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Virtual patient framework for the testing of mechanical ventilation airway pressure and flow settings protocol

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ABSTRACT

Background and Objective: Model-based and personalised decision support systems are emerging to guide mechanical ventilation (MV) treatment for respiratory failure patients. However, model-based treatments require resource-intensive clinical trials prior to implementation. This research presents a framework for generating virtual patients for testing model-based decision support, and direct use in MV treatment.
Methods: The virtual MV patient framework consists of 3 stages: 1) Virtual patient generation, 2) Patient-level validation, and 3) Virtual clinical trials. The virtual patients are generated from retrospective MV patient data using a clinically validated respiratory mechanics model whose respiratory parameters (respiratory elastance and resistance) capture patient-specific pulmonary conditions and responses to MV care over time. Patient-level validation compares the predicted responses from the virtual patient to their retrospective results for clinically implemented MV settings and changes to care. Patient-level validated virtual patients create a platform to conduct virtual trials, where the safety of closed-loop model-based protocols can be evaluated.
Results: This research creates and presents a virtual patient platform of 100 virtual patients generated from retrospective data. Patient-level validation reported median errors of 3.26% for volume-control and 6.80% for pressure-control ventilation mode. A virtual trial on a model-based protocol demonstrates the potential efficacy of using virtual patients for prospective evaluation and testing of the protocol.
Conclusion: The virtual patient framework shows the potential to safely and rapidly design, develop, and optimise new model-based MV decision support systems and protocols using clinically validated models and computer simulation, which could ultimately improve patient care and outcomes in MV.

1. Introduction

Mechanical ventilation (MV) is the primary form of care provided to respiratory failure patients [1,2]. Existing MV treatment guidelines are general and utilise a '*one-size-fits-all*' approach, which benefits some patients, but may harm others [3–5]. Model-based decision support systems, which are mathematical models used to suggest appropriate treatment settings based on patient physiology, have been developed to provide precise and personalised approaches to MV treatment, with the hope of bringing benefit to all and harm to none [6–13].

Clinical trials are a prerequisite for validating the efficacy and safety of a model-based treatment or protocol. However, substantial resources are required for the implementation of a clinical trial [14]. Furthermore, to achieve statistical significance, a sufficient trial sample size is also required depending on the measured outcome metric and assumed effect size, both of which can be variable [15]. To overcome some of these barriers, the concept of digital twins (DT) for clinical application has been devised, [16,17] based on work in other fields [18,19]. A DT is defined as a digital copy of a physical system capable of accurately simulating, replicating, and predicting the behaviour of the physical system in various scenarios [20]. A DT approach to clinical trials, even be-

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fore clinical use, implements virtual modelling to ensure robustness and statistical significance of in-silico experimental results, thus utilising far fewer resources, exposing fewer patients to trial conditions and risks, and facilitating more rapid evaluation of new protocols [21,22].

Physical and virtual modelling, the basis of DT technology, are already well-established techniques in the industry, where they have helped to rapidly evaluate interventions that improve productivity and quality [18–20]. DT technology has been successfully applied in different manufacturing industries such as product design and production while increasing attention has been shown in medicine [16,17,20,23]. It is characterised by the integration of *cyber-physical* systems, enabling predictive diagnosis and performance optimisation of physical systems (in the physical layer) in a virtual environment (in the cyber layer) that is low-risk and inexpensive, [18,19] before implementation in physical world systems [24].

In the context of MV research, the physical system includes the patient-specific respiratory system, its physiology and mechanics parameter profiles. The physical system related to MV also includes related physiological systems which can interact with the goals of the system under development, such as hemodynamic and metabolism interactions with the respiratory system in deciding blood oxygenation [25–27]. The DT in the cyber layer is the virtual patient, which can be developed using respiratory mechanics models and other data-driven approaches capable of capturing patient responses. In other words, the virtual patient takes the form of an identified sensitivity profile extracted/ created from retrospective patient data [21,22,28,29]. A validated virtual patient can then represent an actual patient where in-silico tests of various MV treatments, protocols, interventions, or even real-time guidance towards adjustment of MV settings can be performed [16].

Virtual patients have been used extensively in the validation of glycaemic control protocols before being put to clinical use, [30–32] and recently, virtual patients have been derived using different physiological lung models [33–37]. However, these studies investigate a limited number of prediction cases that are derived over sporadic points in time, rendering continuous assessment of patient conditions not possible. A virtual cohort consisting of multiple validated virtual patients could provide a platform for clinical trial simulation, allowing safe, effective, rapid, and low-cost assessment of novel interventional strategies and approaches to care.

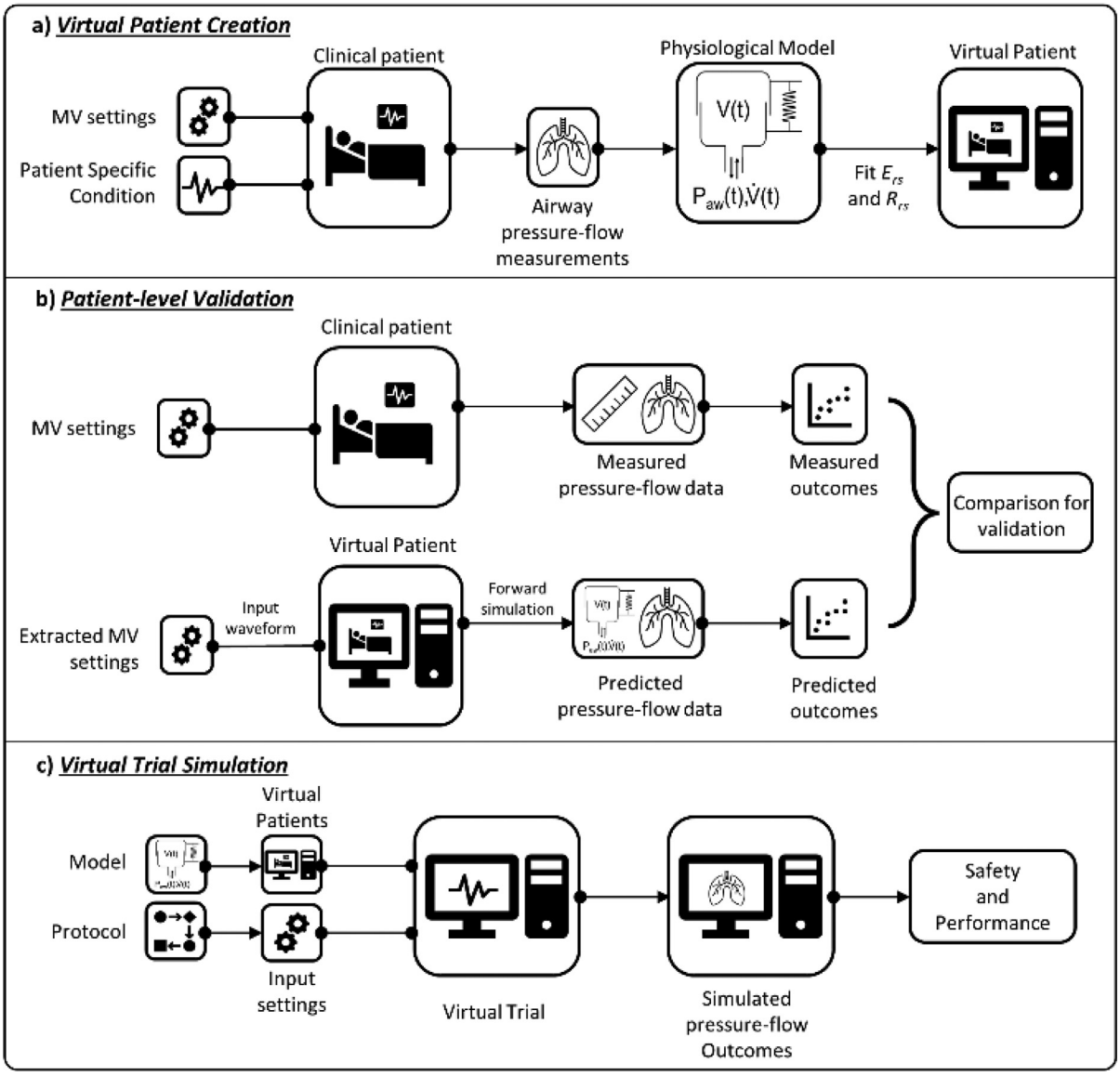

Fig. 1. a) Virtual patient creation, b) Patient-level validation and c) Virtual trial simulation process for protocol analyses.

Such a cohort may also serve to validate clinical trial results by assessing the performance and safety of the intervention [38]. This paper presents a framework for the generation of virtual patients to be used in MV treatment, validation of virtual patients at the patient level, and outlines how a virtual patient cohort can be used as a platform for the development and testing of model-based protocols in a longitudinal study before proceeding into actual clinical trials. The developed virtual cohort consists of ∼1,416 hours of breath data from 100 virtual patients developed from two clinical cohorts. The virtual patients enable a more realistic and continuous assessment of patient-specific respiratory mechanics and measured outcomes over an extended period of time. Furthermore, the development of virtual patients could improve the statistical power of measured outcomes without having to recruit more patients in clinical trials.

2. Methods

An illustration of the virtual patient framework presented in this research is shown in Fig. 1. The framework can be divided into 3 sections. The first is the virtual patient creation (Fig. 1a), where retrospective data is used to form digital twins of real clinical patients using physiological models. The second is the patient-level validation (Fig. 1b), involving data comparisons between the virtual patients predicted responses and actual retrospective patient responses, and thus crucial for validating the model used to form these virtual patients. The final section is the virtual-trial simulation (Fig. 1c), where cohorts of validated virtual patients are used as a platform for rapid prototyping, development, and validation of MV setting selection protocols.

2.1. Virtual patient generation

A virtual MV patient is generated using a respiratory mechanics model. Retrospective clinical pressure-flow (P-$\dot{V}$) and integrated volume (V) data are used to identify patient-specific respiratory model parameters, including respiratory elastance, E_{rs} and respiratory resistance, R_{rs} from a single compartment model via integral-based parameter identification [39,40]. The resultant E_{rs} and R_{rs} profiles over time, from breath-to-breath, along with other patient-specific data, such as weight and trial length, create a fundamental computational model to form a DT of the clinical patient [16].

2.1.1. Clinical patient data

This study uses measured airway P-$\dot{V}$ data from 35 retrospective patients in two clinical cohorts receiving invasive MV for respiratory failure [41–43] (IREC: IRC666 and DSRB Ref:2018/00042). Detailed patient demographics are shown in Tables I and II. The inclusion criteria are: 1) Patients requiring invasive mechanical ventilation (MV) (Intubation or tracheotomy); 2) Patients with PF ratio [oxygen partial pressure to fraction of inspired oxygen] $<$ 300 mmHg); and 3) Arterial line in situ. Patients are excluded from the trial if: 1) Patients who are likely to be discontinued from MV within 24 hours; 2) Patients with age $<$ 16; 3) Any medical condition associated with a clinical suspicion of raised intracranial pressure and/or a measured intracranial pressure $\geq$ 20 cmH_2O; 4) Patients with high spinal cord injury and loss of motor function and/or have significant weakness from any neurological disease; 5) Patients who are moribund and/or not expected to survive for $>$ 72 hours; and 6) Lack of clinical equipoise by ICU medical staff managing the patient.

The patients of both cohorts provide a total of 198 days of MV data with 100 virtual patients generated. Ventilator data was recorded using the CURE soft [44] connected to a Puritan Bennet PB840 or PB980 ventilator [86]. Airway pressure (cmH_2O) and flow (L/min) were recorded at a sampling rate of 50 Hz.

2.1.2. Data Processing

$P\dot{V}$ data is filtered and processed according to criteria set in previous works [9,43]. This is done to remove breaths with excessive

Table 1
Patient information for Cohort 1 (Malaysian cohort).

Patient No.	Sex	Age	Weight (KG)	Diagnosis	Ventilation Mode	Days of recording
1	F	43	52.0	Thyroid carcinoma with metastasis lung, liver, and bone	VC (SIMV)	16
2	M	54	70.2	Hypoxic respiratory failure 2^0 to aspiration pneumonia	VC (SIMV)	3
3	M	52	65.0	Lung cancer and superior vena cava obstruction	PC (SIMV)	3
4	M	64	81.0	CRBSI and HAP	VC (SIMV)	2
5	F	63	38.0	Sepsis	VC (SIMV)	11
6	F	73	70.2	CRF 2^0 to septicaemia cause and ascites, HPT, DM, CKD, COAD	VC (SIMV)	6
7	F	64	44.2	CAP, acute pulmonary oedema, stage 2 acute kidney injury	VC (SIMV)	8
8	M	48	79.4	Severe CAP with moderate ARDS	VC (SIMV)	5
9	M	42	53.7	Sepsis 2^0 CAP with Lung Abscess	PC (SIMV)	9
10	F	60	77.7	Acute Coronary Syndrome with Cardiac Asthma	VC (SIMV)	3
11	M	64	47.8	CAP	VC (SIMV)	2
12	M	74	77.0	Sepsis, HAP	PC (BiLevel)	2
13	M	63	55.0	HAP with parapneumonic effusion	VC (SIMV), PC (BiLevel)	7
14	M	53	54.0	Severe Sepsis 2^0, HAP, TRO, Melioidosis	VC (SIMV)	3
15	F	62	75.0	HAP	PC (SIMV)	3
16	F	34	65.0	ARDS 2^0 Pneumonia	VC (SIMV)	7
17	M	43	80.0	Acute Pancreatitis	VC (SIMV)	3
18	F	61	97.3	Right Lobar Pneumonia	VC (SIMV), PC (BiLevel)	4
19	M	48	56.0	CAP	VC (SIMV) and PC (SIMV)	14
20	F	53	72.0	Neutropenic Sepsis 2^0, CAP, Underlying Breast Cancer	PC (SIMV)	8
21	F	65	50.0	Recurrent Multifocal Infarct with Poor Neurological Recovery	PC (SIMV and BiLevel)	6
22	M	48	91.9	Partially Treated Pneumonia	PC (SIMV)	6
23	F	66	60.0	Septic Shock 2^0 to HAP with bronchospasm	VC (SIMV) and PC (SIMV)	7
24	M	53	62.0	Sepsis secondary to HAP	VC (SIMV)	3
Total	-	-	-	-	-	**141**
Median	-	**67**	**65.0**	-	-	**5.5**
[IQR]		**[54-70]**	**[53.9-77.2]**			**[3-7]**

*CRBSI–Catheter-related bloodstream infection, HAP–Hospital-acquired pneumonia, CRF–Chronic renal failure, HPT–Hyperparathyroidism, DM–Diabetes mellitus, CKD–Chronic kidney disease, COAD–Chronic obstructive airway disease, CAP–Community-acquired pneumonia, ARDS–Acute respiratory distress syndrome, TRO–Thyroid-related orbitopathy, VC–Volume control, SIMV–Synchronised intermittent mandatory ventilation, PC–Pressure control.

Table 2
Patient information for Cohort 2 (Singaporean Cohort).

Patient No.	Sex	Age	Weight (KG)	Diagnosis	Ventilation Mode	Days of recording
1	M	65	60.0	Relapsed DLBCL, carbapenem resistant klebsiella	PC (PS)	4
2	M	70	90.0	Pneumonia likely aspiration related	VC (AC)	3
3	M	54	85.0	Septic shock	VC (AC)	3
4	M	69	75.1	Acute on chronic liver failure secondary to Hep B reactivation flare requiring PLEX	VC (AC), PC (PS)	5
5	M	70	66.0	Pneumonia	VC (AC)	6
6	F	77	45.1	Refractory PD peritonitis with septic shock	VC (AC)	4
7	F	70	49.7	AOCKD Diabetic ketoacidosis, NSTEMI	VC (AC), PC (PS)	4
8	M	35	77.9	Acute exacerbation of asthma	VC (AC)	4
9	M	72	50.0	Infective exacerbation of ILD then desaturated with T1RF	VC (AC), PC (AC, PS)	4
10	M	46	70.0	T1RF secondary to pneumonia	VC (AC)	5
11	M	55	82.2	T1RF	VC (AC)	4
Total	-	-	-	-	-	**57**
Median	-	**67**	**68.5**	-	-	**4**
[IQR]		**[54-70]**	**[59.4-77.2]**			**[4-4.75]**

*DLBCL–Diffuse large B-cell lymphoma, NSTEMI–non-ST segment elevation myocardial infarction, Hep V–Hepatitis B, PLEX–Plasma exchange, PD–Peritoneal dialysis, AOCKD–Acute on Chronic Kidney Disease, ILD–Interstitial Lung Disease, T1RF–Type 1 respiratory failure, DKA–Diabetic ketoacidosis

Table 3
Ventilator input settings extracted from different MV modes.

MV Mode	Pressure Control	Volume Control
Extracted Settings	• Respiratory rate, *RR* • Positive end-expiratory pressure, *PEEP* • Inspiratory pressure, P_I • Inspiratory time, T_I • Rise percent, *RP* • Plateau pressure, P_{PLAT} • Driving pressure, P_{PLAT} - *PEEP*	• Respiratory rate, *RR* • Positive end-expiratory pressure, *PEEP* • Tidal volume, V_T • Peak inspiratory flow, $\dot{V}_{MAX}$ • Plateau time, T_{PLAT} • Waveform • Plateau pressure, P_{PLAT} • Driving pressure, P_{PLAT} - *PEEP*

noise, patient effort, and asynchronies to ensure accurate identification of E_{rs} and R_{rs}. Specific details regarding the filtering criteria are available in the **Supplementary Material (Section A)**. Mean E_{rs} and R_{rs} over time intervals of length, N were used to represent the patients' respiratory mechanics within this time interval. For this study, N is chosen as 10 minutes for all further analyses in this study. These E_{rs} and R_{rs} profiles form the virtual patient as a DT of the retrospective patient data. For consistency, E_{rs} and R_{rs} are referred to as the averaged E_{rs} and R_{rs} over each interval ($E_{rs\ ave}$ and $R_{rs\ ave}$).

Clinically implemented MV settings and important MV parameters are also extracted and identified from each patient's MV data to form interval settings, along with the patient weight. MV settings and parameters extracted from patients in each ventilation mode are summarised in Table 3 [2,45,46].

While patients in this cohort undergo a variety of ventilation modes based on their underlying condition and clinician decision, virtual patients and their clinically implemented interval settings were only generated and extracted from patients undergoing volume-control modes (AC/VC, SIMV/VC), or pressure-control modes (AC/PC, SIMV/PC, PS, and BiLevel/PC) to minimise breaths where there is considerable effort from the patient, which may distort the data by artificially lowering E_{rs} [47,48].

2.1.3. Physiological model

A physiological model defines the patient-specific condition of these virtual patients. This study uses the single compartment linear lung model [49], shown in (1):

$$P(t) = E_{rs}(t)V(t) + R_{rs}(t)\dot{V}(t) + P_0 \tag{1}$$

Where $P(t)$ is the airway pressure delivered by the ventilator (cmH_2O) at time t, $V(t)$ is the volume of air delivered (L), $\dot{V}(t)$ is the flow of air delivered (L/s), and P_0 is the offset pressure which is set to *PEEP* (cmH_2O) when there is no auto-*PEEP*. Respiratory system elastance (cmH_2O/L) and respiratory system resistance (cmH_2Os/L) are represented by $E_{rs}(t)$ and $R_{rs}(t)$ respectively. Captured over time, the profiles of $E_{rs}(t)$ and $R_{rs}(t)$ represent and reveal the evolution of patient-specific conditions throughout their stay [28,50].

2.2. Patient-level validation

An illustration of the patient-level validation is shown in Fig. 1b. This analysis validates the single compartment model presented in (1) and is used to generate the virtual patients. This validation also tests the overall ability of the generated virtual patients in predicting clinical patient responses to changes in MV care or settings, given that the accurate identification of patient-specific $E_{rs}(t)$ and $R_{rs}(t)$ is achieved [21]. The extracted MV settings in Fig. 1b are shown in Table 3.

2.2.1. Input waveform generation

The extracted clinical interval settings from the data processing step are used as input variables to simulate input pressure waveforms or volume and flow waveforms depending on the ventilation mode. The equations used for flow and volume waveform generation (VC ventilation) and pressure waveform generation (PC ventilation) are shown and illustrated in Fig. 2. The specific definitions for the setting parameters used in Fig. 2 are presented in Table 3.

The mathematical equations used to generate the input waveforms for the different ventilation modes in Fig. 3 are given in (2)–(9), where (2)–(4), (5)–(7) and (8)–(9) are used for the VC square waveform, VC ramp waveform and PC square waveform, respectively.

$$T_I = \frac{V_T}{\dot{V}_{MAX}} - \alpha \tag{2}$$

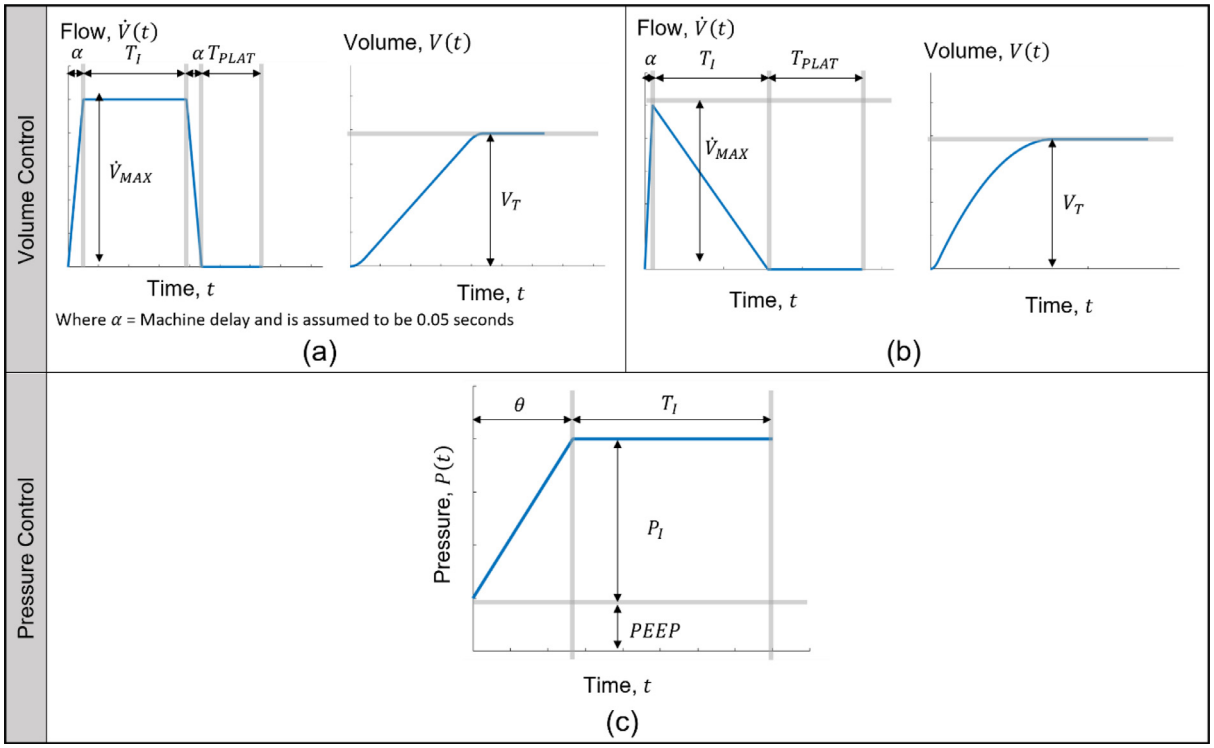

Fig. 2. Input waveforms for different ventilation modes: (a) VC square waveform, (b) VC ramp waveform, (c) PC square waveform

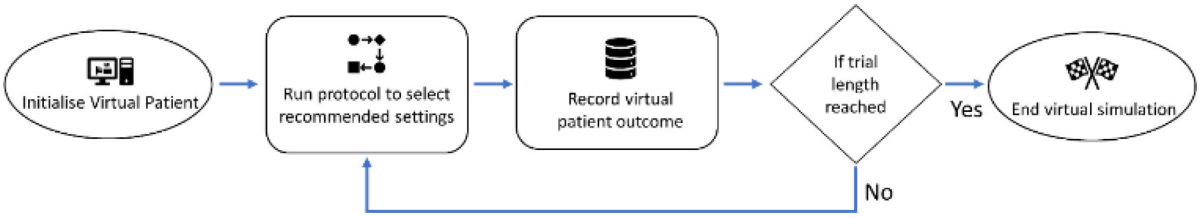

Fig. 3. Illustration of virtual trial for a single virtual patient within the cohort

$$\dot{V}(t) = \begin{cases} \frac{\dot{V}_{MAX}}{\alpha} t, & 0 \le t \le \alpha \\ \dot{V}_{MAX}, & \alpha < t \le T_I + \alpha \\ \frac{\dot{V}_{MAX}}{\alpha}(T_I + 2\alpha) - \frac{\dot{V}_{MAX}}{\alpha} t, & T_I + \alpha < t \le T_I + 2\alpha \\ 0, & T_I + 2\alpha < t \le T_{PLAT} + T_I + 2\alpha \end{cases} \tag{3}$$

$$V(t) = \int_0^{T_{PLAT}+T_I+2\alpha} \dot{V}(t)dt \tag{4}$$

$$T_I = \frac{2V_T}{\dot{V}_{MAX}} - \alpha \tag{5}$$

$$\dot{V}(t) = \begin{cases} \frac{\dot{V}_{MAX}}{\alpha} t, & 0 \le t \le \alpha \\ \frac{\dot{V}_{MAX}}{\alpha}(T_I + \alpha) - \frac{\dot{V}_{MAX}}{\alpha} t, & \alpha < t \le T_I + \alpha \\ 0, & T_I + \alpha < t \le T_{PLAT} + T_I + \alpha \end{cases} \tag{6}$$

$$V(t) = \int_0^{T_{PLAT}+T_I+\alpha} \dot{V}(t)\, dt \tag{7}$$

$$P(t) = \begin{cases} \frac{P_I}{\theta} + PEEP, & 0 \le t \le \theta \\ P_I + PEEP, & \theta < t \le T_I \end{cases} \tag{8}$$

$$\theta = \begin{cases} \min\left(2,\ \frac{2}{3}T_I\right), & RP = 1 \\ \min\left(2,\ \frac{2}{3}T_I \times \left(1 - \frac{RP}{100}\right)\right), & 1 < RP \le 100 \end{cases} \tag{9}$$

2.2.2. Forward simulation

The generated waveforms are then used as inputs to the single compartment model to simulate and predict clinical outputs. Specifically, if the patient was undergoing VC ventilation, the VC interval settings are used to generate input flow and volume waveforms, which are then used to forward simulate the uncontrolled pressure output. For PC ventilation, PC interval settings are used to create input pressure waveforms, which are then used to forward simulate the uncontrolled flow and volume outputs. In both cases, the magnitude and shape of these uncontrolled outputs are a function of patient-specific pulmonary mechanics and response to MV, where accurate prediction of outcomes validates the model performance in capturing these patient-specific elements.

The predicted virtual patient responses are then compared with the clinically measured patient responses which are median values over the time interval, N to assess the validity and prediction accuracy of the single compartment model. For PC and VC MV modes, the measured patient responses monitored are tidal volume and peak pressure, respectively, V_T and P_{MAX}, respectively. The median [Interquartile range, IQR] error and absolute percentage error between the clinical and simulated respiratory waveforms are calcu-

Table 4
Implemented narrowing objectives for the VENT protocol.

Criteria and Parameter	Parameter Equation	Reference
5 L/min $\leq$ Minute ventilation $\leq$ 12 L/min	$V_T \times RR \times Weight$	[2]
Mechanical power $<$ 17 J/min	$RR \cdot \{\Delta V \cdot [\frac{1}{2} \cdot E_{rs}(t) + RR \cdot \frac{(1+I:E)}{60 \cdot I:E} \cdot R_{rs}(t)] + \Delta V \cdot PEEP\}$	[56]
Minimum driving pressure, ΔP (cmH_2O)	$P_{PLAT} - PEEP$	[87]
Most identical to previous interval settings	-	-

lated. The square of the Pearson correlation coefficient, R^2 between the actual and virtual patient predicted patient responses (tidal volume and peak pressure) is also determined, evaluating the accuracy of the identified, patient-specific model. To evaluate the divergence between the clinically measured and predicted data, the Kullback-Leibler (KL) divergence, D_{KL} is also calculated for the two variables V_T and P_{MAX} [51,52]. This procedure is performed on all extracted interval settings on the respective patients. This process is summarised in Fig. 1b.

2.3. Virtual trial

A virtual trial is defined to be an in-silico experimentation of treatment protocols performed on a developed virtual patient platform. The virtual trial in this study requires a cohort of validated virtual patients, which can be generated using a respiratory system model. The virtual cohort forms a platform for the rapid prototyping and development of novel, personalised MV treatment approaches and protocols. To showcase the virtual trial in this proof-of-concept study, the model used to generate the cohort is the single compartment model shown in Eq. (1) and the protocol used to select input settings is the *VENT* protocol [9]. The *VENT* protocol is summarised in the **Supplementary Material (Section B)** provided. A summary of the virtual trial simulation process is illustrated in Fig. 1c.

2.3.1. Ventilation protocol for testing - VENT Protocol

The *VENT* protocol [9] consists of four consecutive stages: **A)** V-stage; **B)** E-stage; **C)** N-stage and **D)** T-stage. The V-stage forward simulates all feasible MV setting combinations to obtain their predicted patient responses. The E-stage removes harmful combinations according to safety thresholds established in landmark clinical trials. The N-stage allows clinicians to set clinical objectives to further remove combinations. The T-stage then presents clinicians with a narrowed range of recommended MV settings. This open-loop system was designed to provide clinicians with insight into the possible patient responses to the recommended MV settings and allow them to select the best MV setting combination.

However, to work independently in this virtual trial, the *VENT* protocol is modified into a closed-loop system to provide a single, optimal recommended MV setting combination. These additional narrowing (N-stage) objectives are summarised in Table 4. Finally, in the event the *VENT* protocol cannot provide a recommendation, the previous interval settings are maintained and implemented.

2.3.2. Virtual trial procedure

The virtual trial procedure is thus further illustrated in Fig. 3 and described below:

1. Initialise virtual patient by feeding initial values of the patient profile to the protocol.
2. Implement protocol (*VENT* Protocol) to introduce intervention (MV settings) for the current time interval.
3. Record resultant virtual patient responses.
4. Maintain protocol-recommended settings for one hour following the virtual patient profile and record the resultant patient responses for each interval.
5. Repeat steps 2 to 4 until the end of trial length (all patient data is analysed).

In this research, the virtual patients are generated using Eq. (1). The patient profile refers to patient-specific $E_{rs}(t)$ and $R_{rs}(t)$ profiles identified from the retrospective data of each patient, and the protocol used is the *VENT* protocol. However, the procedure presented is general and can be used for virtual patients generated by any clinically validated and predictive respiratory model (e.g. [53,54,37]), using any patient-specific profile, and for any protocol.

In this study, the clinical data is compared with the results of the virtual trial across several measured patient responses in a longitudinal study to assess the overall accuracy of the virtual trial in predicting clinical patient responses, a cohort-level validation [28]. In the PC ventilation trial, these patient responses are: V_T, minute ventilation, and mechanical power. In the VC ventilation trial, the patient responses are: P_{PLAT}, minute ventilation, and mechanical power. In addition, the cumulative distribution function (CDF) of each metric from the VC (Volume control) and PC (Pressure control) ventilation trial are analysed. This allows the data distribution of each parameter to be compared between the clinically measured data and the simulated data (VENT protocol chosen settings and predicted patient responses). In this case study, protocol safety is defined as having the measured patient responses within the following safety thresholds [2,5,55,56]:

- 4 mL/kg $\leq V_T \leq$ 8mL/kg
- $P_{PLAT} < 30$ cmH_2O
- 5 L/min $\leq$ Minute ventilation $\leq$ 12 L/min
- Mechanical power $<$ 17 J/min

3. Results

3.1. Virtual cohort

A cohort of 100 virtual patients was created from the retrospective ventilation data from 35 patients. A single patient provides multiple virtual patients based on the number of recording sessions, where clinical interruptions are used to start a new virtual patient for the next recorded data segment. Such clinical interruptions are common. More specifically, 35 virtual patients underwent PC ventilation, and 65 underwent VC ventilation. The virtual patient profiles of each virtual patient in the cohort are shown in Fig. 4, which also shows the median and 5th and 95th percentile values of $E_{rs}(t)$ and $R_{rs}(t)$ of each interval for the whole cohort. The median [5th–95th] trial length of the virtual cohort is 14.58 [0.67–23.75] hours.

3.2. Patient-level validation

This virtual cohort consists of ~1,416 hours of breath data, producing 8,576 pairs of $E_{rs}(t)$ and $R_{rs}(t)$ values. A total of 8,576 clinically implemented interval settings were also extracted, with 3,150 of them coming from PC ventilation patients and the remaining 5,426 from VC ventilation patients. These extracted settings recreate the input waveforms provided to patients during ventilation. Fig. 5 shows an example of all measured input data within an interval along with the generated input waveform from the extracted

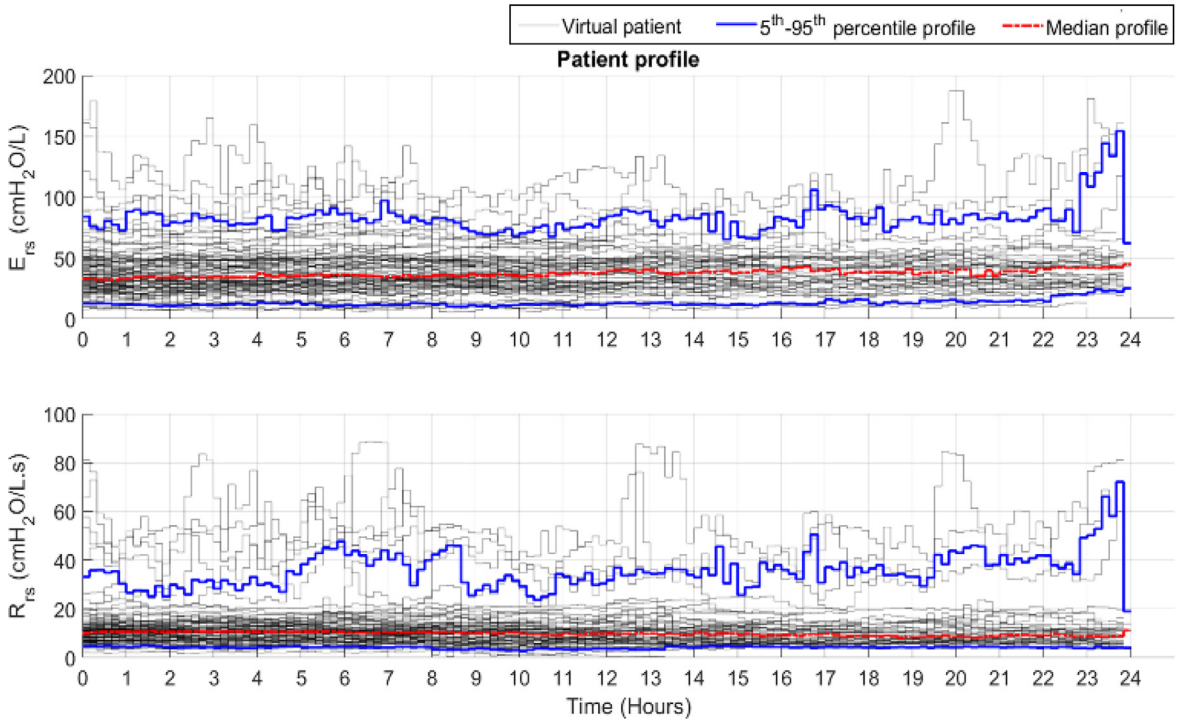

Fig. 4. E_{rs} (top panel) and R_{rs} (bottom panel) profiles of the generated virtual patient cohort

Table 5
Predicted patient responses of peak tidal volume and peak pressure for the PC and VC ventilation trial, respectively.

	V_T prediction	P_{MAX} prediction
Prediction cases	2,485	3,644
Median [IQR] Error	26.42 [11.83-61.73] mL	0.80 [0.38-1.63] cmH_2O
Percentage [IQR] Error	6.80 [2.80-17.81]%	3.26 [1.50-6.21]%
R^2	0.737	0.915

settings for a PC ventilated patient (top) and a VC ventilated patient (bottom). Note, only inspiration is generated and analysed as it provides all the desired measured patient responses, whereas expiration is passive and assumed not to affect these measures. Fig. 6 and Table 5 show the prediction accuracy results for these measured patient responses, and thus assesses the patient-level validation of this approach. The statistical and error analysis in Table 5 is based on the total number of prediction cases in each of the PC and VC trials.

3.3. VENT *Protocol implementation on virtual cohort*

An example of a virtual trial of Virtual Patient 3_b and Virtual Patient 16_b in PC mode and VC mode, respectively, are shown in Fig. 7. The top row shows the patient profile, and the second row shows both the clinically implemented settings (solid black lines) and the *VENT* protocol input settings (dotted blue lines). Their corresponding measured patient responses are shown in the third row. The red vertical lines separate the hourly changes in intervention settings obtained from the *VENT* protocol, where ventilator input settings are determined by the *VENT* protocol and then maintained for each hour before re-evaluation and any change. As such, the first interval before the 0^{th} hour represents patient initialisation and is used as input for the first intervention for the *VENT* protocol.

The results of the virtual trial of the entire virtual cohort are shown in Table 6. It shows the number of virtual patients generated for each ventilation mode, as well as the cumulative trial length of the virtual patients in each mode. The total measurements refer to the number of identified values of $E_{rs}(t)$ and $R_{rs}(t)$, extracted settings and measured patient responses. The specified measured patient responses of the clinical data are compared with the results of the virtual trial, as shown in Table 6. In the PC ventilation trial, the percentage of time the clinical data and *VENT* protocol keeps the measured patient responses within the defined safety threshold values are 33.8% and 64.8%, respectively. In the VC ventilation trial, the percentage of time the clinical data and *VENT* protocol keep the measured patient responses within the defined safety threshold values are 37.0% and 97.0%, respectively. For each of the PC and VC virtual trials, the CDF plots of the patient respiratory profiles and ventilator input settings are shown in Fig. 8. Similarly, the CDF plots of the predicted patient responses are shown in Fig. 9.

4. Discussion

Patient-level validation and prediction accuracy for the single compartment virtual patient model shows a low prediction error, with prediction percentage errors for V_T and P_{MAX} of 6.8% and 3.26%, respectively. The results show a good correlation between the clinical data and virtual patient predicted responses, with an R^2 value of 0.737 and 0.915 for V_T (PC mode) and P_{MAX} (VC mode), respectively. Within the range of clinical V_T = 200-400 mL, there are significant differences between the predicted and clinically measured V_T. This could be due to the presence of small asynchronies and/ or spontaneous breaths that were not being filtered entirely, resulting in incorrect parameter identification using the single compartment lung model. The lower than expected clinical V_T within that range could be due to the obstruction of airflow within the respiratory system in the actual patient. Despite this, the low median [IQR] error for tidal volume prediction is 6.80 [2.80-17.81%] suggests a good correlation between the predicted and clinically measured values. Furthermore, the calculated D_{KL} of 0.0603 and 0.0082 for V_T and P_{MAX} respectively also sug-

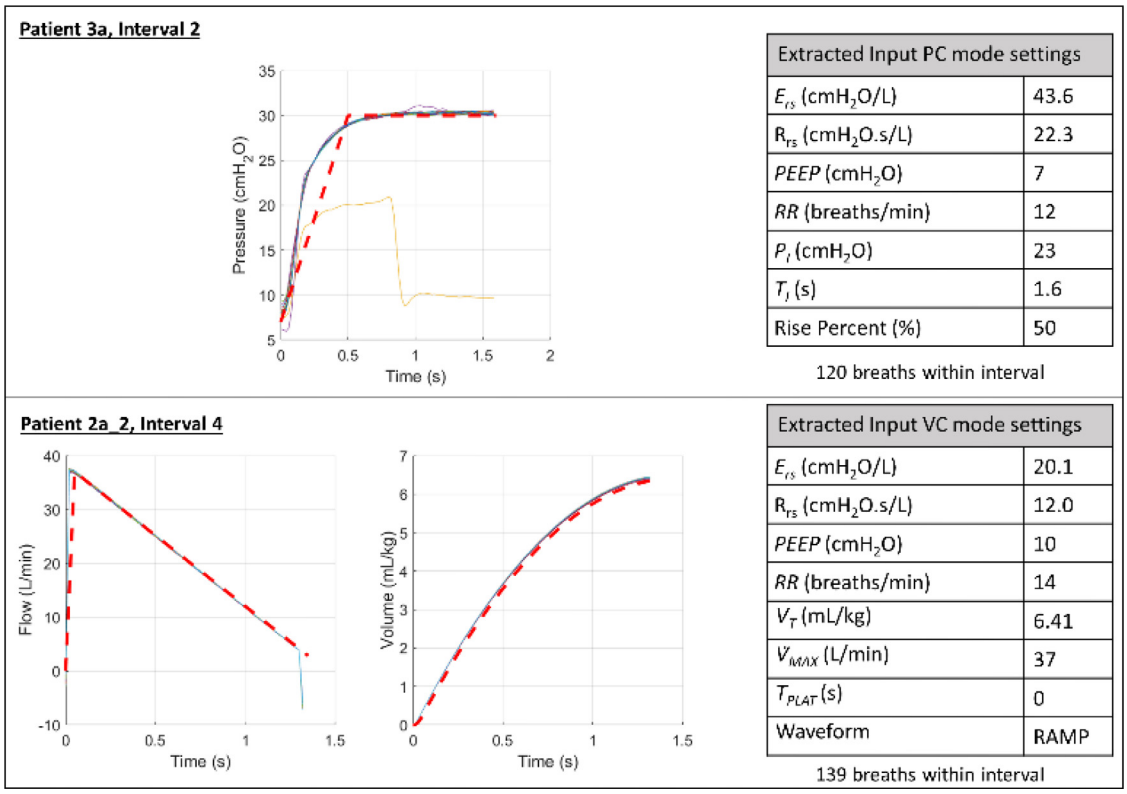

Fig. 5. The coloured thin lines show the actual measured breaths whereas the dotted red lines are the simulated breaths generated from the extracted settings. A comparison between the actual measured breaths (coloured thin lines) vs simulated breaths generated from extracted settings (dotted red line) is made. The resulting median [IQR] absolute percentage errors (%) are: 1.52 [1.43–1.60] (top: pressure waveform), 8.39 [8.18–8.54] (bottom: flow and volume waveform)

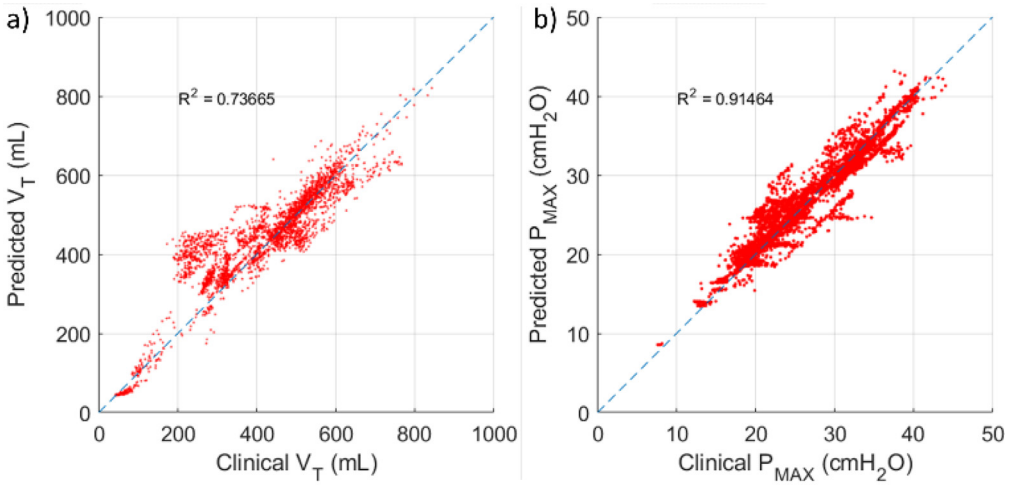

Fig. 6. Clinical patient responses vs predicted patient responses of a) peak tidal volume and b) peak pressure of the PC trial using the single compartment model

gest reduced divergence between the simulated and actual (clinical) data. This patient-level validation demonstrates the accurate identification of patient-specific sensitivities using the single compartment model, thus enabling an accurate prediction of respiratory patient responses under a range of protocol settings and typical MV modes, [21,28] which is a robust approach. However, it is important to note that the correlation analysis can only determine the linear relationship between the two variables, but not their agreement, especially when a systematic measurement error is present [57].

The virtual patients were developed using a simple single compartment lung model to avoid excessive model complexity, while ensuring sufficient granularity of the captured data [58]. As the model captures patient conditions at a particular point in time, it is assumed that the change in ventilator settings does not influence the patient's condition. While an increasingly complex model may improve data fitting performance, the increased parameterisation could lead to parameter trade-off and non-identifiability [41,59,60]. Furthermore, the presence of spontaneous breathing could also cause poor model fitting and incorrect parameter estimation [41,61,62]. Similar patient-level validation studies have been performed with different models and have used similar validation methods [34,36,37]. In addition, these issues are being further addressed by new models capturing patient-specific breathing effort and ventilator unloading, which can both induce added error in the personalised models used [33,63–65]. As such, this

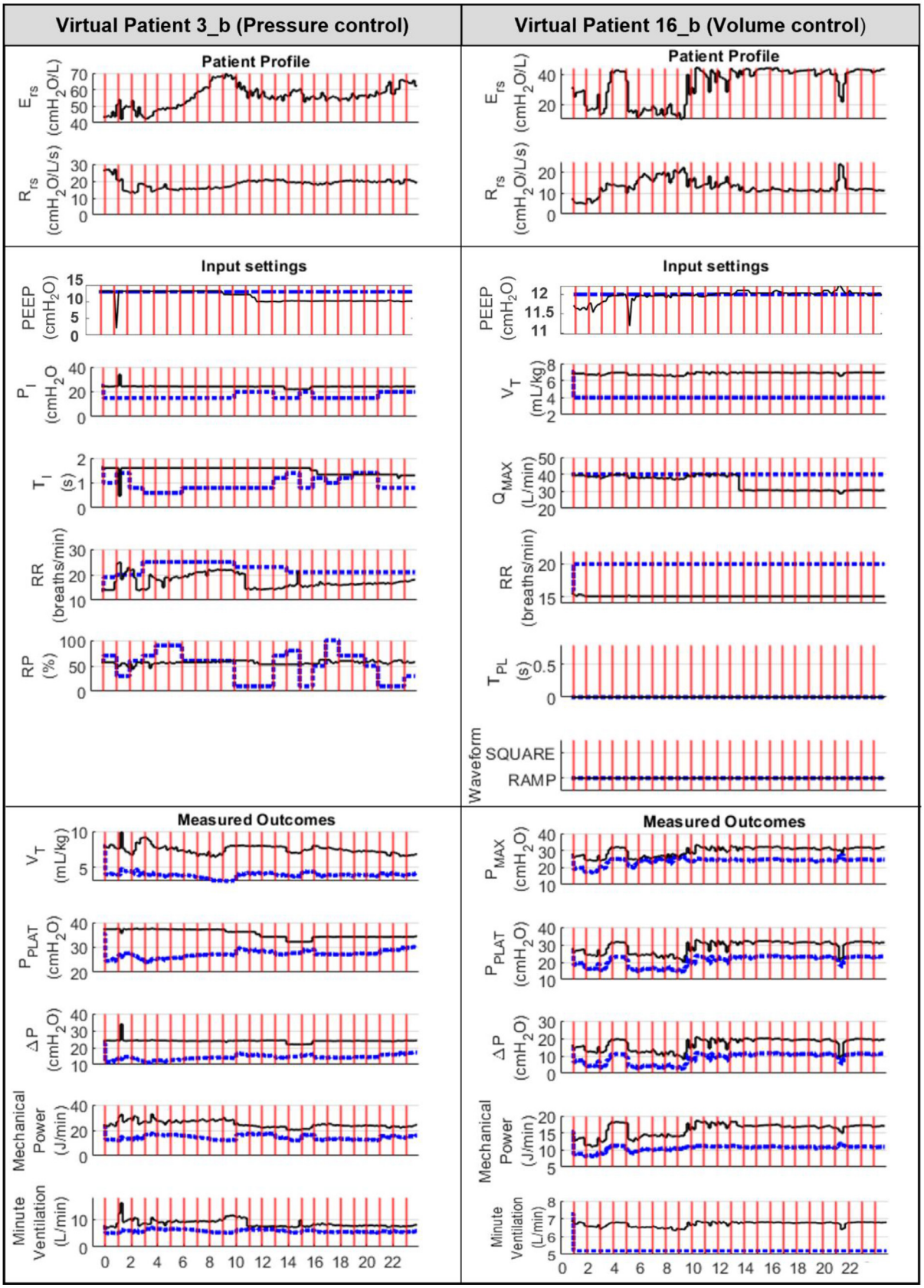

Fig. 7. Example of a virtual trial showing clinical data (black), and the VENT protocol's chosen settings and predicted patient responses (blue)

Table 6
Virtual trial results compared to clinical data for PC and VC ventilation patients.

Pressure Control Ventilation		
Overall data	**Clinical data**	**Virtual Trial**
Number of virtual patients	35	35
Cumulative trial length	519.17 hours	519.17 hours
Total measurements	3,150	3,117 (33 failed to converge)
V_T (mL/kg)	6.86 [5.89- 7.97]	4.06 [3.96- 4.77]*
Minute Ventilation (L/min)	7.74 [6.54- 9.41]	5.78 [5.19- 6.92]*
Mechanical power (J/min)	16.67 [13.91-21.34]	11.33 [9.16-15.12*
ΔP (cmH_2O)	16.54 [13.32-20.76]	12.77 [8.54-14.45]*
V_T between 4–8 mL/kg	68.98%	68.85%
Minute Ventilation between 5–12 L/min	84.32%	87.36%
Mechanical Power < 17 J/min	53.81%	95.96%
Within all safety thresholds	**33.81**%	**64.84**%
Volume Control Ventilation		
Number of virtual patients	65	65
Cumulative trial length	897.17 hours	897.17 hours
Total measurements	5,426	5,426
P_{PLAT} (cmH_2O)	23.69 [20.17–29.39]	17.09 [14.20-22.69]*
Minute Ventilation (L/min)	9.06 [7.29–10.74]	5.20 [5.13–6.44]*
Mechanical power (J/min)	18.71 [13.81–27.80]	10.07 [7.08–13.03]*
ΔP (cmH_2O)	14.22 [11.9 - 18.78]	9.00 [5.55–11.19]*
P_{PLAT} < 30 cmH_2O	77.86%	98.53%
Minute Ventilation between 5–12 L/min	84.14%	99.82%
Mechanical Power < 17 J/min	41.72%	97.10%
Within all safety thresholds	**36.97**%	**97.08**%

* $P < 0.05$ using Wilcoxon signed rank test when compared to clinical data.
Results are reported as median [IQR] values over the total measurements made for each category.

patient-level validation highlights the need of validating model performance, particularly at the patient level, to ensure the accurate identification of patient-specific sensitivities to generate well-validated virtual patients and resulting virtual cohorts that are accurate.

In the virtual protocol implementation study, the closed-loop *VENT* protocol is implemented on the virtual cohort, and the results are compared to the measured patient responses of the clinical protocols used. As the VENT protocol aims to optimise the implemented MV settings for lung protective ventilation, this results in the differences between data distributions of the input settings and patient responses as seen in Figs. 8 and 9. By using the virtual patients as a platform for the virtual trial, the *VENT* protocol is shown to significantly increase the percentage of time where the implemented MV settings fall within the clinically derived safety thresholds, with improvements of 31.03% and 60.11% for PC and VC mode, respectively. In addition, the *VENT* protocol also significantly increases the percentage of time within the safety threshold (<17 J/min) by 42.15% and 55.38% for PC and VC modes, respectively, showing the capability of the virtual trial platform for an in-silico implementation and validation of setting mechanical power. These results demonstrate the potential to virtually, and thus safely, test new care approaches in terms of quantifiable, clinically accepted safety and performance metrics.

The results of the virtual trial presented thus demonstrate the feasibility of the virtual patient as a platform for testing and validating MV protocols, in this case, the *VENT* protocol [9]. This study is thus the first virtual trial analysis for MV. This virtual patient and digital twin based approach is more common in glycaemic control, [22,30,38,66–68] but still rare, especially in other areas of care [28]. While the *VENT* protocol is only an open-loop single-step protocol, this study introduces a modified closed-loop *VENT* protocol. The testing of the modified *VENT* protocol on the virtual patient platform will provide the opportunity to create a protocol that enables dynamic patient monitoring while adapting to evolving patient conditions over an extended period of time.

The selection of models and retrospective data used to develop the virtual patient is highly dependent on the patient response measures of a specific protocol. As a proof of concept, the virtual patients presented were only used to test protocols dependent on measured patient responses such as V_T, P_{PLAT}, ΔP, minute ventilation and mechanical power. However, these measured patient responses are directly related to patient-specific respiratory conditions, thus providing an appropriate metric to quantify and capture patient-specific responses towards MV protocols.

In MV research, virtual patient cohorts can be used to design and validate MV protocols in-silico, whereby virtual patients increase the amount of available data without needing to recruit more patients in clinical trials. Thus, this reduces the risks of harm subjected to actual patients while ensuring data sufficiency to achieve statistical significance of results. In addition, this study applies a deterministic model approach to virtual patients, thus the developed virtual patients enable patient-specific analysis as opposed to a cohort generalised approach.

Model-based decision support systems have been explored in the past with goals of optimising MV support. Banner et al. [69] developed a ventilator advisory system to provide automatic and valid recommendations for setting pressure support ventilation (PSV) settings. This approach is however limited to PSV and fails to cater to the various modes of MV available. In the works of Das et al. [70] a model-based method is used to optimally manage MV settings such as V_T, ventilation rate, inspiratory/expiratory ratio, PEEP, and inspired fraction of oxygen. However, this study is based on a limited number of in-silico patients, disease states, and a short analysis period of only 20 minutes. Other model-based MV decision support systems [7] are capable of producing valid MV setting suggestions, but do not track the dynamic evolution of patient-specific respiratory mechanics and MV settings over time. The *VENT* protocol-based virtual patient platform developed in this study addresses these issues posed whereby a closed-loop decision support system is introduced for pressure- and volume-based MV. Furthermore, the dynamic change of patient-specific $E_{rs}(t)$ and $R_{rs}(t)$ is also analysed over an extended period of time for virtual patients developed from 2 clinical cohorts, encompassing various patient demographics and disease states. The developed virtual patients enable the development of a dynamic, "*one method fits all*"

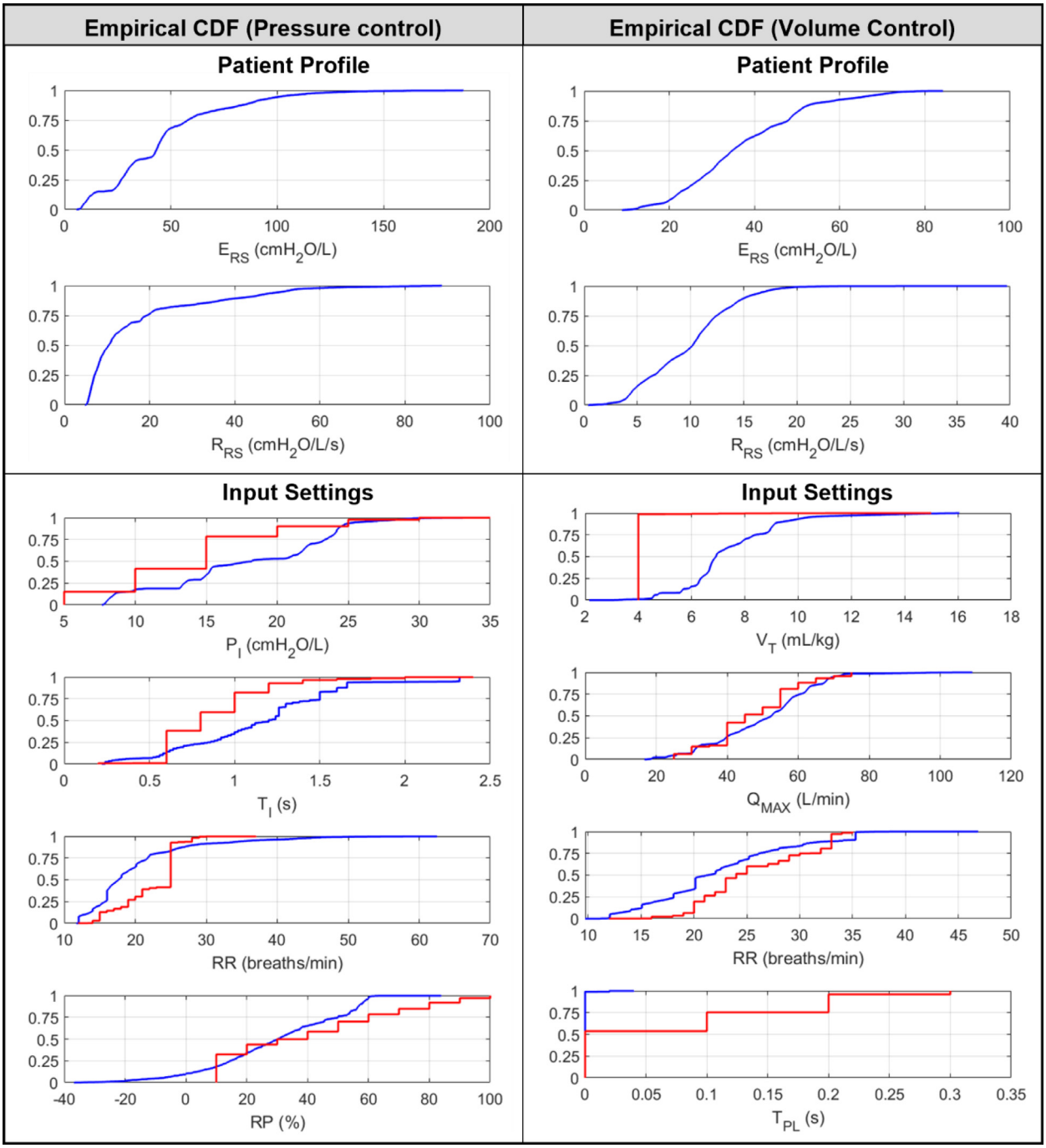

Fig. 8. The empirical cumulative distribution function (CDF) plots of the PC (left column) and VC (right column) trial. The clinically measured data are plotted as blue lines, whereas the VENT protocol chosen settings are plotted as red lines.

personalised MV protocol. Furthermore, the continuous and extended monitoring of patient-specific respiratory mechanics such as E_{rs} via the virtual patient platform allows tracking of patient disease progression, thus providing a platform for the long-term validation of MV protocols.

While machine learning methods may be helpful in cases where there are large quantities of training data, the proposed work demonstrates a well-trodden path of using key sensitivities to generate virtual patients that are deterministic, which are proven in other studies [28,71]. Furthermore, machine learning models are dependent on the selected patient cohort data and can be biased toward "common" or typical patients and thus not generalise well to outliers [72,73]. Therefore, it would be hard to validate such a model as it does not relate back to specific patients from the clinical cohort. Thus, the proposed virtual patient framework enables the development of virtual patients which are patient-specific, allowing comparison and validation with the available clinical data.

4.1. Limitations

In terms of limitations, the identified profiles of $E_{rs}(t)$ and $R_{rs}(t)$ of the virtual patients are static and may not reflect the impact of the new MV settings implemented by the protocols. Patient-specific values of E_{rs} are affected by patient condition and disease progression [43]. However, it may also be affected by ventilator settings [39,47,49]. In these virtual trials, the virtual pa-

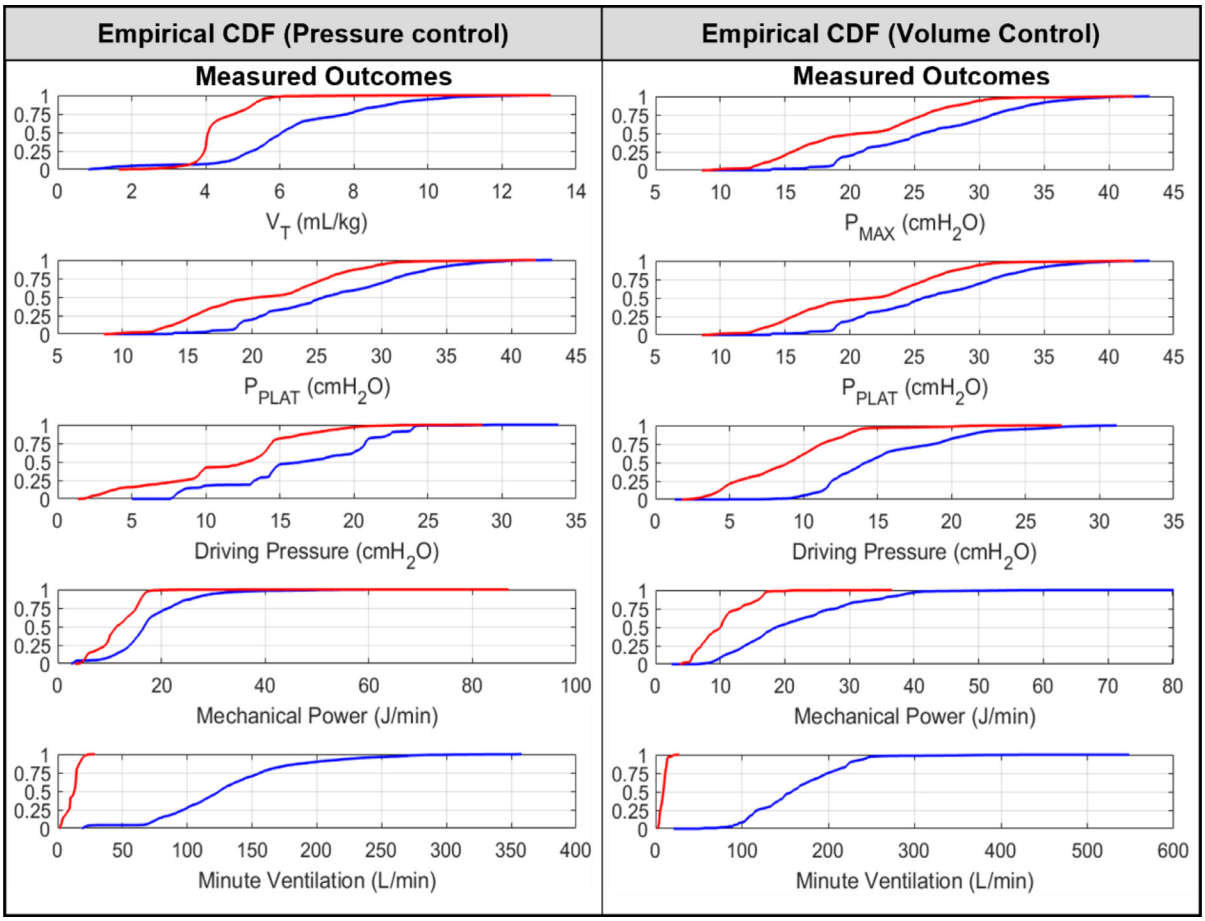

Fig. 9. The empirical cumulative distribution function (CDF) plots of the PC (left column) and VC (right column) trial. The clinically measured data are plotted as blue lines, whereas the predicted patient responses are plotted as red lines.

tient $E_{rs}(t)$ and $R_{rs}(t)$ profiles will remain constant regardless of the protocol implemented as the profiles of $E_{rs}(t)$ and $R_{rs}(t)$ were identified from the retrospective patient data. This study assumes that breath-to-breath respiratory elastance and resistance are unaffected by PEEP values and are constant over an entire breath. In clinical settings, patient ventilator settings (including PEEP) are evaluated on an hourly basis and show little variation, and thus would not have a significant influence on the breath-to-breath identification of respiratory mechanics. Hence, future work leads to a more realistic virtual trial considering both the effect of $E_{rs}(t)$ and $R_{rs}(t)$ evolution on implemented MV settings.

Due to the limited complexity of the virtual patients, the results of the virtual trials can only indicate potential in translation from virtual findings to bedside performance. When transitioning between protocol conception to clinical trials, the virtual trials are limited in their role as an intermediary stage of performance analysis and validation. Despite this limitation, we believe that the intermediary role of the virtual patient platform and virtual trials are vital for providing preliminary evaluation and understanding of treatment protocol performance, where harm to clinical patients can be avoided.

Furthermore, as noted, current virtual trials only encompass the mechanical aspect of ventilation without the perfusion aspect, which is of equal importance. Several important perfusion parameters, such as blood oxygenation, partial pressure of oxygen (PaO_2), fraction of inspired oxygen (F_IO_2), and pressure of end-tidal CO_2 ($PetCO_2$) could provide further insight into MV patient condition, but remain to be incorporated into the work of this research [74,75]. In particular, gas exchange models are proven and might be directly integrated with the models and methods presented here [76–79].

This paper clearly demonstrates the potential and feasibility of developing a virtual MV patient and establishes a methodology for prospective evaluation and testing. The development of a functional virtual MV patient will have a widespread application from providing real-time bedside guidance of treatment, to in-silico testing of various treatment protocols [28,80]. In-silico development allows for the safe validation of treatment protocols in a virtual environment prior to clinical implementation, thus preventing unnecessary harm to physical patients.

In addition, the virtual patients generated in this study are based only on a total of 35 clinical patients. While 100 virtual patients have been generated from this clinical cohort, further investigation of the effective sample size required for statistical power of the results is required [15]. However, the primary aim of this study is to demonstrate the feasibility and concept of a generalisable virtual patient framework which has potential use with larger patient cohorts and in other fields of research.

This concept of a virtual MV patient can be further extended with the use of more complex models [37,41,54,64,81–84] to better capture the dynamics of the patient's respiratory system. As noted, a model providing a more comprehensive overview of patient condition and variability in response to MV care would also add utility. Furthermore, future works could also include the development of a dynamic virtual patient whereby patient sensitivity profiles can dynamically evolve based on the implemented MV

interventions. This would provide a more realistic virtual patient and provide a platform for the development of personalised treatment protocols. The ability to predict patient responses to a treatment protocol would facilitate healthcare providers in determining the cost and adequacy of these treatment protocols. In addition to this work, there are possibilities of exploring machine learning methods in virtual patient generation if large quantities of clinical data are gathered for training purposes. Loo et al. and Ang et al. have investigated the use of models to generate synthetic data for machine learning model training, which can perform fairly. It was found that additional clinical MV data are needed to train the model better [41,85]. The virtual patient framework also has the potential to provide open access to data, improving reproducibility and encouraging the use of virtual trials. While these outcomes remain in future, the building blocks are already available for model-based and digital twin driven decision support in MV care.

5. Conclusions

A virtual cohort generated from retrospective patient data provides a platform to test and validate different MV treatment selection protocols. The virtual trials in this research show the potential to design, develop, and optimise MV setting selection protocols safely and rapidly through computer simulation. The patient-level model validation and resulting virtual clinical trials are the first demonstrations of the potential for digital twin models and virtual patients in this high-cost clinical space. The overall results thus present a platform upon which significant improvements made in modelled mechanics would greatly provide added clinical utility.

Conflict of Interest

None declared.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cmpb.2022.107146.

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