients are equally or slighter better with a simpler calculation, while convergence problems are avoided with a low computational cost.

Overall, the prediction errors are quite small for both VCV and PCV patients, considering 90% of prediction errors are within 1.0cmH_2O and 3.3cmH_2O in CURE and McREM respectively, which is clinically highly effective. There is no current means to predict lung response, and these errors are well within clinically accepted variability.

This study uses 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 results here show promise.

The cost of the model simplification presented compared to prior studies is less physiological information, which may concern some clinicians. While effective, it does not have the physiological and clinical relevance of the dynamic functional residual capacity (V_{frc}) calculation in (Morton et al., 2019b, Zhou et al., 2021a). Thus, this model is effective and generalizes well across MV modes and patients, but may not meet some clinical requirements or provide greater physiological or clinical insight. This outcome is expected, and occurs in many modelling areas.

In all, this model provides accurate and robust prediction from low PEEP levels to higher PEEP levels both for VCV and PCV trials, without complicated procedures or iterative calculation (Morton et al., 2019a, Morton et al., 2020, Zhou et al., 2021b). It is also computationally efficient to identify the required parameters, avoiding the training or updating of black box models and minimizing computation and identifiability issues seen in more complex deterministic models. Finally, despite simplification, nonlinear elastance evolution is effectively captured, offering new insight into the required level of complexity for a virtual patient model for clinical use in MV.

5. CONCLUSIONS

This paper presents a simplified predictive model capturing nonlinear lung elastance and its evolution to predict lung mechanics response during VCV and PCV for optimising patient-specific MV settings. It is simpler and more efficient in use to reproduce overall pressure and volume waveform with an accurate PIP and PIV prediction use bedside available MV data at one single PEEP to predict pulmonary outcomes when titrating PEEP or potentially other MV parameters. It is robust to fixed parameter choices and over the two independent VCV data sets and one PCV data set used for validation. It could thus be employed as a useful tool for clinicians to safely provide personalized MV treatment.

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