Computer Methods and Programs in Biomedicine 165 (2018) 77–87

Contents lists available at ScienceDirect

Computer Methods and Programs in Biomedicine

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

A virtual patient model for mechanical ventilation

S.E. Morton[a,*], J. Dickson[a], J.G. Chase[a], P. Docherty[a], T. Desaive[b], S.L. Howe[a], G.M. Shaw[c], M. Tawhai[d]

[a] Department of Mechanical Engineering, University of Canterbury, New Zealand
[b] GIGA Cardiovascular Science, University of Liege, Liege, Belgium
[c] Department of Intensive Care, Christchurch Hospital, Christchurch, New Zealand
[d] Auckland Bioengineering Institute, University of Auckland, Auckland, New Zealand

ARTICLE INFO

Article history:
Received 31 January 2018
Revised 24 July 2018
Accepted 8 August 2018

Keywords:
In-silico
Virtual patient
Mechanical ventilation
Prediction
Intensive care
PEEP

ABSTRACT

Background and Objectives: Mechanical ventilation (MV) is a primary therapy for patients with acute respiratory failure. However, poorly selected ventilator settings can cause further lung damage due to heterogeneity of healthy and damaged alveoli. Varying positive-end-expiratory-pressure (PEEP) to a point of minimum elastance is a lung protective ventilator strategy. However, even low levels of PEEP can lead to ventilator induced lung injury for individuals with highly inflamed pulmonary tissue. Hence, models that could accurately predict peak inspiratory pressures after changes to PEEP could improve clinician confidence in attempting potentially beneficial treatment strategies.

Methods: This study develops and validates a physiologically relevant respiratory model that captures elastance and resistance via basis functions within a well-validated single compartment lung model. The model can be personalised using information available at a low PEEP to predict lung mechanics at a higher PEEP. Proof of concept validation is undertaken with data from four patients and eight recruitment manoeuvre arms.

Results: Results show low error when predicting upwards over the clinically relevant pressure range, with the model able to predict peak inspiratory pressure with less than 10% error over 90% of the range of PEEP changes up to 12 cmH_2O.

Conclusions: The results provide an in-silico model-based means of predicting clinically relevant responses to changes in MV therapy, which is the foundation of a first virtual patient for MV.

1. Introduction

Mechanical ventilation (MV) is a core therapy for intensive care unit (ICU) patients with respiratory failure or acute respiratory distress syndrome (ARDS) [1–3]. MV settings that are poorly suited to the patient can have unintended consequences such as ventilator induced lung injury (VILI) [4–8]. While optimising respiratory treatment is simple in theory, achieving sufficient gas exchange while concomitantly minimising lung damage is difficult in practice. In particular, respiratory failure is often a secondary outcome of a heterogeneous range of conditions that can cause localised lung damage, and thus, healthy and damaged lung units must be exposed to similar pressures and volumes during MV [9].

The ultimate goal of MV is to achieve gas exchange, while minimising VILI [10–14]. Application of positive end expiratory pressure or PEEP at the end of each breathing cycle can prevent alveoli from collapsing during expiration [15–18]. An optimal PEEP for gas exchange will increase recruited volume, and thus opportunity for gas exchange, without increasing dead space volume or the risk of VILI. [19]. Alternatively, sometimes the fractional inspired oxygen (FiO_2) delivered to the patient is increased. Increases in FiO2 represent negligible mechanical risk as tidal volume or airway pressure are unchanged. However, there are risks associated with exposure to high FiO_2 [20,21]. In practice, both approaches can be used in isolation or in combination, but carry different risks if poorly suited to the patient condition [22–25]."

PEEP allows recruited alveoli to stay open at the end of expiration, including those that would otherwise collapse [26]. However, there is a balance point between recruitment of more alveoli, and distension of open ones. While more recruitment could be achieved at a higher pressure, it comes with higher pressures and the resulting risk of over-stretching and distension. Several

* Corresponding author.
E-mail addresses: sophie.morton@pg.canterbury.ac.nz (S.E. Morton), jennifer.dickson@canterbury.ac.nz (J. Dickson), geoff.chase@canterbury.ac.nz (J.G. Chase), paul.docherty@canterbury.ac.nz (P. Docherty), tdesaive@ulg.ac.be (T. Desaive), sarah.howe@pg.canterbury.ac.nz (S.L. Howe), geoff.shaw@cdhb.health.nz (G.M. Shaw), m.tawhai@auckland.ac.nz (M. Tawhai).

https://doi.org/10.1016/j.cmpb.2018.08.004
0169-2607/

studies suggest that setting PEEP at maximum lung compliance, or equivalently minimum lung elastance, can improve patient outcomes [4,13,26–29]. In particular, minimum elastance is associated with maximum tidal volume and higher oxygenation for a given tidal pressure input [26–28,30]. More specifically, it means that a particular tidal volume can be achieved for the minimum driving pressure and minimum risk.

More recent work has shown PEEP levels can be titrated to minimum elastance through a staircase recruitment manoeuvre (RM) [31,32]. An RM gradually increases PEEP in steps of 2–4 cmH_2O up to a threshold in either PEEP or Peak Inspiratory Pressure (PIP). PEEP is then reduced again in steps until it reaches the initial level. These RMs also improve overall alveolar recruitment [18,33], thus increasing functional lung volume. However, some RMs apply very high PEEP and thus risk alveolar distension and VILI, which could defeat the therapeutic purpose [27–29,34]. Development of a model to predict future airway mechanics could allow clinicians to better manage the trade-off between improving recruitment and reducing the risk of barotrauma and volutrauma.

Current clinical practice lacks the ability to predict changes in respiratory mechanics over PEEP transitions. Hence, in order to determine a patient's respiratory mechanics at a particular PEEP level, they must be physically ventilated at that PEEP. This requirement increases the risk of over-distension and VILI when pressure unintentionally rises too high [35]. The ability to accurately predict peak inspiratory pressure outcomes for a change in PEEP before it was applied would reduce the risks of barotrauma, while the ability to predict increases in gained recruited volume can reflect diminishing returns for increased risk of volutrauma. Hence, a robust identifiable lung mechanics model with predictive power is needed to enable safe, patient specific RM design and implementation by clinicians. In essence, a virtual patient model [36,37].

Basis function models have been developed to characterise and predict mechanical lung response to recruitment manoeuvres [35,38]. However, these prior efforts are either comprised of shapes that are not explicitly linked to lung mechanics and/or are unable to accurately predict more than one PEEP level ahead, limiting clinical utility despite acceptable prediction. In particular, increased physiological relevance would enable potential further diagnostics to be derived from patient- and breath-specific basis functions and their evolution over time.

This research uses a validated single-compartment lung mechanics model [31,39,40], which is made patient-specific by identifying physiologically relevant basis functions. This basis function model is designed to allow prediction of expected lung mechanics and pressure/volume dynamics. This work will focus on and the prediction of airway pressure throughout a volume controlled RM at pressures and volumes extrapolated beyond the PEEP levels used to train the model. The identified basis functions create the opportunity to personalise care, by predicting lung behaviour throughout an RM represent an opportunity to improve patient outcomes.

2. Methods

2.1. Patients and data

This study used pressure-flow data from four mechanically ventilated patients that were treated in the Christchurch Hospital Intensive Care Unit (ICU) in August 2016 as part of the CURE pilot trial (ANZTR Number: ACTRN12613001006730) [41]. The CURE pilot trial was a randomised control trial where the intervention arm received repeated RMs. All patients were intubated and fully sedated, receiving volume controlled MV. Those with APACHE III diagnostic codes associated with prior pulmonary disease admission (asthma, COPD), or neurological, spinal injury, or head trauma, were excluded from the pilot trial.

All patients were fully sedated with muscle relaxants, which is common to prevent spontaneous breathing during RMs. Inclusion criteria for the trial require a PaO2/FiO2 ratio (PF) < 300 mmHg, classifying the patient as having ARDS according to the Berlin definition [42]. Pressure, flow, and time data were extracted at 50 Hz from a Puritan Bennett 840 ventilator (Covidien, Boulder, CO, USA). Patient demographic and clinical data is shown in Table 1. More information about the CURE trial can be found in [26,41,43]. Only the four patients from the intervention arm of the CURE pilot trial underwent major RMs, per protocol [41], and are thus the only data available for this development and validation study. Each of these patients had mild (200–300 mmHg) or moderate (100–200 mmHg) ARDS.

Each RM comprised two staircase increases and decreases in PEEP. The first was performed to recruit lung volume, and the second to assess lung mechanics at different PEEP levels once recruitment was achieved [26,43]. As lung mechanics change throughout an RM, each data set was split into four sections: two upwards and two downwards staircase sections, as shown in Fig. 1. PEEP levels containing less than eight usable breaths were excluded to reduce the impact of outliers; this issue occurs when the ventilator does not achieve exactly the stated PEEP in some breaths. The average length of PEEP levels studied in this research was (median [IQR]) 10 [7–12] breaths.

2.2. Model

A single compartment model of lung elastance and pressure was used as a starting point for model development [31,39,40].

$$P(t) = EV(t) + RQ(t) + PEEP \tag{1}$$

where $P(t)$ is the airway pressure delivered by the ventilator (cmH_2O), $V(t)$ is the volume of air delivered to the lungs (L), $Q(t)$ is the flow of air delivered by the ventilator (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 by E and R, respectively.

Elastance is a key physiological indicator of pulmonary distension [44,45]. The model was designed to identify distension by allowing non-linear elastance characteristics across the range of respiratory mechanics. A pair of recruitment (E_{rec}) and distension (E_{dist}) basis functions for elastance were developed as functions of volume and pressure. These basis functions, shown in Table 2, were shaped to match observed mechanical lung behaviour during inspiration and, in particular, the impact and trade-off between alveolar recruitment and distension across the full range of pressure and tidal volume. The general elastance and resistance basis function shapes are shown in Fig. 2 and defined over the pressure range 0–60 cmH_2O (elastance), volume range 0–1 L (elastance), and flow range −2 to 2 L/s (resistance), which more than covers the typical mechanical ventilation ranges. The recruitment basis function is defined over volume, as it changes with tidal volume delivered. Distension is defined with respect to pressure as its risk increases with pressure. These are combined to create an overall elastance basis function. Resistance basis functions were developed with respect to flow and followed the form of the Rohrer equation [46,47].

The elastance (E, cmH_2O/L) is defined:

$$E(P(t), V(t)) = E_{rec} + E_{dist} = E_1\Phi_1(V(t)) + E_2\Phi_2(P(t)) \tag{2}$$

where $\Phi_1(V(t))$ and $\Phi_2(P(t))$ are dimensionless recruitment and distension basis functions, and E_1 and E_2 are constant coefficients.

Recruitment (E_{rec}) is defined as a function of volume, as

$$E_{rec} = E_1\Phi_1V(t) = E_1e^{b(V(t))} \tag{3}$$

where b is a constant controlling the rate of recruitment with increased tidal volume delivered, which also makes it useful for assessing different levels of volume deficiency.

Table 1
Patient demographic information.

Patient number	Sex	Age (years)	Length of MV	# RMs	Clinical diagnostic	Initial PEEP (cmH_2O)	Suggested PEEP (cmH_2O)	P/F Ratio
1	M	33	22 days, 14 h	2	Peritonitis	10	18	177
2	M	77	24 days, 5 h	2	Legionella pneumonia	12	16	209
3	M	61	23 days	2	Staphylococcus Aureus pneumonia	12	15	109
4	F	73	1 day, 22 h	2	Streptococcus pneumonia	12	20	155

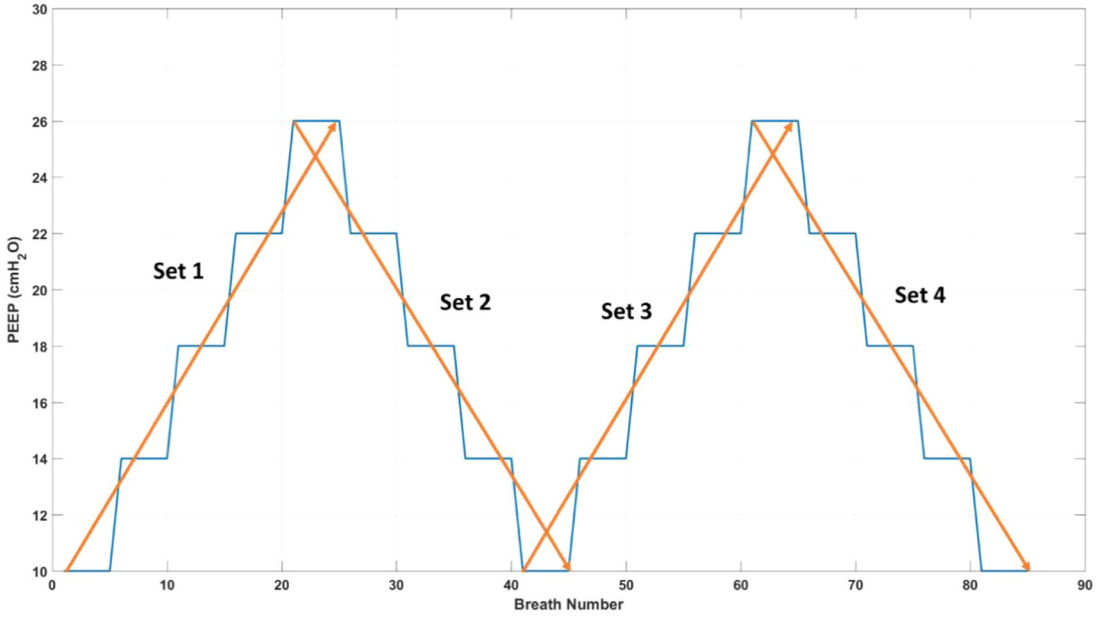

Fig. 1. Example of demarcation of data sets across a recruitment manoeuvre where two staircase manoeuvres are performed. For this Example 5 PEEP levels are shown.

Table 2
List of basis function shapes. These are also presented in Fig. 2.

Relevance	Title	Coefficient	A function of	Chosen shape
Recruitment (Elastance)	E_{rec}	Φ_1	Volume	Exponentially decreasing curve
Distension (Elastance)	E_{dist}	Φ_2	Pressure	Linearly increasing slope
Resistance 1	R_1	Θ_1	Constant	Constant value
Resistance 2	R_2	Θ_2	Flow	The absolute value of ventilator flow throughout the breath

Distension (E_{dist}) is defined as a linear increase with pressure:

$$E_{dist} = E_2\Phi_2(P(t)) = E_2\frac{P(t)}{60}. \tag{4}$$

Defining recruitment with respect to volume, and distension with respect to pressure, allows more physiological behaviours of the lungs to be captured compared with the constant, lumped parameter single compartment model of Eq. (1) [31,39,40].

Resistance was defined per the structure of the Rohrer equation for flow resistance [46,47]:

$$R = R_1\Theta_1 + R_2\Theta_2(Q(t)), \tag{5}$$

where

$$\Theta_1 = 1,$$
$$\Theta_2 = |Q(t)|. \tag{6}$$

These terms capture the linear and non-linear components of resistance; R_1 and R_2 are constants to be identified. This equation is also similar to those used to model endotracheal tube resistance [46,48] which is a major form of resistance encountered in MV.

As a result, combining Eqs. (1) and (3)–(6) yields a final model, defined as:

$$P(t) = (E_{rec} + E_{dist})V(t) + (R_1\theta_1 + R_2\theta_2)Q(t) + PEEP$$
$$= \left(E_1e^{b(V(t))} + E_2\frac{P(t)}{60}\right)V(t) + (R_1 + R_2|Q(t)|)Q(t) + PEEP \tag{7}$$

2.3. Model identification

Identification of the basis function coefficients (E_1, E_2, R_1, R_2, b) at each $PEEP_n$ is achieved in five steps as summarised in Fig. 3. The first 10 data points are discarded as this 0.2 s of initial pressure rise is a function of ventilator mechanics and not lung mechanics.

First, resistance is estimated using constant and linear elastance functions. Next, elastance parameters (E_1, E_2, b) are identified iteratively, as φ_2 in Eq. (4) is non-linear. These iterations alternately identify E_2 and (E_1, b) in convex least-squares parameter identification problems. Convergence is not guaranteed, but typical convergence in this study for the elastance basis functions is shown in Fig. 4, and no cases failed to converge.

2.4. Forward prediction

The solution for an identified model is generated using volume controlled MV and thus specified $V(t)$ and $Q(t)$ at the same PEEP to assess fit error of simulated $P(t)$. Forward simulation using $V(t)$ and $Q(t)$ inputs at different PEEP levels, which are specified

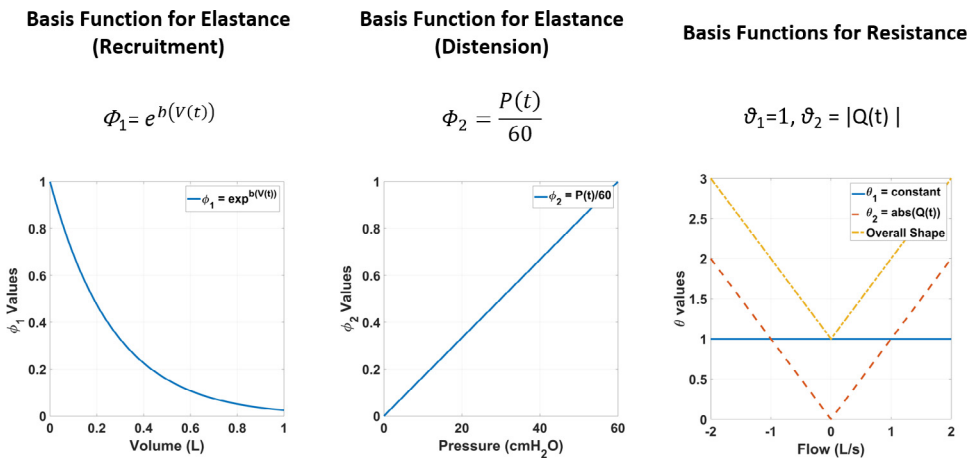

Fig. 2. Depiction of basis functions for elastance and resistance. The shapes above assume coefficient values of 1 and an exponential constant of −3.77 for E_{rec}. All basis functions are dimensionless.

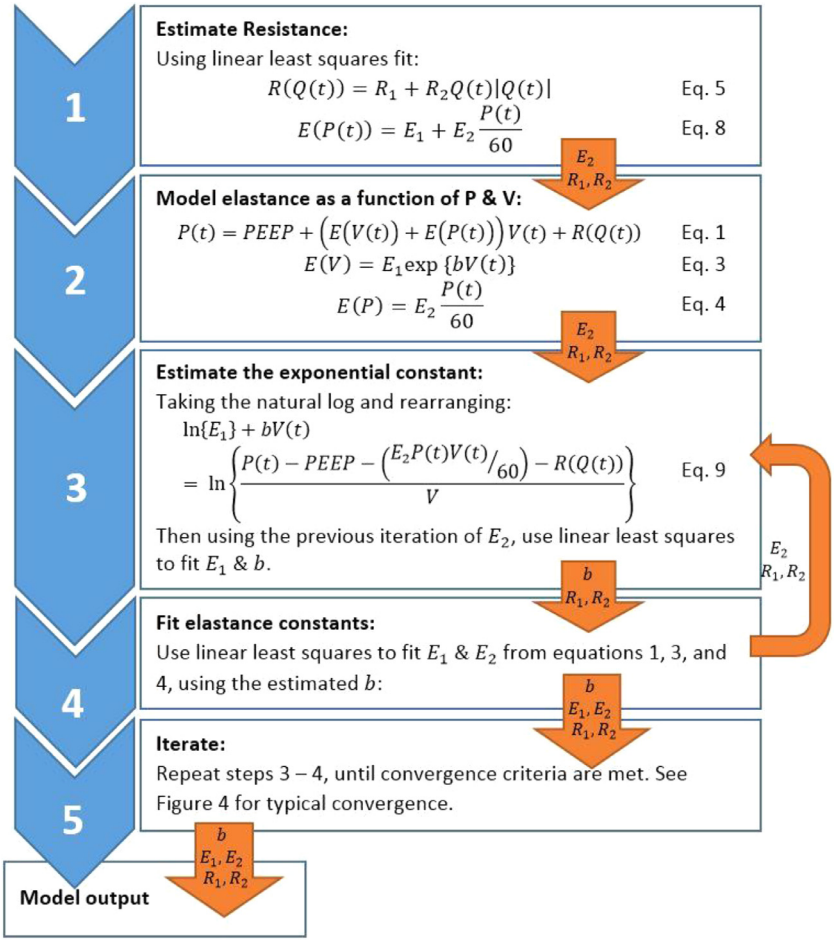

Fig. 3. Model fitting process for parameter identification using clinical data, including Eqs. (1) and (3)–(9).

and known ahead of time in volume controlled MV, can be computed to assess prediction and utility. Inspiration was defined as pressure corresponding to positive flow. Prediction was carried out for PEEP increases in each upwards RM arm (1 and 3 in Fig. 1). There was a focus on prediction on increasing PEEP as an increase in pressure and volume pose a greater immediate risk to patient safety. PIP and gained recruitment volume (V_{frc}) can be used to reflect the relative gains and risks of mechanical ventilation, for the purposes of avoiding barotrauma and volutrauma. This entire process is summarised in the 3 steps shown in Fig. 5.

2.5. Model validation

Model efficacy is initially assessed by testing its ability to precisely predict pressure within the identification PEEP level. The second assessment of model efficacy measures the ability of the

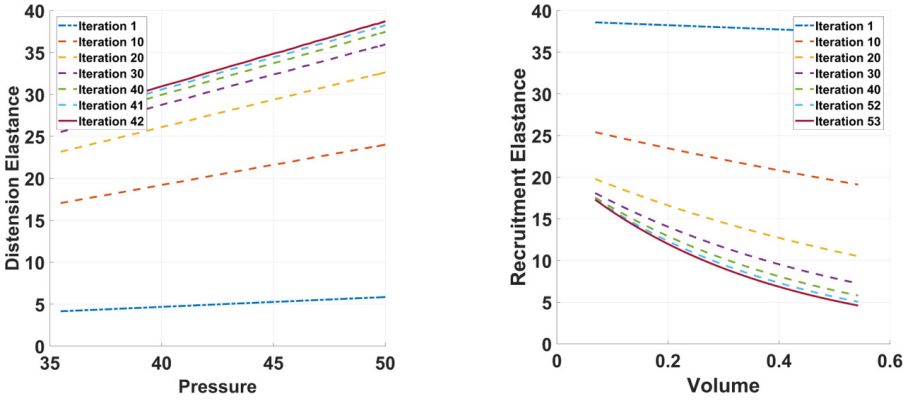

Fig. 4. Example of convergence for the two elastance basis functions.

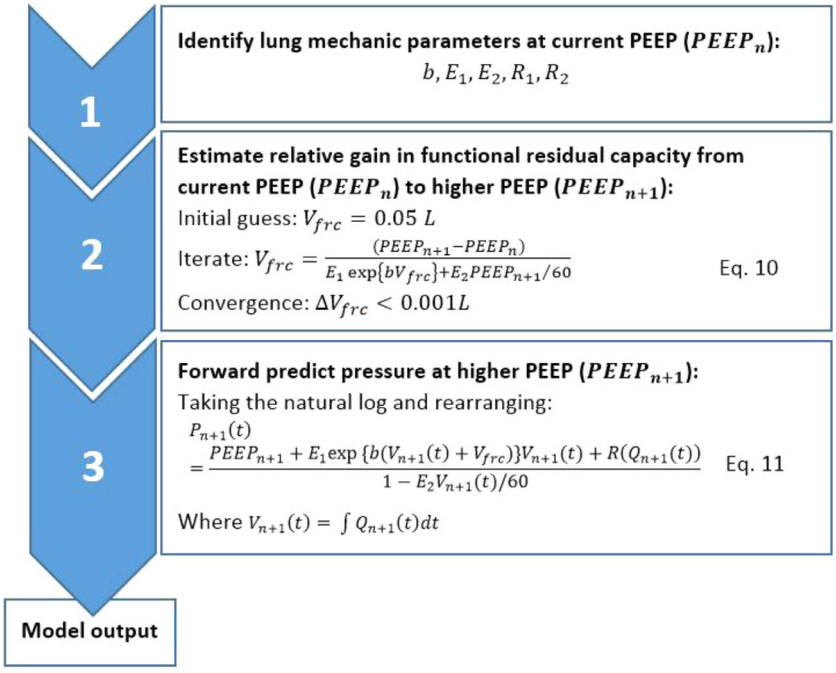

Fig. 5. Forward prediction process for evaluating like pressure outcomes at a higher PEEP, including Eqs. (10) and (11) in Steps 1–3.

model to predict elastance and thus pressure for volume controlled MV at a higher PEEP level.

2.5.1. Model fit

Model fit error assesses whether identified models capture all observed mechanics at a given PEEP level. Root mean square (RMS) errors and percentage RMS errors were assessed over the inspiratory section for each pressure measurement of 796 RM breaths across all PEEP levels and patients. Since PIP is a critical risk factor for VILI, absolute and percentage error in PIP is also reported [49–51].

2.5.2. Prediction error

Forward predictions of pressure are made for different PEEP levels up both arms of the two RMs. Forward predictions were thus made over 1–4 PEEP steps of 4 cmH_2O each. The initial PEEP step of the RM section is used to predict the pressure for every following PEEP step in the arm. Subsequent PEEP steps only predict the remaining available increased PEEP steps. Due to some variation in how well the ventilator achieved the clinician-set PEEP, some predictions use 2 or 6 cmH_2O steps when a 4 cmH_2O step was not available or was not achieved by the ventilator.

Predicted pressure fit was assessed by RMS error over inspiration to ensure all critical lung mechanics were predicted. The absolute error at PIP, an indication of potential VILI with poor prediction, is also calculated as PIP correlates with risk of barotrauma. The percentage error of both metrics is reported for all predicted future higher PEEP steps $j = 1 \ldots 4$.

3. Results

3.1. Model fit

Elastance and resistance basis functions were fit over 796 breaths, for four patients, and 10 PEEP levels. Fig. 6 shows typical sets of recruitment and distension elastance functions for Patient 1, Set 1. RMS fit errors for each PEEP level are shown in Table 3. These results consider all data sets across all patients. Median [IQR] absolute error for all PEEP and patients across the 796 breaths analysed was 0.31 [0.21–1.28] cmH_2O yielding average RMS % errors of 0.1%. Model fit in Table 3 is very good, with higher error in PIP at the highest PEEP levels, possibly due to shorter clinician-set inspiratory times at high pressures, and/or some lung mechanics at higher pressures/volumes that were not modelled.

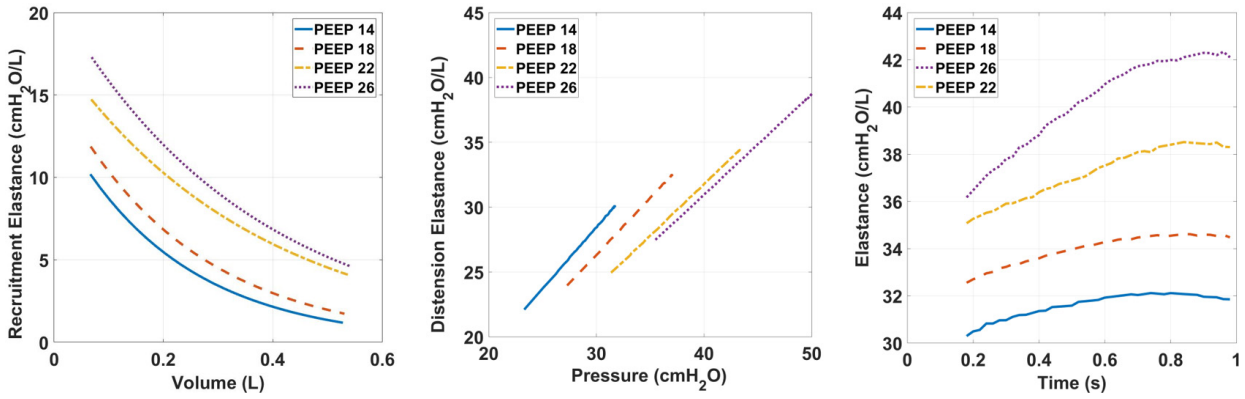

Fig. 6. Elastance for a Patient 1 recruitment manoeuvre (Set 1, rising PEEP): recruitment, distension, and overall elastance over a 1 s inspiration, respectively.

Table 3
Model fit for PEEP levels across all patients. This includes data from both upwards and downwards arms.*This fit was to data from one patient only.

PEEP level (cmH_2O)	Number of breaths	RMS median error [IQR] (cmH_2O)	RMS % error	PIP error (cmH_2O)	PIP error (%)
PEEP 12	117	0.32 [0.21 −0.97]	0.3 [0.2–0.5]	−0.01	0.3
PEEP 14	55	0.41 [0.29–1.40]	0.3 [0.2–0.5]	−0.04	0.4
PEEP 16	77	0.31 [0.23–0.36]	0.2 [0.2–0.4]	−0.04	0.3
PEEP 18	69	0.24 [0.13–1.26]	0.2 [0.2–0.3]	−0.01	0.2
PEEP 20	104	0.30 [0.28–0.65]	0.2 [0.2–0.4]	−0.06	0.3
PEEP 22	67	0.24 [0.10–0.51]	0.1 [0.1–0.2]	−0.04	0.2
PEEP 24	118	0.35 [0.25–0.45]	0.3 [0.2–0.4]	−0.09	0.3
PEEP 26	115	0.21 [0.13–0.29]	0.2 [0.1–0.2]	0.01	0.2
PEEP 28	20*	1.47 [1.46–1.49]	0.2 [0.1–0.2]	−0.06	1.5
PEEP 30	54	1.17 [0.75–1.50]	0.2 [0.1–0.4]	−0.10	1.2

Table 4
Fitting and prediction errors for Patients 1 to 4, Set 1. Fitting results are shaded in light grey.

		RMS (cmH_2O)	PIP (cmH_2O (%))	ΔV_{frc}	RMS (cmH_2O)	PIP (cmH_2O (%))	ΔV_{frc}	RMS (cmH_2O)	PIP (cmH_2O (%))	ΔV_{frc}	RMS (cmH_2O)	PIP (cmH_2O (%))	ΔV_{frc}
Patient 1		PEEP 14			PEEP 18			PEEP 22			PEEP 26		
	14	0.06	0.01 (0.0%)	-	0.51	0.45 (1.2%)	0.17	0.69	0.32 (0.7%)	0.30	0.52	-0.03 (0.1%)	0.42
	18				0.04	-0.03 (0.1%)	-	0.49	-0.91 (2.1%)	0.14	1.33	-2.11 (4.2%)	0.27
	22							0.06	-0.05 (0.1%)	-	0.26	0.38 (0.8%)	0.14
	26										0.06	-0.14 (0.3%)	-
Patient 2		PEEP 16			PEEP 20			PEEP 24			PEEP 26		
	16	0.09	-0.06 (0.2%)	-	1.30	0.39 (1.2%)	0.23	2.41	2.74 (7.2%)	0.38	2.28	1.85 (4.3%)	0.44
	20				0.16	-0.58 (1.7%)	-	1.06	0.44 (1.2%)	0.21	0.91	-0.71 (1.7%)	0.29
	24							0.15	-0.02 (0.0%)	-	0.47	-1.16 (2.7%)	0.10
	26										0.21	-0.41 (1.0%)	-
Patient 3		PEEP 12			PEEP 16			PEEP 20			PEEP 24		
	12	0.07	-0.05 (0.2%)	-	0.78	-1.44 (4.2%)	0.12	1.71	-3.00 (7.4%)	0.23	2.46	-4.02 (8.7%)	0.33
	16				0.06	-0.05 (0.1%)	-	0.44	0.52 (1.3%)	0.13	1.09	2.01 (4.3%)	0.24
	20							0.03	0.00 (0.0%)	-	0.32	-0.09 (0.2%)	0.11
	24										0.13	0.00 (0.0%)	-
Patient 4		PEEP 16			PEEP 20			PEEP 24			PEEP 28		
	16	0.07	-0.01 (0.0%)	-	1.09	1.35 (3.6%)	0.03	2.58	3.58 (8.4%)	0.18	4.28	6.22 (13.2%)	0.26
	20				0.06	-0.02 (0.1%)	-	0.74	1.17 (2.8%)	0.03	1.85	3.01 (6.4%)	0.14
	24							0.06	-0.06 (0.1%)	-	1.07	1.64 (3.5%)	0.02
	28										0.07	-0.03 (0.1%)	-

Fig. 7 shows model fit results for a range of PEEP values for Patient 1. At the highest PEEP of 28 cmH_2O, the error is greatest, but all observed dynamics are captured.

3.2. Prediction

Identified patient-specific models predicted pulmonary pressure response to a PEEP increase of up to 12 cmH_2O with less than 3 cmH_2O RMS fitting error in 90% of cases. The model predicts the peak inspiratory pressure, PIP, with less than 10% error in more than 90% of cases of up to 12 cmH_2O changes in PEEP. As expected, prediction error increases with magnitude between identified and predicted PEEP level. Slightly greater prediction accuracy was seen in the first arm of the recruitment manoeuvre than the second. Prediction results for Patients 1–4 are shown in Table 4 for Set 1 and Table 5 for Set 3. As can be seen in Fig. 8, model prediction error is often within the range of observed pressures at that PEEP. Summarised statistics are shown in Table 6.

Typical prediction results are shown in Fig. 8. They are for the first row of a given patient in Table 4 or 5, as noted. The light grey lines show all breaths at a PEEP step, highlighting the natural variability versus the average prediction. Most '1 step ahead' predictions are within the observed pressures and inter-breath variability. As in Tables 4 and 5, error increases with further, larger steps upward in PEEP, and error also varies by patient. It can be seen in Fig. 8 that Patient 4 has a shorter inspiratory time, but model fit and prediction are comparable to other patients, as expected from our model-based approach.

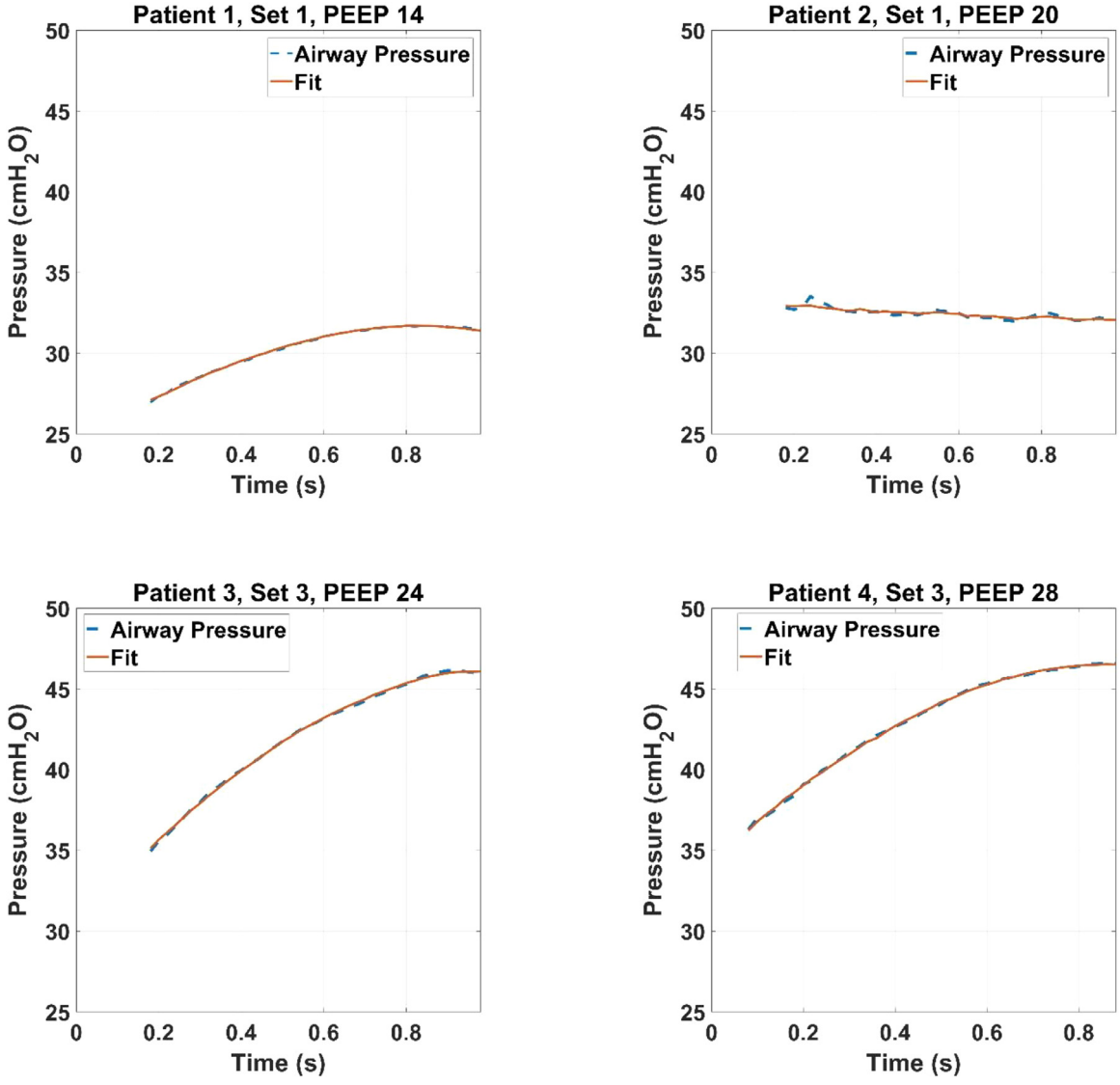

Fig. 7. Typical fit results for each patient at four different PEEP levels. Dashed lines show measured airway pressure and solid lines shown the simulated identified model fit.

Table 5
Fitting and prediction errors for Patients 1 to 4, Set 3. Fitting results are shaded in light grey.

		RMS (cmH_2O)	PIP (cmH_2O (%))	ΔV_{frc}	RMS (cmH_2O)	PIP (cmH_2O (%))	ΔV_{frc}	RMS (cmH_2O)	PIP (cmH_2O (%))	ΔV_{frc}	RMS (cmH_2O)	PIP (cmH_2O (%))	ΔV_{frc}
Patient 1		PEEP 14			PEEP 20			PEEP 22			PEEP 26		
	14	0.13	0.04 (0.1%)	-	5.21	6.24 (17.4%)	0.31	4.35	5.63 (13.8%)	0.38	5.52	7.23 (15.1%)	0.48
	20				0.10	-0.01 (0.0%)	-	1.79	-2.08 (5.1%)	0.10	2.67	-3.57 (7.4%)	0.27
	22							0.05	-0.03 (0.1%)	-	2.07	-2.99 (6.2%)	0.12
	26										0.07	0.01 (0.0%)	-
Patient 2		PEEP 12			PEEP 16			PEEP 20			PEEP 24		
	12	0.09	-0.15 (0.6%)	-	1.95	1.41 (5.0%)	0.27	2.73	2.92 (8.7%)	0.43	4.12	5.27 (13.8%)	0.54
	16				0.17	-0.23 (0.8%)	-	0.40	-0.26 (0.8%)	0.26	1.22	0.90 (2.4%)	0.43
	20							0.14	-0.23 (0.7%)	-	0.77	0.42 (1.1%)	0.25
	24										0.17	-0.23 (0.6%)	-
Patient 3		PEEP 12			PEEP 16			PEEP 20			PEEP 24		
	12	0.09	-0.01 (0.1%)	-	0.45	-0.32 (1.0%)	0.14	1.17	-2.10 (5.3%)	0.27	1.89	-3.28 (7.1%)	0.38
	16				0.04	-0.03 (0.1%)	-	1.52	-2.56 (6.5%)	0.11	2.95	-4.57 (9.9%)	0.22
	20							0.06	-0.05 (0.1%)	-	0.72	-0.85 (1.8%)	0.11
	24										0.09	-0.05 (0.1%)	-
Patient 4		PEEP 12			PEEP 16			PEEP 20			PEEP 24		
	12	0.11	-0.04 (0.2%)	-	0.46	-0.70 (2.3%)	0.06	0.82	-1.39 (3.9%)	0.20	1.24	-2.05 (5.0%)	0.29
	16				0.05	0.00 (0.0%)	-	0.90	1.15 (3.2%)	0.05	1.95	2.75 (6.7%)	0.18
	20							0.09	-0.09 (0.2%)	-	1.33	1.65 (4.0%)	0.03
	24										0.09	-0.11 (0.3%)	-

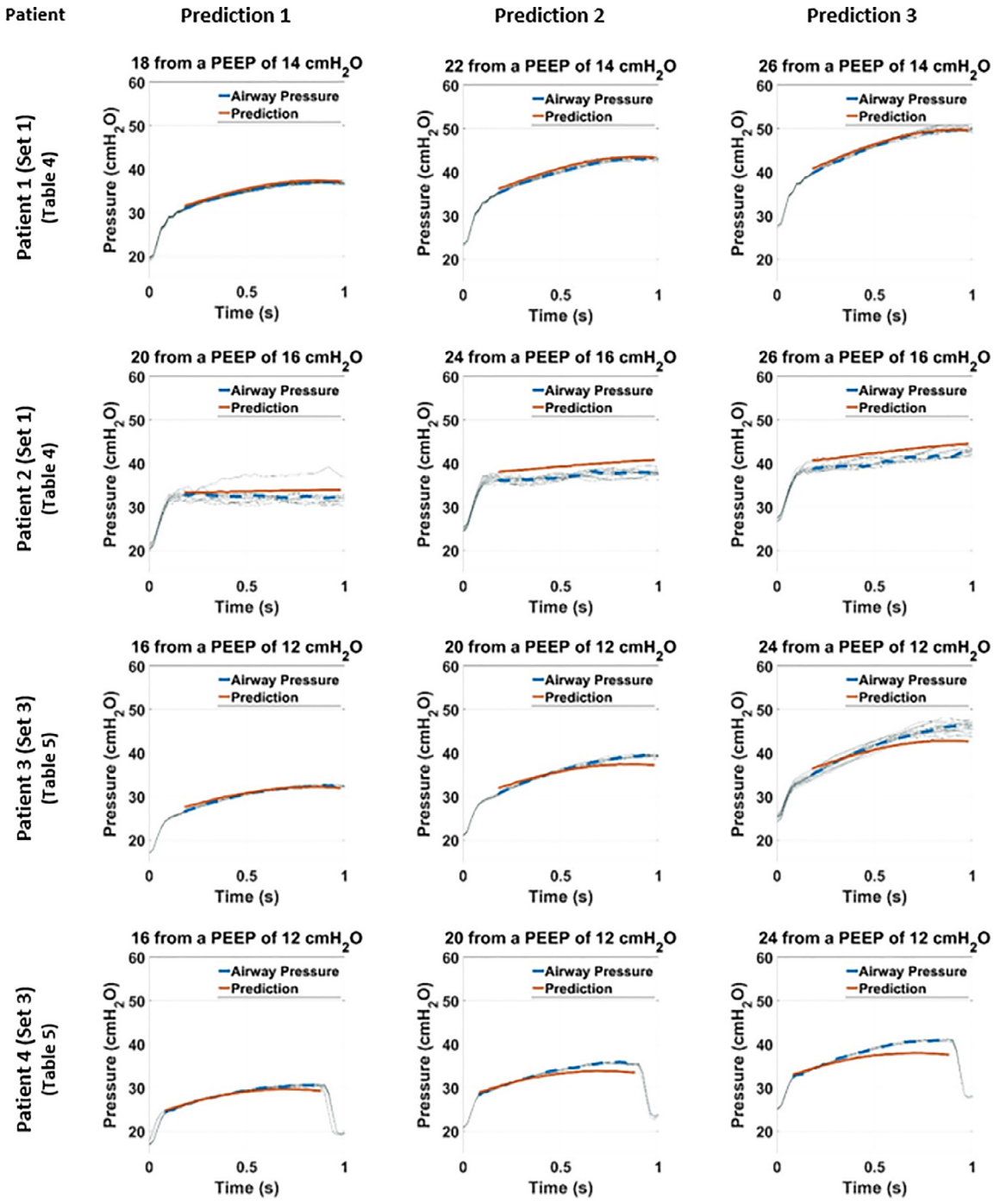

Fig. 8. Typical prediction results for three PEEP steps (up) of prediction from the lowest PEEP level in an RM for each patient. The red, solid line shows the model prediction. The light grey lines show all breaths at that PEEP level.

Table 6
Summarised prediction error results by PEEP step forward, presented as median [IQR] across all patients and RMs (Sets 1 and 3).

	RMS (cmH_2O)	RMS % error	PIP error (cmH_2O)	PIP error (%)
Fit	0.08 [0.06–0.12]	0.23 [0.16–0.31]	−0.05 [−0.09 – −0.01]	0.1 [0.0–0.3]
1 Step	0.78 [0.46–2.65]	0.78 [0.51–1.59]	0.38 [−0.87 – 1.17]	2.5 [1.2–4.1]
2 Steps	1.78 [1.11–2.65]	1.39 [1.20–2.64]	0.61 [−2.10 – 2.87]	6.5 [4.1–8.2]
3 Steps	2.37 [1.41–4.24]	2.31 [1.91–3.70]	0.91 [−2.36 – 5.99]	7.9 [4.7–13.6]

4. Discussion

4.1. Model development

The model was developed to capture relevant lung mechanics with minimal parameters. The elastance model was comprised of functions describing recruitment and distension. Lung distension is a function of stress, increasing with pressure. Alveolar recruitment is representative of strain, and the rate of recruitment reduces exponentially as volume delivered by the ventilator increases. Both elastance function shapes could be explicitly linked to the standard behaviour by these two processes. Previous predictive models have used a larger number of basic functions and more generic shapes to capture mechanics, increasing the risk of overfitting [35]. In addition, increased physiological relevance enables potential further diagnostics to be derived from patient- and breath-specific basis functions and their evolution over time. The resistance part of the model followed the form of the Rohrer equation [46,47]. The first term is representative of momentum, and the second, kinetic energy. These cover both the linear and non-linear forms of resistance.

4.2. Model efficacy (Fit and prediction)

This analysis focussed on volume controlled ventilation data, where pressure is the uncontrolled factor. While these experiments use volume controlled ventilation, the field is increasingly changing towards pressure controlled ventilation. However, the methods presented are readily generalisable to the choice of controlled variables (volume or pressure) and fitted model outputs (pressure or volume). The patient-specific identified model was able to accurately predict respiratory mechanics up to a PEEP increase of 12 cmH_2O with 90% of predicted RMS less than 3 cmH_2O. Additionally, the model prediction was typically within the range of observed pressure across multiple breaths at that PEEP (Fig. 8). Peak inspiratory pressure was predicted with less than 10% error in 90% of cases. The maximum PIP error was an over-prediction of 7 cmH_2O from a PEEP of 14 to a PEEP of 26 cmH_2O, and all of the predictions with a PIP error greater than 10% were due to an overestimation of pressure. This overestimation is clinically preferable, as it represents the conservative case for the risk of distension. In particular, this overestimation of PIP will lead to lower peak PEEP levels in RM design.

The ultimate goal of MV is to maximise recruitment of alveoli and thus gas exchange, while minimising incidences of VILI [10–14]. It should be noted that higher PEEP and pressures increase shunt [52] which can reduce perfusion, potentially causing significant reductions in gas exchange. Thus, some higher PEEP levels are not necessarily optimal. However, the model-based approach using this type of model [41] defines the optimal PEEP to yield minimum elastance. The work of Suarez-Sipmann et al [27] showed that minimum shunt occurred at maximum compliance (minimum elastance). Therefore, this type of model-based MV management using this model would seem likely to avoid low perfusion scenarios.

More specifically, as shown in Table 6, the model could predict lung mechanics at one PEEP step higher with very high accuracy over the entire expected MV pressure range (RMS: 0.78 [0.46–2.65] cmH_2O, PIP Error 0.38 [−0.87–1.17] cmH_2O). This result suggests the model can capture lung dynamics across a nearer, more local pressure range very well. Clinically, predictions of respiratory mechanics across one PEEP step ensures that the step will be safe. This one step ahead prediction could be applied recursively, further reducing errors (Tables 4 and 5, third row and last column compared to the predictions for the highest PEEP in the first row, last column). Equally, the method could be extended to include data from more than the current PEEP step to further reduce errors [35].

Predictions for two (RMS: 1.78 [1.11–2.65] cmH_2O, PIP 0.61 [−2.10–2.87] cmH_2O) and three (RMS: 2.37 [1.41–4.24] cmH_2O, PIP 0.91 [−2.36–5.99] cmH_2O) PEEP steps ahead were less accurate. However, predictions were generally within a clinically relevant range of observed pressures across multiple breaths at that PEEP.

Set 3 of Patient 1 yielded less accurate PIP predictions at PEEP 14 than for most other cases. This patient differed from the other patients as they presented with no major lung disease. This suggests that this model may not be as useful for healthier lungs or may be missing additional mechanics.

Overall, the prediction error was also higher in the Set 3 data than the Set 1 data for all patients. This difference is expected to be due to the dynamics of the recruitment process. The first arm of an RM is designed to open up the lungs and recruit alveoli that were previously closed. As recruitment and derecruitment are time-dependent processes, the second arm is performed primarily to titrate PEEP and to maintain recruitment [32]. The results imply that the model may be more accurate for the lung mechanics during the recruitment and distension shown during the first half of the RM, and less accurate where higher recruitment has already been achieved. Thus, it may be that threshold closing pressure dynamics have a significant effect on the shape of lung dynamics, as they would change between the two RMs [2]. However, errors for 1–2 steps ahead were still relatively very low, so this issue only affects very large prediction intervals, which can be avoided or ameliorated as noted.

Interestingly, Set 1 for Patient 3 yielded much more accurate PIP predictions than Set 3. If the patient lung was fully recruited at low PEEP in Set 3, the model may not have been able to generate accurate parameter values at low PEEP leading to poor predictions. This hypothesis would have to be confirmed in further subjects who present this way, using EIT [53–56] or CT imaging.

Adjusting the elastance curves for use at a higher PEEP level was achieved by adding on an iterated value (V_{FRC}) for dynamic functional residual capacity (dFRC), as shown in Fig. 5. The determined values for V_{FRC} in Eq. (10) and Fig. 6 correlate well with independent values from the literature [57–59]. In addition, the accuracy was verified by retrospectively determining the actual volume change across a PEEP change from the clinical data and comparing it to our V_{frc} metric. This process was effective for predictions in both the increasing PEEP arms of the RMs that were studied. The success in predicting 1 PEEP step ahead suggests the relative V_{FRC} values calculated may be reasonably reflective of lung recruitment due to PEEP steps. Cumulatively, the model could potentially be used to estimate the potential to gain lung capacity due to changes in PEEP. Recent clinical trials have shown that the patient benefit provided by RMs are outweighed by risks when high PEEP pressures are used in certain patients [34]. This research has the potential to alert the operating clinician when proposed PEEP levels may present increased risk to patient safety. However, the clinical value of such estimation requires further investigation and validation [57–59].

Preliminary results show that the model is capable of predicting respiratory responses of critically ill patients during RM using data from a baseline PEEP level. The prediction of potential respiratory mechanics at different MV settings may allow more informed decisions around ventilation practice to be made. In addition, these sorts of predictions could be used to test potential treatment strategies in silico, rather than direct testing in patient cohorts, thus increasing safety. One potential application is the estimation of minimum elastance without the need to perform RM steps at much higher pressures. In addition, the model would also offer clinicians an idea of the risk of over-distension resulting from excessive airway pressure and volume. After implementation, the

downward arm may be predicted as well. The overall capability should make the process of PEEP titration to find minimum elastance and the implementation of RMs much safer and more efficient. These models are thus the first initial proof of concept of a true virtual patient model for MV [60].

This work has focussed on characterising lung mechanics, with a focus on predicting respiratory mechanical and PIP pressure outcomes at different PEEP levels. Future work will also consider the relationship between mechanical ventilation and gas exchange, with aim to optimise ventilation in terms of mechanical safety from VILI, and optimisation of gas exchange.

4.3. Limitations and future work

The focus of this study was on development of a predictive model using only measurements that are easily accessible at the patient bedside, limiting model complexity [36,61]. The model uses a single compartment to model complex pulmonary mechanics. However, in contrast to typical single compartment models, it exhibits dynamic elastance and resistance behaviours that seem to capture all of the airway pressure and flow dynamics exhibited across a wide range of respiratory dysfunction patients.

This analysis focussed on volume controlled ventilation data. Pressure control is another common mode of ventilation. In this case, the uncontrolled variable is volume, not pressure, so forward prediction of volume would be the goal. Future work will utilise pressure control data to forward predict volume outcomes across a recruitment manoeuvre, where peak tidal volume could be a clinically interesting risk metric.

The initial analysis carried out in this study used data from a limited number of patients. In addition, three of the four patients presented with forms of bacterial pneumonia, which may lead to reduced pulmonary recruitability along with limiting patient disease type [3]. However, all had PF < 300 mmHg, meeting ARDS guideline definitions for impaired function [42]. To mitigate the impact of this small sample size, a large number of breaths and RM steps were studied from each patient to ensure that a diverse range of lung mechanics was assessed. Given the quality of the results it should suffice as initial proof of concept of the model and methods, justifying a prospective clinical validation.

Pneumonia-affected lungs often display very heterogeneous localised lung mechanics, with optimal PEEP potentially occurring over a large range [3]. Furthermore, airflow resistance in patients presenting with pneumonia-induced ARDS often shows wide variation, making achieving optimal ventilation challenging [3,62]. The model was developed to account for heterogeneity in lung disease: Where lung stiffness in certain lobes reduces the ability of the lung to be recruited, the model captures this as increased overall elastance (stiffness), and a decreased ability to gain, V_{frc}. Future work with access to airway pressure/flow data from a broader range of patients will be used to test the robustness of this data. In addition, future work could allow the model to be combined with spatial and temporally varying models [63,64] to improve upon patient monitoring and care.

The predictive properties of the model utilise an estimation of the dynamic functional residual capacity (V_{FRC} in Eq. (10)) of the lungs throughout an RM. Functional residual capacity is often measured using plethysmography or a helium dilution technique [65–67]. However, there are no clinically useful methods to define the dynamic behaviour of this property, and model-based results have shown some preliminary potential [57]. For validation, V_{FRC} was retrospectively calculated from the integral of flow over a PEEP change, with median error in model-based V_{frc} from Eq. (10) of 15.6 [9.0–23.0] %, or 30 [10–40] mLs compared to the actual values. Thus, the values obtained were physiologically relevant [58,59,68], reasonably accurate from a clinical uncertainty perspective, and their constant decrease in rate of change with rising PEEP matches clinical expectations of decreasing recruitment gains with increasing PEEP. In addition, the parameter values were reasonable compared to the integration of airway flow between the two PEEP levels. The calculated values of V_{FRC} were on the low end of the range of those found in the literature. However, this outcome is expected due to the higher starting PEEP levels (12 or 14 cmH_2O opposed to 5 cmH_2O) than used in Dellamonica et al. and Wallet et al. [58,59].

5. Conclusions

A predictive respiratory elastance model was developed with the goal of using predictions in clinical use to minimise the risk of over-distension during, or in planning, recruitment manoeuvres. This model showed a good accuracy in capturing and predicting lung mechanics and airway pressure at high PEEP levels using information from only a single low PEEP level breath, with an average fitting error of $< 0.5\%$ RMS (0.2–0.4 cmH20), and less than 10% prediction error in PIP over more than 90% of the PEEP changes. The predictive capacity shown in this initial proof of concept makes it a first patient-specific virtual patient model for MV for predicting lung mechanics responses to changes in MV settings.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

This work was supported by the NZ Tertiary Education Commission (TEC) fund MedTech CoRE (Centre of Research Expertise) and the NZ National Science Challenge 7, Science for Technology and Innovation

The authors also acknowledge support from the Engineering Technology-based Innovation in Medicine (eTIME) consortium grant [eTIME 318943]; the EU FP7 International Research Staff Exchange Scheme (IRSES) grant [#PIRSES-GA-2012-318943];

References

[1] A.S. Slutsky, ACCP consensus conference - mechanical ventilation, Chest 104 (6) (1993) 1833–1859.
[2] A. Sundaresan, T. Yuta, C.E. Hann, J.G. Chase, G.M. Shaw, A minimal model of lung mechanics and model-based markers for optimizing ventilator treatment in ARDS patients, Comput. Methods Progr. Biomed. 95 (2) (2009) 166–180.
[3] A. Lorx, et al., Airway and tissue mechanics in ventilated patients with pneumonia, Respir. Physiol. Neurobiol. 171 (2) (2010) 101–109.
[4] P.P. Terragni, G.L. Rosboch, A. Lisi, A.G. Viale, V.M. Ranieri, How respiratory system mechanics may help in minimising ventilator-induced lung injury in ARDS patients , Eur. Respir. J. 22 (42) (2003) 15–21.
[5] F.D. Simonis, et al., PReVENT - protective ventilation in patients without ARDS at start of ventilation: study protocol for a randomized controlled trial, Trials 16 (1) (2015) 226.
[6] A. Slutsky, V.M. Ranieri, Ventilator-Induced Lung Injury, N. Engl. J. Med. 370 (2014) 980.
[7] L. Pinhu, T. Whitehead, T.W. Evans, M. Griffiths, Ventilator-associated lung injury, Lancet 6736 (2003) no. January 2014.
[8] T.E. Van der Kloot, et al., Recruitment Maneuvers in Three Experimental Models of Acute Lung Injury Effect on Lung Volume and Gas Exchange, Am. J. Respir. Crit. Care Med 161 (2000) 1485–1494.
[9] C.S.N.B. Garcia, L.F.M. Prota, M.M. Morales, P.V. Romero, W. a. Zin, P.R.M. Rocco, Understanding the mechanisms of lung mechanical stress, Braz. J. Med. Biol. Res. 39 (6) (2006) 697–706.
[10] J.H.T. Bates, C.G. Irvin, Time dependence of recruitment and derecruitment in the lung: a theoretical model, J. Appl. Physiol. 93 (2) (2002) 705–713.
[11] R. Valentini, J. Aquino-Esperanza, I. Bonelli, P. Maskin, Gas exchange and lung mechanics in patients with acute respiratory distress syndrome: comparison of three different strategies of positive end expiratory pressure, J. Crit. Care 30 (2) (2014) 334–340.
[12] A. Mercat, et al., Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome, JAMA 299 (6) (2008) 646.

[13] B. Lambermont, et al., Comparison of functional residual capacity and static compliance of the respiratory system during a positive end-expiratory pressure (PEEP) ramp procedure in an experimental model of acute respiratory distress syndrome, Crit. Care 12 (4) (2008) R91.
[14] P.R.M. Rocco, P. Pelosi, M.G. de Abreu, Pros and cons of recruitment maneuvers in acute lung injury and acute respiratory distress syndrome, Expert Rev. Respir. Med. 4 (4) (2010) 479–489.
[15] A.S. Slutsky, L.D. Hudson, PEEP or no PEEP–lung recruitment may be the solution, N. Engl. J. Med. 354 (17) (2006) 1839–1841.
[16] M. Amato, C. Barbas, D. Medeiros, R. Magaldi, G. Schettino, Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome, N. Engl. J. Med. 338 (6) (1998) 347–354.
[17] R.E. Al Brower, Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome, N. Engl. J. Med. 342 (18) (2000) 1301–1308.
[18] J.M. Halter, et al., Positive end-expiratory pressure after a recruitment maneuver prevents both alveolar collapse and recruitment/derecruitment, Am. J. Respir. Crit. Care Med. 167 (12) (2003) 1620–1626.
[19] G. Nieman, A. Paskanik, C. Bredenberg, Effect of positive end-expiratory pressure on alveolar capillary perfusion, J. Thorac. Cardiovasc. Surg. 95 (4) (1988) 712–716.
[20] S. Rachmale, G. Li, G. Wilson, M. Malinchoc, O. Gajic, Practice of excessive FiO_2 and effect on pulmonary outcomes in mechanically ventilated patients with acute lung injury, Respir. Care 57 (11) (2012) 1887–1893.
[21] D. Chu, et al., Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta–analysis, Lancet 391 (10131) (2018) 1693–1705.
[22] J. Aboab, B. Louis, B. Jonson, L. Brochard, Relation between PaO_2/FIO_2 ratio and FIO_2: a mathematical description, Appl. Physiol. Intensiv. Care Med. (Second Ed.), pp. (2009) 57–60.
[23] J. O'Brien, Absorption atelectasis: incidence and clinical implications, AANA J. 81 (3) (2013) 205–208.
[24] P.P. Terragni, et al., Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome, Am. J. Respir. Crit. Care Med. 175 (2) (2007) 160–166.
[25] K. Schirrmann, M. Mertens, U. Kertzscher, W.M. Kuebler, K. Affeld, Theoretical modeling of the interaction between alveoli during inflation and deflation in normal and diseased lungs, J. Biomech. 43 (6) (2010) 1202–1207.
[26] Y.S. Chiew, et al., Feasibility of titrating PEEP to minimum elastance for mechanically ventilated patients, Pilot Feasibility Stud 1 (1) (2015) 1–10.
[27] F. Suarez-Sipmann, et al., Use of dynamic compliance for open lung positive end-expiratory pressure titration in an experimental study, Crit. Care Med. 35 (1) (2007) 214–221.
[28] A.R.S. Carvalho, et al., Positive end-expiratory pressure at minimal respiratory elastance represents the best compromise between mechanical stress and lung aeration in oleic acid induced lung injury, Crit. Care 11 (4) (2007) R86.
[29] C.L. Hodgson, et al., A randomised controlled trial of an open lung strategy with staircase recruitment, titrated PEEP and targeted low airway pressures in patients with acute respiratory distress syndrome, Crit. Care 15 (3) (2011) R133.
[30] P.M. Suter, H.B. Fairley, M.D. Isenberg, Effect of tidal volume and positive end expiratory pressure on compliance during mechanical ventilation, Chest 73 (2) (1978) 158–162.
[31] E.J. van Drunen, et al., Visualisation of time-varying respiratory system elastance in experimental ARDS animal models, BMC Pulm. Med. 14 (1) (2014) 33.
[32] C. Stahl, et al., Dynamic versus static respiratory mechanics in acute lung injury and acute respiratory distress syndrome, Crit. Care Med. 34 (8) (2006) 2090–2098.
[33] J.C. Richard, S.M. Maggiore, B. Jonson, J. Mancebo, F. Lemaire, L. Brochard, Influence of tidal volume on alveolar recruitment: respective role of PEEP and a recruitment maneuver, Am. J. Respir. Crit. Care Med. 163 (7) (2001) 1609–1613.
[34] A.B. Cavalcanti, et al., Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome, JAMA 318 (14) (2017) 1335.
[35] R. Langdon, P.D. Docherty, Y.S. Chiew, J.G. Chase, Extrapolation of a non-linear autoregressive model of pulmonary mechanics, Math. Biosci. 284 (2016) 32–39.
[36] J.G. Chase, T. Desaive, J.-C. Preiser, Virtual patients and virtual cohorts: a new way to think about the design and implementation of personalised ICU treatments, in: J.-L. Vincent (Ed.), Annual Update in Intensive Care and Emergency Medicine 2016, 2, Springer, 2016, pp. 435–448.
[37] J.G. Chase, A.J. Le Compte, J.-C. Preiser, G.M. Shaw, S. Penning, T. Desaive, Physiological modeling, tight glycemic control, and the ICU clinician: what are models and how can they affect practice? Ann. Intensiv. Care 1 (1) (2011) 11.
[38] R. Langdon, P.D. Docherty, Y.-S. Chiew, K. Möller, J.G. Chase, Use of basis functions within a non-linear autoregressive model of pulmonary mechanics, Biomed. Signal Process. Control 27 (2016) 44–50.
[39] J.H.T. Bates, Lung Mechanics: An Inverse Modeling Approach, Cambridge University Press, 2009.
[40] G.L. Chelucci, et al., A single-compartment model cannot describe passive expiration in intubated, paralysed humans, Eur. Respir. J. 4 (1991) 458–464.
[41] A. Szlavecz, et al., The clinical utilisation of respiratory elastance software (CURE Soft): a bedside software for real-time respiratory mechanics monitoring and mechanical ventilation management, Biomed. Eng. Online 13 (1) (2014) 140.
[42] The ARDS Definition Task Force*, Acute Respiratory Distress syndrome : the Berlin definition, JAMA J. Am. Med. Assoc. 307 (23) (2012) 2526–2533.
[43] S.M. Davidson, et al., Clinical utilisation of respiratory elastance (CURE): pilot trials for the optimisation of mechanical ventilation settings for the critically Ill, IFAC Proc. Vol. 19 (2014) 8403–8408 no. October.
[44] L. Gattinoni, E. Carlesso, P. Cadringher, F. Valenza, F. Vagginelli, D. Chiumello, Physical and biological triggers of ventilator-induced lung injury and its prevention, Eur. Respir. J. 22 (Suppl. 47) (2003) 15s–25s.
[45] L.E. Bayliss, G.. Robertson, The visco-elastic properties of the lungs, Exp. Physiol. 29 (1) (1938) 27–47.
[46] A.G. Flevari, et al., Rohrer's constant, K2, as a factor of determining inspiratory resistance of common adult endotracheal tubes, Anaesth. Intensive Care 39 (3) (2011) 410–417.
[47] F. Rohrer, Physiologie der Atembewegung, Handbuch der normalen und pathologischen Physiologie, 2, Springer-Verlag, Berlin, 1925, pp. 70–127, doi:10.1007/978-3-642-91002-9_3.
[48] P.H. Jarreau, et al., Estimation of inspiratory pressure drop in neonatal and pediatric endotracheal tubes, J. Appl. Physiol. 87 (1) (1999) 36–46.
[49] D.N. Hager, J. a. Krishnan, D.L. Hayden, R.G. Brower, Tidal volume reduction in patients with acute lung injury when plateau pressures are not high, Am. J. Respir. Crit. Care Med. 172 (10) (2005) 1241–1245.
[50] V.M. Ranieri, et al., Pressure-time curve predicts minimally injurious ventilatory strategy in an isolated rat lung model, Anesthesiology 93 (5) (2000) 1320–1328.
[51] D. Dreyfuss, G. Saumon, Ventilator-induced lung injury: lessons from experimental studies, Am. J. Respir. Crit. Care Med. 157 (1998) 294–323.
[52] A.J. Walkey, et al., Higher PEEP versus lower PEEP strategies for patients with acute respiratory distress syndrome. a systematic review and meta-analysis, Ann. Am. Thorac. Soc. 14 (Suppl. 4) (2017) S297–S303.
[53] S. Heizmann, M. Baumgärtner, Z. Zhao, K. Möller, 3-D lung visualization using electrical impedance tomography combined with body plethysmography, in: Proceedings of the Fifteenth International Conference on Biomedical Engineering, 43, 2014, pp. 172–173.
[54] J. Karsten, et al., Electrical impedance tomography may optimize ventilation in a postpartum woman with respiratory failure, Int. J. Obstet. Anesth. 22 (1) (2013) 67–71.
[55] Z. Zhao, R. Fischer, I. Frerichs, U. Müller-Lisse, K. Möller, Regional ventilation in cystic fibrosis measured by electrical impedance tomography, J. Cyst. Fibros. 11 (5) (2012) 412–418.
[56] M. Balleza-Ordaz, E. Perez-Alday, M. Vargas-Luna, J.P. Riu, Tidal volume monitoring by electrical impedance tomography (EIT) using different regions of interest (ROI): Calibration equations, Biomed. Signal Process. Control 18 (2015) 102–109.
[57] E.J. van Drunen, J.G. Chase, Y.S. Chiew, G.M. Shaw, T. Desaive, Analysis of different model-based approaches for estimating dFRC for real-time application, Biomed. Eng. Online 12 (1) (2013) 9.
[58] J. Dellamonica, et al., PEEP-induced changes in lung volume in acute respiratory distress syndrome. Two methods to estimate alveolar recruitment, Intensiv. Care Med. 37 (10) (2011) 1595–1604.
[59] F. Wallet, et al., Evaluation of recruited lung volume at inspiratory plateau pressure with PEEP using bedside digital chest X-ray in patients with acute lung injury/ARDS, Respir. Care 58 (3) (2013) 416–423.
[60] J.G. Chase, et al., Validation of a model-based virtual trials method for tight glycemic control in intensive care, Biomed. Eng. Online 9 (1) (2010) 84.
[61] J. Chase, et al., Next-generation, personalised, model-based critical care medicine: a state-of-the art review of in silico virtual patient models, methods, and cohorts, and how to validation them, Biomed. Eng. Online 17 (1) (2018) 24.
[62] P. Wright, G. Bernard, The role of airflow resistance in patients with the adult respiratory distress syndrome, Am. Rev. Respir. Dis. 139 (5) (1989) 1169–1174.
[63] M.H. Tawhai, K. Burrowes, Multi-scale Models of the lung airways and vascular system, Integr. Respir. Control 605 (5) (2008) 190–194.
[64] M.H. Tawhai, E.A. Hoffman, C.-L. Lin, The lung physiome: merging imaging-based measures with predictive computational models, Wiley Interdiscip. Rev. Syst. Biol. Med. 1 (1) (2009) 61–62.
[65] J. Stocks, P.H. Quanjer, Reference values for residual volume, functional residual capacity and total lung capacity: ATS workshop on lung volume measurements official statement of the european respiratory society, Eur. Respir. J. 8 (3) (1995) 492–506.
[66] S.B. Hooper, M.L. Siew, M.J. Kitchen, A.B. te Pas, Establishing functional residual capacity in the non-breathing infant, Semin. Fetal Neonatal Med. 18 (6) (2013) 336–343.
[67] C. Harrison, P.A. Phan, C. Zhang, D. Geer, A. Farmery, S. Payne, Modeling mixing within the dead space of the lung improves predictions of functional residual capacity, Respir. Physiol. Neurobiol. 242 (2017) 12–18.
[68] A. Sundaresan, J.G. Chase, C.E. Hann, G.M. Shaw, Dynamic functional residual capacity can be estimated using a stress – strain approach, Comput. Methods Progr. Biomed. 101 (2) (2010) 135–143.