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Prediction of lung mechanics throughout recruitment maneuvers in pressure-controlled ventilation

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ABSTRACT

Mechanical ventilation (MV) is a core therapy in the intensive care unit (ICU). Some patients rely on MV to support breathing. However, it is a difficult therapy to optimise, where inter- and intra- patient variability leads to significantly increased risk of lung damage. Excessive volume and/or pressure can cause volutrauma or barotrauma, resulting in increased length of time on ventilation, length of stay, cost and mortality. Virtual patient modelling has changed care in other areas of ICU medicine, enabling more personalized and optimal care, and have emerged for volume-controlled MV. This research extends this MV virtual patient model into the increasingly more commonly used pressure-controlled MV mode. The simulation methods are extended to use pressure, instead of both volume and flow, as the known input, increasing the output variables to be predicted (flow and its integral, volume). The model and methods are validated using data from $N = 14$ pressure-control ventilated patients during recruitment maneuvers, with $n = 558$ prediction tests over changes of PEEP ranging from 2 to 16 cmH_2O. Prediction errors for peak inspiratory volume for an increase of 16 cmH_2O were 80 [30 - 140] mL (15.9 [8.4 - 31.0]%), with RMS fitting errors of 0.05 [0.03 - 0.12] L. These results show very good prediction accuracy able to guide personalised MV care.

1. Introduction

Respiratory failure is a common primary or secondary presentation in intensive care patients, in whom mechanical ventilation (MV) is required to maintain breathing and subsequent gas exchange. MV delivers air under positive pressure to the lungs, with the goal of maintaining open alveoli and hence allowing for O_2 exchange and CO_2 removal. However, excessive or insufficient pressure and/or volume can cause ventilator induced lung injury (VILI) [1–3]. These contrasting criteria require MV optimisation balanced between sufficient O_2 delivery and minimisation of injury. However, at the bedside, it can be difficult to achieve optimised and patient-specific MV settings due to a lack of precise data for current lung volume and/or clarity as to the mechanisms of injury, especially in patients with ARDS where ventilation distribution is very heterogeneous.

A commonly used lung protective strategy is to titrate positive end expiratory pressure (PEEP) to minimum elastance through a staircase recruitment manoeuvre (RM), recruiting additional alveoli while ensuring open alveoli do not collapse [30–32]. However, this process can expose a patient's lungs to increased risk of barotrauma or volutrauma during the RM process if excessively high pressures or volumes are used [30]. Hence, it is not as widely used as increasing FiO_2 or other non-mechanical methods.

Model-based methods can aid clinicians in RM design and PEEP optimisation by providing real-time insight into lung state and tissue behaviour, while improving patient oxygenation by providing real time information on lung behaviour [7]. There are many lung models in the literature [4–6], but very few [7,8] reviews, which are general and not clinically focused. However, relatively few models are personalisable due to identifiability issues and/or complexity [9–13]. Further, from those personalised models (e.g. [14–20]) used for monitoring or assessing care or patient status, the authors found none predicting changes in mechanics, and thus ventilator pressure and volume, in response to changes in ventilator settings. However, this prediction capability is the key

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Table 1
Demographic and diagnostic information for patients studied. CABG = Coronary Artery Bypass Grafting, AVR = Aortic Valve Replacement, SAB = Subarachnoid Haemorrhage, MVP + TVP = Mitral And Tricuspid Valve Replacement.

Patient Number	Sex	Age	Diagnosis	Initial P/F Ratio (mmHg)	Set PEEP (cmH_2O)
Patient 1	M	77	CABG	255	8
Patient 2	F	85	CABG	308	8
Patient 3	M	57	CABG	323	10
Patient 4	M	47	CABG	233	5
Patient 5	M	73	AVR	150	8
Patient 6	M	75	CABG	383	5
Patient 7	F	71	AVR	443	8
Patient 8	M	76	CABG	398	8
Patient 9	F	64	SAB	255	12
Patient 10	F	68	Pneumonia	428	8
Patient 11	F	78	Pneumonia	143	10
Patient 12	F	18	MVP + TVP	83	14
Patient 13	F	71	Pneumonia	443	8
Patient 14	M	36	CABG	158	14

requirement in guiding care using virtual patients, where a model is personalised to guide care via this prediction.

Equally, several groups have developed methods to automate MV within standard protocols or closed-loop feedback. However, these works seem limited to animal studies at this time [21,22]. Similarly, non-model-based studies have assessed the feasibility of recommending optimal PEEP in small studies using EIT for example [23]. These types of studies have shown the feasibility of closing the feedback loop to automate MV, but do not address virtual patient prediction for personalising care.

Personalizing MV accounting for inter- and intra-patient variability using computational modelling has been described in simulations [24], retrospective comparison studies [25] or prospective feasibility/pilot studies aiming to provide recommendations [15,26,27]. One group has recently commercialized a model-based decision support system, which does not use prediction of outcomes, but their published data is limited to small, feasibility studies [28,29]. To our knowledge, no large, outcome-focused trial assessing the clinical utility and efficacy of model-based MV has been published, with or without prediction of outcomes by the model. Thus, despite the potential of model-based methods to guide care, as seen in other areas [4], there is a dearth of predictive, model-based MV in the literature, where this research proposes a modelling approach to fill this need.

The predictive approach developed in this paper using virtual patient models would reduce the risk in using RMs and in setting PEEP in general [33]. Single-compartment elastance models have been extended to provide accurate predictions on how an individual patient will respond to a change in treatment [34,35]. This model was originally developed to provide real-time clinical information to reduce the risk of barotrauma-related VILI during volume-controlled ventilation (VCV). However, pressure-controlled ventilation (PCV) has seen an increase in use over the past few decades such that it is now the more commonly used mode in intensive care units [2].

Pressure-controlled ventilation does not reduce the risk of VILI, and too much pressure is still a concern [36]. Equally, volutrauma under pressure-controlled ventilation is an equally severe form of VILI [37,38]. From a modelling perspective the difficulty increases as the number of predicted variables changes from one in VCV (pressure) to two related variables in PCV (flow and its integral, volume), creating greater potential difficulty. There is thus no guarantee a virtual patient model and methods for VCV will extend, with accuracy, to PCV.

This paper provides an initial proof-of-concept analysis and validation of whether predictive lung mechanics models can be extended to work accurately in pressure-controlled ventilation. The aim is to forward-predict volume and flow outcomes based on a controlled pressure input. Accurate prediction of volume outcomes could help prevent or reduce the risk of volutrauma during an RM using pressure-controlled ventilation, as well as add significant generality to the underlying models and methods used.

2. Methods

2.1. Patients and data

Data from fourteen ventilated patients in the 'Automated Analysis of EIT Data for PEEP Setting' trial (Maastricht, Netherlands) (METC 17–4-053) between November 2017 and February 2018 were used. All patients were treated with Bi-level Positive Airway Pressure (BIPAP) pressure-controlled ventilation, an increasingly common mode of (of many) in pressure-controlled ventilation, which enables different pressures to be applied for inspiration and expiration. Patient demographic and diagnostic data are shown in Table 1. Each patient received one full staircase recruitment man ranging at the onset of ventilation, comprising one upward and one downward arm of stepwise changing PEEP values ranging from 6 cmH_2O to around 22 cmH_2O depending on patient response. Each step was held for several breaths. Pressure and flow data were captured at 125 Hz from this manoeuvre.

2.2. Model

The basis function model developed in [34,35] for volume-controlled ventilation was rearranged to enable prediction of volume outcomes under pressure-controlled ventilation inputs. The initial model used in [34,35] was defined:

$$P(t) = \left(E_1(\max(0, V - V_m))^2 + E_2\frac{P(t)}{60}\right)V(t) + (R_1 + R_2|Q(t)|)Q(t) + PEEP \quad (1)$$

where $P(t)$ is the airway pressure delivered by the ventilator (cmH_2O), PEEP is the positive end-expiratory pressure (cmH_2O), $Q(t)$ is the flow of air delivered by the ventilator (L/s), and $V(t)$ is the tidal volume of air delivered to the lungs (L). $V(t)$ is the integral of $Q(t)$, starting at $t = 0$ for each breath and ending at the end of the breath, to reduce the impact of drift. V_m is defined as 1 L for this study [39]. The E_1 coefficient function $(V - V_m)^2$ is piecewise parabolic with respect to tidal volume above end-expiratory volume at the current PEEP, and is defined as zero for $V > V_m$. V_m is defined as 1 L for this study [39]. Pulmonary elastance, E_1 and E_2,

(cmH_2O/L) and pulmonary resistance, R_1 and R_2, (cmH_2O*s/L) are identified from measured data using a linear least squares identification method [35].

The model was rearranged to identify flow from measured pressure data under pressure-controlled ventilation. This approach is the reverse of that used for volume-controlled ventilation in [34,35]. As R_2 was often zero due to the laminar behaviour of most mechanical ventilation data [35], this parameter was omitted from the amended equation in this analysis as it did not improve model outcomes, giving:

$$P(t) = \left(E_1(\max(0, V - V_m))^2 + E_2\frac{P(t)}{60}\right)V(t) + R_1Q(t) + PEEP \tag{2}$$

2.3. Model parameter fitting

Inspiration onset was taken as the time for first positive flow (above 0 L/s), and end-expiration when flow returned to 0 L/s. PEEP was defined as the minimum pressure value for a given breath, as the measured value sometimes differed from the actual ventilator setting for PEEP. The third breath at each PEEP level was chosen as representative of the patient's lung mechanics as it was assumed lung mechanics had stabilised from the PEEP change by this point [40]. The value of parameters E_1, E_2, R_1 were identified using a linear least squares fitting analysis on Eq. (2).

Parameter values were identified using data from the third breath at given PEEP level, where this breath is representative of later breaths and all transient dynamics from a PEEP change have settled. The parabolic basis function for E_1 and linear function for E_2 are described in detail elsewhere [35]. The goal is to generalise Eqs. (1) and (2) to pressure-controlled ventilation, where the input is known pressure, and the output flow and its integral, volume, are more complex to predict.

Measured pressure-flow data was truncated to 60 data points per breath, to ensure equal weighting of inspiration and expiration (30 points each). In the data studied, the median [IQR] of the end of inspiration occurred at 27 [23–30] points, so this cut-off split the data into approximately equal sections of inspiration and expiration data. Truncation of data to 30 points also served to capture the beginning of expiration mechanics while avoiding the end-expiratory pause plateau of near-zero flow, typically occurring at the end of expiration, which creates identifiability issues and does not provide significant added information on dynamic behaviours.

As flow and volume in Eq. (2) are non-unique, Newton's method was used for the forward simulation of flow from pressure data. An initial guess of +3 L/s flow over the entire breath was used for all patients, and each iteration updated this flow to be more physically realistic. Model optimisation and computational speed would be improved with use of a patient-specific initial guess. However, for clinical use, as the model runs until convergence, the initial guess has little effect on the final volume and flow fit. Volume was defined as the integral of flow with respect to time. This process uses two equations:

$$V_{i-1}(t) = \int^{Q_{i-1}}(t)\,dt \tag{3}$$

And

$$Q_i(t) = \frac{\left(P(t) - PEEP - \left(E_1(V_{i-1}(t) - V_m)^2\right)V_{i-1}(t) - \left(E_2\frac{P(t)}{60}\right)V_{i-1}(t)\right)}{R_1} \tag{4}$$

The process outlined for Eqs. (3) and (4) was repeated 500 times or until convergence of <0.1% change of maximum flow was obtained. The iterations were stabilised with a weighted update of Q_i as 20/80% updated/previous flow vector.

2.4. Model prediction

Predictions were performed for PEEP increases in the upwards RM arm. There was a focus on prediction with increasing ventilator-set PEEP as greater increases in pressure and volume in an RM pose a greater immediate risk to patient safety. This choice is thus based on how such a model might be used clinically.

Prediction across PEEP levels also requires calculation of the change in V_{frc} or the volume recruited by a PEEP step change relative to the current PEEP. Peak inspiratory volume (PIV) and the recruitment volume gained across a PEEP change (ΔV_{frc}) also reflect the relative gains and risks of mechanical ventilation, for the purpose of avoiding volutrauma, providing clinical relevance. The change in V_{frc} was positive or zero when PEEP was increased, and negative or zero when PEEP is decreased. The change in V_{frc} across a particular PEEP step (n to $n+1$) was assessed iteratively for the zero-flow, end-expiratory condition [34,35]:

$$\Delta V^n_{frc} = \frac{(PEEP_{n+1} - PEEP_n)}{E_1(V_{frc} - V_m)^2 + E_2PEEP_{n+1}/60} \tag{5}$$

2.5. Comparing model ΔV_{frc} estimation with clinical estimation of ΔV_{frc}

To determine what could be key factors in improving prediction accuracy, the error in ΔV_{frc} estimation was determined by comparing it to an estimation of gained volume from clinical data, $\Delta V_{frc,clin}$. Volume was calculated across the final breaths at $PEEP_n$ and the initial 2 breaths at $PEEP_{(n+1)}$ by integrating clinical flow data with respect to time. $\Delta V_{frc,clin}$ was determined to be the difference in end expiratory volume across this PEEP change. For multiple steps up in PEEP, $\Delta V_{frc,clin}$ across this larger PEEP change was calculated as the sum of the $\Delta V_{frc,clin}$ calculations for single steps up in PEEP, to avoid flow sensor noise causing drift effects that confound volume estimation.

A number of breaths with air leakage were noted in the data, where for some patients at selected PEEP levels, end expiratory tidal volume never returned to zero, indicating air loss during inspiration or expiration. Thus, a leak compensation adjustment was added to the final $V_{frc,clin}$ value. To estimate this leakage, the flow across five breaths in the middle of the PEEP level was integrated against time to determine volume. The volume at the end of each of the 5 breaths was noted, and the average of these values was used for leak compensation (V_{leak}). If this V_{leak} value was negative, 0 was used instead. V_{leak} was multiplied by three to account for the 3 breaths used for the $\Delta V_{frc,clin}$ value, and then used to adjust the measured value of $\Delta V_{frc,clin}$ obtained from the data, yielding a revised value for these patients, defined:

$$V_{frc,clin} = V_{frc,clin} - V_{leak} \tag{6}$$

2.6. Model validation

This study uses data from pressure-controlled MV, and thus $P(t)$ is the controlled input used to identify E_1, E_2 and R_1, and simulate model-based $V(t)$ and $Q(t)$ outputs. Fit error describes the difference between measured and simulated volume from the identified model at the same PEEP, and prediction error describes the difference between measured and simulated volume at a higher PEEP including ΔV_{frc} from Eq. (5). Thus, fit error validates model structure, dynamics and methods, while prediction error flow and especially volume validates the clinical utility and accuracy of the model.

Both fit and predict error were analysed using Root Mean Square (RMS) error, and the percentage difference between modelled and measured peak inspiratory volume (PIV). Root Mean Square (RMS) indicates the average sum-squared error residuals

Table 2
Results for flow prediction, peak flow estimation and fitting error metrics (RMS, mean (signed) and mean (absolute) shown).

Prediction Interval Size	Peak Flow Estimation Error (L/s)	RMS Error (L/s)	Mean Error (signed) (L/s)	Mean Error (absolute) (L/s)
0 cmH_2O	0.75 [0.55 - 0.99]	0.02 [0.01 - 0.03]	−0.01 [−0.02 - 0.01]	0.40 [0.31 - 0.51]
4 cmH_2O	0.76 [0.56 - 1.10]	0.03 [0.01 - 0.06]	−0.02 [−0.05 - 0.01]	0.47 [0.37 - 0.55]
8 cmH_2O	0.85 [0.64 - 1.31]	0.04 [0.01 - 0.09]	−0.03 [−0.07 - 0.00]	0.53 [0.45 - 0.63]
12 cmH_2O	0.94 [0.68 - 1.40]	0.04 [0.02 - 0.12]	−0.03 [−0.09 - −0.00]	0.57 [0.49 - 0.68]
16 cmH_2O	0.93 [0.51 - 1.26]	0.07 [0.03 - 0.11]	−0.03 [−0.08 - 0.03]	0.58 [0.54 - 0.79]

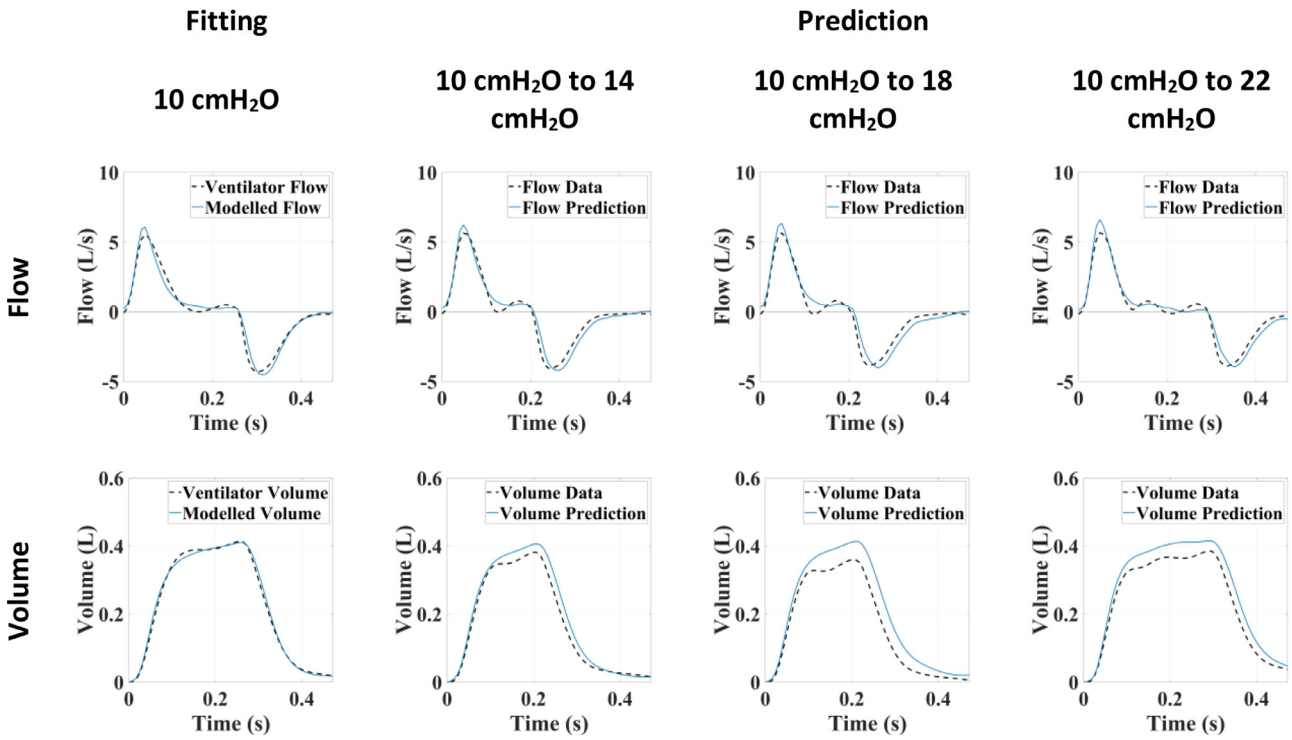

Fig. 1. Typical error in volume fit and prediction, shown for Patient 1.

throughout the breath. To ensure this value is normalised across all PEEP levels the percentage RMS error is also calculated.

PIV is used as a key clinical indicator of the risk of error are calculated for identified model fit and prediction. In all cases measured volume is taken as the integral of measured flow on a breath-by-breath basis. To assess the clinical relevance and safety of the model, both the error in PIV and its percentage predictions are made for 1 – 8 PEEP steps forward for all PEEP levels where there was data covering ΔPEEP prediction ranges of 6 – 22 cmH_2O. In this data, there are typically 8 steps of 2 cmH_2O for each patient with a total of 558 prediction intervals studied over the fourteen patients.

As flow prediction accuracy is linked to volume prediction accuracy, the accuracy of the model in predicting maximum flow was assessed. The fit was analysed using RMS error along with the absolute and signed mean values.

To assess the accuracy of the model across the entire PEEP range, model fit and prediction error are compared across the entire range and for different prediction step sizes. Absolute PIV error and percentage PIV error were both taken in their absolute forms. Finally, the added lung volume gained in changing PEEP, ΔV_{frc}, is compared to an estimation of this value from the measured clinical data based on calculating the lung volume gained across a PEEP change, $\Delta V_{frc,clin}$.

3. Results

3.1. Flow fit

Compiled peak flow prediction and fitting results are shown in Table 2, where fit results are those with a PEEP Interval Size of 0 cmH_2O. Flow was fit with (median) RMS error of 0.02 L/s and peak flow was fit with error of 0.75 L/s across all patients studied. Over the prediction interval sizes (ΔPEEP) studied, peak flow was determined with an (median) absolute error of 0.76 L/s (ΔPEEP = 4 cmH_2O), 0.85 L/s (ΔPEEP = 8 cmH_2O), 0.94 L/s (ΔPEEP = 12 cmH_2O), and 0.93 L/s (ΔPEEP = 16 cmH_2O).

3.2. Flow prediction

The flow prediction results in Table 2 show increasing mean and RMS error with increasing ΔPEEP. Peak flow estimation is similar across all PEEP changes. The discrepancy between the RMS error and mean (signed) error, and the mean (absolute) error indicates the model captures the general shape of flow throughout the breath. However, its timing sometimes does not reach the peaks or troughs precisely, as can be seen in the top row of Fig. 1 which shows typical flow predictions from a PEEP of 10 cmH_2O up to a PEEP of 22 cmH_2O.

Table 3
Specific error results for model prediction. Absolute error (L) in predicting peak inspiratory volume across all peep interval sizes, absolute error (%) in predicting peak inspiratory volume across all peep interval sizes, and rms error (L) in predicting lung mechanics across all peep interval sizes.

PEEP Interval Size		PIV Error Error (L)	RMS Error (L) Error (%)
0 cmH_2O	0.01 [0.00 - 0.01]	1.4 [0.8 - 2.0]	0.01 [0.01 - 0.02]
4 cmH_2O	0.03 [0.02 - 0.05]	7.1 [3.2 - 11.5]	0.03 [0.02 - 0.04]
8 cmH_2O	0.05 [0.02 - 0.09]	13.3 [5.2 - 20.0]	0.04 [0.03 - 0.07]
12 cmH_2O	0.07 [0.03 - 0.12]	15.4 [8.0 - 25.0]	0.05 [0.03 - 0.09]
16 cmH_2O	0.08 [0.03 - 0.14]	15.9 [8.4 - 31.0]	0.05 [0.03 - 0.12]

Table 4
Difference in Vfrc estimation between the modelled estimate and the clinical estimate.

PEEP Interval Size	V_{frc} Error (L)	PIV Error (L)
4 cmH_2O	0.19 [0.11 - 0.28]	0.03 [0.02 - 0.05]
8 cmH_2O	0.25 [0.12 - 0.38]	0.05 [0.02 - 0.09]
12 cmH_2O	0.22 [0.14 - 0.36]	0.07 [0.03 - 0.12]
16 cmH_2O	0.27 [0.12 - 0.46]	0.08 [0.03 - 0.14]

3.3. Volume fit

Table 3 shows compiled volume fit and prediction results across the fourteen patient data sets studied, where the fit results are those with a PEEP Interval Size of 0 cmH_2O. The model fit of volume was assessed across all PEEP levels for all fourteen data sets. PIV was modelled with absolute error (median) of 0.01 L, with an RMS fit error of 0.01 L. Timing errors that are evident in flow are less evident in volume, which is overall better simulated by the model. This reflects the fact that timing offsets are smoothed out during the integration calculation. The relatively low error and improved timing accuracy of the volume prediction suggests that the model that was originally developed to capture lung mechanics throughout volume-controlled ventilation can also accurately capture mechanics throughout pressure-controlled ventilation.

3.4. Volume prediction

Over the prediction interval sizes (ΔPEEP) studied, PIV was determined with an (median) absolute error of 30 mL (ΔPEEP = 4 cmH_2O), 50 mL (ΔPEEP = 8 cmH_2O), 70 mL (ΔPEEP = 12 cmH_2O), and 80 mL (ΔPEEP = 16 cmH_2O). It was noted that while there was a direct relationship between PEEP interval size and prediction accuracy in volume-controlled ventilation work, this did not occur in the pressure-controlled ventilation study. An example of typical volume prediction error is shown in Fig. 1 for Patient 1, with predictions from an initial PEEP level of 10 cmH_2O and until a PEEP of 22 cmH_2O. The volume fitting results for a PEEP of 10 cmH_2O are also included for clarity.

3.5. ΔV_{frc} estimation

Table 4 compares modelled ΔV_{frc} estimation to an estimation of this value from the measured clinical data based on calculating the lung volume gained across a PEEP change. Table 4 also shows compiled results across all patients for each PEEP interval size. The relatively high ΔV_{frc} errors in Table 4 did not translate to particularly high errors in PIV indicating the change in volume with an increase in PEEP does not significantly affect the ability to predict tidal volumes at a given controlled pressure profile. The leak compensation of Eq. (6) reduced $\Delta V_{frc,clin}$ for some patient data sets to more realistic values. Fig. 2 shows a comparison between clinical and model ΔV_{frc} results, showing better accuracy and consistency in V_{frc} estimation over smaller PEEP interval sizes, with more variation for clinically unrealistic PEEP step sizes of 12 and 16 cmH_2O.

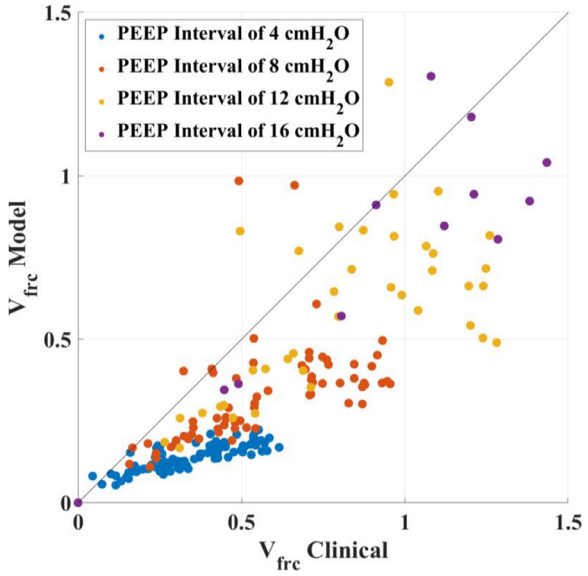

Fig. 2. Comparison of model estimate and clinical estimate of ΔVfrc. Units are in L. The 1:1 line shows the desired direct match, PEEP intervals are colour coded, but larger intervals have larger ΔVfrc.

4. Discussion

The model fit both flow and volume in a recruitment manoeuvre well with a maximum peak inspiratory volume error of 0.19 L across PEEP increases of up to 16 cmH_2O. These results further validate the basis functions developed in [34,35] as capturing the physiological behaviour of recruitment and distension on elastance well. This outcome should be expected as fundamental lung mechanics should not be expected to be substantially different between ventilation modes. PIV was focussed on as the clinical outcome of the prediction model as maximum volume delivered is a key indicator of the risk of volutrauma [2,39,41]. While PIV cannot be directly translated to volutrauma risk due to patient and lung heterogeneity, when used in conjunction with information about V_{frc} it can be used to estimate and manage the risk.

While Morton et al. [34,35] primarily focussed on patients with ARDS or who were ventilated due to acute respiratory failure, the majority of patient data studied in this study was from cardiac surgery patients during recovery. Due to the difference in lung disease and pulmonary dysfunction in this cohort (Table 1), the model may not capture as many of the lung mechanics in this cohort. However, the overall high accuracy in flow and volume prediction indicates the model can be used for a variety of ventilation cases, and is generalisable from volume control to pressure control ventilation.

The model predicted peak inspiratory volume with (median [IQR]) error of 0.08 [0.03 – 0.14] L across a PEEP interval of 16 cmH_2O. While the clinical use of a large prediction interval such as 16 cmH_2O is limited, as a clinician would typically not use a single prediction across the entirety of a recruitment manoeuvre to set PEEP, the relatively low PIV error in this case suggests the model does provide an idea of how a patients lungs may be anticipated to respond throughout an entire recruitment manoeuvre.

While the error metric of PIV prediction has relatively high percentage errors at ~15% over larger PEEP changes, this magnitude of error is due to the small volume increases being estimated making these errors seem larger than they are clinically. For example, the

largest clinical tidal volume value in the data studied was 0.68 L (median [IQR] of 0.42 [0.37 – 0.53] L), whereas the largest tidal volume error was 0.08 L (80 mL). In comparison to these values, the functional residual capacity of a healthy adult is around 1.8 L for women and 2.4 L for men [42]. Thus, the tidal volumes are measurable fractions but errors may appear large.

It was anticipated that volume being the integral of flow with respect to time, small errors in flow fit could lead to larger errors in volume prediction. While there were relatively high maximum flow prediction errors, this error did not consistently correspond to poor PIV prediction. This result is due to errors in flow being due to overall timing of flow being delayed, rather than stretched or inaccurate. Essentially, the same flow but delayed led to larger flow errors, but far lower volume errors when integrated.

Previous work examined the relationship between error in ΔV_{frc} estimation and error in prediction of peak inspiratory pressure in volume-controlled ventilation [43]. Often a lower error in ΔV_{frc} corresponded with lower error in pressure prediction and It was anticipated this error would have a larger impact when volume is the output. However, while errors in ΔV_{frc} were comparatively high, these errors had much less to very little impact on the accuracy of predicting the clinically relevant PIV value, which had very low errors. This perhaps indicates that the role of additional gained volume in static (functional residual) vs. dynamic (tidal) may be different. Overall, the prediction of volume gain over a PEEP change appears to have lower impact on model prediction results than the accuracy of lung mechanics estimation throughout the breath. However, it is challenging to determine the specific level of impact each of these factors have on prediction accuracy. Regardless, improvements in estimating ΔV_{frc} may result in improved prediction in this mode, as well as an improved metric of clinical relevance in decision-making for mechanical ventilation in general.

The scatter plot in Fig. 2 showed the model was effective at estimating ΔV_{frc} across lower, clinically relevant and realistic PEEP interval sizes. However, more variability and error was seen past a PEEP interval step change size of 8 cmH_2O, which already double the typically largest PEEP step seen clinically of 4 cmH_2O. It is expected this increased error is caused by the model estimate predicting saturation of volume gains from recruitment. However, the clinical data did not display this behaviour for these patients, and investigating this difference is a means towards improving estimation of this ΔV_{frc} parameter.

The leak compensation improved $\Delta V_{frc,clin}$ for some patient data. However, it had a minimal effect on the majority of patients. It would be recommended to continue to use this new estimate to cover cases where a patient's expiratory outflow consistently falls below inspiratory tidal volume, clinically indicating a breathing circuit leak. In this case, there was air loss either during inspiration, where total airflow measured by the sensor does not represent airflow delivered to the lungs, or during expiration. It would require further, more detailed measurements, not typically used clinically, to determine where the loss occurs.

Overall, the promising results from this proof of concept study suggest the model presented readily extends to pressure-controlled ventilation. It accurately captures lung mechanics and accurately predicts patient-specific responses to changes in key mechanical ventilation parameters. Clinically, it is very accurate over prediction intervals used clinically, and remains reasonably accurate well beyond these levels. It thus shows significant potential as a general model-based virtual patient approach to guiding clinical mechanical ventilation care to optimise and personalise care and minimise the risk of unintended ventilator induced lung injury. Prospective clinical studies should be undertaken to confirm these results.

Declaration of Competing Interest

The authors declare no financial or other conflicts of interest.

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