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Stochastic virtual patient-guided mechanical ventilation treatment: A virtual patient study with mechanical power consideration

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ABSTRACT

Background and Objective : Computerised decision support systems (CDSS) in mechanical ventilation (MV) provide individualised, closed-loop treatment but often require extensive input parameters, which are challenging to obtain continuously in clinical settings. Many also fail to incorporate mechanical power (*MP*) and *MP ratio* — recently identified as significant predictors of patient outcomes. This study introduces the Stochastic Virtual Patient Ventilation Protocol (SVP VENT), a model-based CDSS addressing these limitations.

Methods : The SVP VENT Protocol integrates a stochastic virtual patient model to predict temporal lung elastance, E_{rs}, trends and deliver closed-loop, lung protective ventilation minimising *MP ratio* and driving pressure. The protocol was validated against the VENT and SiVENT protocols using an established virtual patient platform comprising over 1229 h of both volume control (VC) and pressure control (PC) retrospective MV data. Patient responses were monitored to ensure adherence to accepted clinical safety guidelines.

Results : The SVP VENT protocol consistently outperformed retrospective clinical data, VENT and SiVENT protocols in ensuring adherence to clinical safety metrics, achieving an all-adherence rate of ∼57% and ∼67% for the VC and PC cohorts, respectively. Across cohorts, the protocol maintained *MP* and *MP ratio* levels below safety thresholds (12 J/min and 4.5, respectively), and extended intervention intervals up to 3 h, potentially reducing clinical workload.

Conclusion : Overall, the virtual trial demonstrates the SVP VENT protocol's potential to enhance MV management by extending intervention intervals, while maintaining patient safety. These findings support initial clinical trials to evaluate the protocol's impact on clinical workload and patient safety over prolonged monitoring periods, facilitating its integration into standard clinical practices.

1. Introduction

Computerised decision support systems (CDSS) have emerged to provide closed-loop and patient-specific mechanical ventilation (MV) treatment. These CDSS aim to overcome the challenges imposed by current care practices, which are based on generalised guidelines. These practices also rely heavily on clinician experience and expertise, and regular patient monitoring (Amerling, Winchester, & Ronco, 2008; Chase et al., 2014; Fernandez et al., 2015), resulting in potentially sub-optimal care and higher clinical burden.

Existing CDSS were developed based on machine learning methods (Akbulut, Akkur, Akan, & Yarman, 2014; Hong et al., 2022; Ossai & Wickramasinghe, 2021), fuzzy logic (Banner et al., 2008; Lozano et al., 2008; Steven , Michael, Neil, Carl, Layon, Andrea, 2011; Wang, Zhang, & Wu, 2016), or model-based methods (Buiteman-Kruizinga et al., 2023; Karbing et al., 2015; Patel et al., 2022; Rees & Karbing, 2017; Rees et al., 2022; Tehrani, 2019; von Platen, Pomprapa, Lachmann, & Leonhardt, 2020; von Platen et al., 2023; Zhang et al., 2021). These CDSS used physiological models and/ or clinical guidelines to adjust MV settings, such as respiratory rate (*RR*), tidal volume (V_T), fraction of inspired oxygen (FiO_2), positive end-expiratory pressure (*PEEP*) and MV mode. They have demonstrated significant potential in improving patient outcomes, underscoring the need for ongoing research to refine and broaden their applications.

However, some CDSS rely on multiple physiological models or very complex models. These CDSS can thus require extensive

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input parameters such as arterial blood gas values and end-tidal partial pressure of CO_2 ($PETCO_2$) measurements, which can increase clinical workload and burden to track (Rees et al., 2022; von Platen et al., 2023). Finally, some variables can be challenging to continuously obtain in clinical settings. Consequently, the complexity and added burden may limit the ability to adopt these systems (Chase, Andreassen, Jensen, & Shaw, 2008; Parmar et al., 2022; Schonthal & Euchner, 2022; Wong, Naswall, Pawsey, Chase, & Malinen, 2023), particularly in clinical environments with limited infrastructure or personnel capacity.

The VENT (Lee et al., 2022) and SiVENT (Lee, Chiew, et al., 2022) CDSS protocols offer personalised MV by providing a selection of MV parameters and settings using only measured airway data. The SiVENT protocol also integrates stochastic prediction to account for temporal changes in patient-specific respiratory elastance (E_{rs}) as patient state evolves (Chiumello et al., 2008; Davidson et al., 2014; van Drunen et al., 2013). The MV settings recommended by each protocol target lung-protective ventilation by titrating patient MV responses based on patient-specific respiratory mechanics. However, the VENT and SiVENT protocols have a limited intervention period of 30 min, limiting clinical practicality as a result of increased clinician workload. Furthermore, both protocols and other CDSS do not account for mechanical power (*MP*) and mechanical power ratio (*MP ratio*), which have been more recently proposed as an important predictor of patient outcomes (Gattarello et al., 2023; Gattinoni, Collino, & Camporota, 2023; Gattinoni et al., 2016; Goedegebuur et al., 2024; Kim, Chung, Nam, Ko, & Suh, 2025; Manrique et al., 2024; Pozzi et al., 2024; Serpa Neto et al., 2018; von Düring et al., 2025; Yoon et al., 2024).

While potentially valuable, *MP* is also not readily monitored in real-time and titrating *MP* requires a delicate balance between several MV parameters (*RR*, *PEEP*, V_T, and driving pressure), which at times may be conflicting (Buiteman-Kruizinga, Serpa Neto, & Schultz, 2022). This problem is further compounded by the heterogeneity and everchanging pulmonary condition of MV patients (Pozzi et al., 2024), where the constant titration of these MV parameters is hindered by limited clinical resources. Hence, there is a need for CDSS with low clinical burden, such as SiVENT and VENT, but with longer intervention intervals and including mechanical power into their decision frameworks, all without adding clinical workload.

This study presents a model-based CDSS for intensive care MV treatment tested in a virtual patient platform. The CDSS integrates a stochastic virtual patient (SVP) prediction method to provide patient-specific prediction of temporal E_{rs} trends, enabling extended intervention intervals based on patient-specific risk defined by evidence-based protective guidelines. The developed CDSS also focuses on delivering individualised, lung protective ventilation in a closed-loop by targeting minimum *MP ratio* and driving pressure (Gattarello et al., 2023). The protocol's extended intervention intervals can potentially reduce clinician workload, thus improving the clinical utility of such CDSS.

2. Methodology

2.1. Patient selection

This study uses measured airway pressure, flow and volume (P-$\dot{V}$-V) data from 12 retrospective MV patients of the $CARE_{SG}$ cohort (Ref: DSRB Ref:2018/00042) (Ang, Chiew, Vu, & Cove, 2022). The patients were ventilated for more than 24 h, with volume-controlled (VC, $N = 8$ subjects, median weight: 73.9 [62.0–82.9] kg, median height: 170.5 [164.3–174.5] cm) or pressure-controlled (PC, $N = 4$ subjects, median weight: 55.0 [49.9–63.8] kg, median height: 158.5 [156.0–165.0] cm) ventilation. Other MV settings were not fixed. Patient data were stratified based on their MV modes, with the demographics of each group of patients detailed in Table 1. The temporal profiles of respiratory system elastance and MV parameters form the digital twin of the clinical patients analysed in this study (Ang et al., 2022), which is a tested virtual patient approach in general (Chase , others, 2021; Chase et al., 2023).

All patients were ventilated using a Puritan Bennett PB980 ventilator. The airway pressure (cmH_2O) and flow (L/min) data were recorded using a data acquisition system at a sampling rate of 50 Hz (Ng et al., 2021, 2022). Individual breathing cycles were processed to remove incomplete breathing cycles or breaths with excessive noise, patient effort, and/or asynchronies. The filtering criteria for each breath are defined in previous work (Ang, Chiew, Wang, et al., 2022; Kim, Knopp, Dixon, & Chase, 2019; Lee et al., 2021). The available retrospective patient data will form the virtual patients used as part of the virtual trial validation process, as detailed in the following sections.

2.1.1. Patient data management

The clinically implemented MV settings and measured patient responses to MV are identified using the ventilator waveform data and are averaged into mean values over 30 min, defined as an interval. These MV settings and measured patient responses for VC and PC patients are summarised in Table 2. E_{rs} characterises the elastic properties of the respiratory system, encompassing both the lungs and the chest wall. It serves as a representation of respiratory system function, where the changes in E_{rs} capture the progression of patient-specific disease state (Chiew et al., 2015; Hess, 2014; Nolley et al., 2023). Mean values of E_{rs} and R_{rs} over 30 min intervals are identified using a recruitment and distension basis function respiratory model:

$$P_{aw}(t) = (E_1 e^{b(V(t))} + E_2 \frac{P_{aw}(t)}{60})V(t) + (R_1 + R_2 \left|\dot{V}(t)\right|)\dot{V}(t) + PEEP \tag{1}$$

where P_{aw} is the airway pressure (cmH_2O), t is the time, $V(t)$ is the volume (L), $\dot{V}(t)$ is the airflow (L/s), *PEEP* (cmH_2O) is the positive end-expiratory pressure. E_1, b, E_2, R_1 and R_2 are all breath-specific basis function coefficients to be determined (Morton et al., 2018, 2019). To simplify model identification, respiratory elastance and resistance is assumed to be a breath-average value (Chiew, Chase, Shaw, Sundaresan, & Desaive, 2011a). As such, Eq. (1) can be rearranged as:

$$P_{aw}(t) = E_{rs}V(t) + R_{rs}\dot{V}(t) + PEEP \tag{2}$$

where

$$E_{rs} = E_1 e^{b(V(t))} + E_2 \frac{P_{aw}(t)}{60}$$

$$R_{rs} = R_1 + R_2 \left|\dot{V}(t)\right|$$

Additional details on the model solution process are provided in **Supplementary material (Stochastic Virtual Patients - Respiratory Elastance)**. Predicted body weight (PBW) is also calculated for each patient (Moreault, Lacasse, & Bussières, 2017).

2.2. Computerised decision support system

2.2.1. Stochastic Virtual Patient MV CDSS (SVP VENT)

The CDSS developed in this study is known as the Stochastic Virtual Patient Ventilation Protocol (SVP VENT). The SVP VENT integrates stochastic virtual patients (**Supplementary material - Stochastic Virtual Patients**) with the modified VENT protocol (**Supplementary material - VENT Protocol**) to predict the variations in future patient E_{rs} trends (Ang et al., 2023). The SVP

Table 1
$CARE_{SG}$ Patient demographics.

No.	Sex	Age (Years)	Weight (kg)	Height (cm)	PF ratio (mmHg)	Diagnosis	MV data (h)
Volume-Controlled (VC) Cohort							
1	M	70.0	90.0	173.0	290.0	Pneumonia	66.5
2	M	54.4	85.0	179.0	244.0	Septic shock	80.0
3	M	70.5	66.0	170.0	259.3	Pneumonia	216.0
4	F	77.0	45.1	152.0	128.7	Septic shock	134.0
5	M	35.0	77.9	183.0	297.0	Acute exacerbation of asthma	125.0
6	M	72.0	50.0	153.0	230.8	Type 1 respiratory failure	19.5
7	M	46.9	70.0	171.0	140.4	Type 1 respiratory failure	152.5
8	M	55.0	82.2	168.0	170.5	Type 1 respiratory failure	103.0
Median		62.5	73.9	170.5	237.4		114.0
[IQR]		[52.5 – 70.9]	[62.0 – 82.9]	[164.3 – 174.5]	[163.0 – 266.9]		[76.6 – 138.6]
Pressure-Controlled (PC) Cohort							
1	M	65.7	60.0	160.0	139.8	DLBCL	56.0
2	M	69.1	75.1	180.0	123.8	Liver Failure	182.0
3	F	70.0	49.7	157.0	198.6	AOCKD, DKA, NSTEMI	46.5
4	M	72.0	50.0	153.0	230.8	Type 1 respiratory failure	48.0
Median		69.5	55 .0	158.5	169.2		52.0
[IQR]		[68.2 – 70.5]	[49.9 – 63.8]	[156.0 – 165.0]	[135.8 – 206.6]		[47.6 – 87.5]

Abbreviations: DLBCL – Diffuse large B-cell lymphoma, AOCKD – Acute-on-Chronic Kidney Disease, DKA – Diabetic ketoacidosis, NSTEMI – non-ST segment elevation myocardial infarction.

Table 2
MV settings and patient responses extracted from patients under VC and PC MV.

Extracted MV settings (VC)	Extracted MV settings (PC)	Measured patient responses
• Respiratory rate, *RR*	• Respiratory rate, *RR*	• Peak pressure, P_{MAX}
• Positive end-expiratory pressure, *PEEP*	• Positive end-expiratory pressure, *PEEP*	• Plateau pressure, P_{PLAT}
• Tidal volume, V_T	• Inspiratory pressure, P_I	• Mechanical power, *MP*
• Peak inspiratory flow, $\dot{V}_{MAX}$	• Inspiratory time, T_I	• Driving pressure, ΔP
• Waveform (Square or ramp wave)	• Rise percent, *RP*	• Minute Ventilation, *MVENT*
• Plateau pressure, P_{PLAT}	• Plateau pressure, P_{PLAT}	• Mechanical power ratio, *MP ratio*
• Driving pressure, P_{PLAT} – *PEEP*	• Driving pressure, P_{PLAT} - *PEEP*	
• Plateau time, T_{PLAT}		

VENT protocol builds upon the existing VENT CDSS framework by incorporating: stochastic virtual patients, physiological lung model, and clinically established safety thresholds.

In short, SVP VENT provides decision support by recommending a combination of MV settings by solving a multi-objective constrained minimisation problem. These constraints are based on clinically established thresholds targeting lung protective ventilation, minimising ΔP and *MP ratio* (Lee et al., 2022). *MP ratio* is the ratio between the actual *MP* (MP_{actual}) of the respiratory system and the expected baseline *MP* (MP_{exp}) (Gattarello et al., 2023; Gattinoni et al., 2016; Silva, Ball, Rocco, & Pelosi, 2019), and is defined as:

$$MPratio = \frac{MP_{actual}}{MP_{exp}} \tag{3}$$

$$where\, MP_{actual} = RR \times \left\{ V_T^2 \times \left[0.5 \times E_{rs} + RR \times \frac{1 + I:E}{60 \times I:E} \times R_{rs} \right] + V_T \times PEEP \right\} \tag{4}$$

$$MP_{exp} = 1.47 \times (0.006 \times IBW)^2 \times \left(\frac{3.57}{0.006 \times IBW} + 7.5 \right) \tag{5}$$

where *I:E* is the inspiratory-to-expiratory time ratio. 1.47, 0.006, 3.57 and 7.5 are conversion constants, and IBW is ideal body weight. The calculation of *MP* using Eq. (4) accounts for the relative contribution and changes of its different components (V_T, *RR*, *PEEP*, *I:E*, pressure and airflow) (Silva et al., 2019). The single combination of suggested MV settings targeting minimum ΔP and *MP ratio* allows SVP VENT to be implemented in a closed-loop fashion.

Key definitions and assumptions used in the SVP VENT protocol include:

- $\boldsymbol{E_{rs,0}}$: The initial respiratory elastance identified at the start of the intervention ($t = 0$) using Eq. (2).
- **Stochastic virtual patients**: A simulated E_{rs} profile over a 3-hour prediction window, divided into six 30 min intervals, and is defined as:

$$E_{rs,N} = SM\left(E_{rs,N-1}[1 + W \cdot z]\right),$$
$$where\, z\, follows\, the\, distribution\, f\,(x) = \frac{1}{\sqrt{2\pi}} e^{-\frac{z^2}{2}} \tag{6}$$

where N is the N^{th} E_{rs} interval, *SM* is the stochastic model, *W* is *X*% random noise, and *z* is a random real variable following a standard normal distribution with a mean of 0 and a variance of 1. This process is more elaborately detailed in **Supplementary material - Stochastic Virtual Patients**.

- **Clinical safety adherence**: Each combination of MV settings and patient responses is assessed against predefined safety thresholds (Table 3).
- **Composite Adherence Score (CAS)**: The CAS is the average adherence rate of each clinical safety parameter (Table 3) across the 5th, 50th and 95th percentiles. The CAS reflects the overall likelihood of maintaining safe ventilation across the predicted range of patient E_{rs}.
- $\boldsymbol{t_{compliant}}$: $t_{compliant}$ represents the longest duration over which the highest CAS can be maintained, defining the intervention interval from $t = 0$ to $t_{compliant}$ minutes. In this study, $t_{compliant}$ is constrained to a range of 30–180 min.
- ***PEEP* independence**: Changes in SVP E_{rs} do not consider the influence of *PEEP* changes, as established in prior studies (Ang, Chiew, Wang, Mat Nor, & Chase, 2023; Ang, Chiew, Wang, et al., 2022; Lee et al., 2021).

- **Protocol consistency**: In alignment with retrospective trial data, retrospective *PEEP* values are used throughout all protocols. If a *PEEP* change of more than ±1 cmH_2O occurs during an intervention interval, the interval is truncated at the point of adjustment to maintain consistency. This approach preserves protocol consistency by preventing *PEEP*-related shifts from impacting the model's performance in predicting E_{rs} trends.

The SVP VENT is illustrated in Fig. 1 and generalised in the following steps:

1. **Initial MV recommendation**:
   Initial MV settings targeting minimum *MP ratio* are recommended using the VENT protocol (**Supplementary material –VENT Protocol**).
2. **Generation of Virtual Patients**:
   For an initial value of $E_{rs,0}$, 200,000 stochastic virtual patients are generated over a 3-hour window, divided into six 30 min intervals.
3. **Identification of E_{rs} Percentiles**:
   The 5th, 50th and 95th percentile E_{rs} values of the 200,000 stochastic virtual patient profiles are then identified for each interval.
4. **Application of VENT Protocol**:
   The identified percentile E_{rs} values (5th, 50th and 95th percentiles) at $t = 180$ minutes are input to the VENT protocol, returning a combination of suggested MV input settings. The corresponding patient responses (Table 2) are forward-simulated over the six intervals using the percentile E_{rs} values. The MV setting selection process is detailed in **Supplementary material – VENT Protocol**.
5. **Safety Threshold Evaluation**:
   The protocol-suggested MVsettings and patient responses for the 5th, 50th and 95th percentile E_{rs} values are evaluated for adherence to established clinical safety thresholds (Table 3) at each interval.
6. **Composite Adherence Scoring and Optimal Interval Selection**:
   The CAS is computed at every interval and the cumulative interval with the highest CAS, denoted as $t_{compliant}$ is then identified. The MV settings from this interval are then applied continuously from $t = 0$ to $t_{compliant}$ minutes (ranging from 30–180 min).
7. **Handling *PEEP* Adjustments**:
   If a *PEEP* change exceeding ±1 cmH_2O occurs within the selected interval, it is truncated just before the adjustment to maintain consistency in E_{rs} prediction and protocol application.
8. **Protocol Reapplication**:
   Steps 2–7 are repeated using the E_{rs} value from the interval immediately following $t_{compliant}$ (i.e., at $t = t_{compliant+1}$).

2.3. CDSS validation via virtual trials

SVP VENT was validated in a longitudinal virtual trial using an established virtual patient (VP) platform (Ang et al., 2022), with 12 retrospective patients from the $CARE_{SG}$ cohort (VC: 8 patients, PC: 4 patients) to obtain the CDSS-suggested MV settings and resultant VP responses to MV as outlined in Table 2. The general procedure for the virtual trial is defined in 4 main steps:

1. The CDSS is initialised using initial values of patient E_{rs} and MV settings.
2. The CDSS is implemented to derive the CDSS-recommended MV settings for the current time interval ($t = 0$ to $t_{compliant}$ minutes, up to 180 min).
3. These MV settings are applied throughout the current time interval and the resulting VP responses are recorded at 30 min intervals throughout the time interval ($t = 0$ to $t_{compliant}$ minutes, up to 180 min).
4. Steps 2–3 are iterated until the entire VP profile has been analysed.

Table 3
Accepted clinical standards of patient response to MV.

Patient responses to MV	Accepted clinical thresholds
Tidal volume, V_T	4 – 8 mL/kg Fan et al. (2017)
Plateau pressure, P_{PLAT}	< 30 cmH_2O Brower , Matthay, Morris, Schoenfeld, Thompson, Wheeler (2000)
Minute ventilation, *MVENT*	5 – 12 L/min Brower et al. (2000)
Mechanical power, *MP*	< 12 J/min Guérin et al. (2016), Russotto, Bellani, and Foti (2018)
Driving pressure, ΔP	< 14 cmH_2O Bellani et al. (2016)
Mechanical Power ratio, *MP ratio*	< 4.5 D'Albo et al. (2024)

To evaluate the performance of the SVP VENT, virtual trials implementing previously developed VENT and SiVENT protocols were also conducted on the same patient cohort using 30 min intervals (Lee, Chiew, et al., 2022; Lee et al., 2022). The narrowing objectives for the VENT and SiVENT protocols were based on prior virtual trial studies (Ang et al., 2024a, 2024b). The total number of intervention intervals implemented by each CDSS were recorded. Furthermore, the resulting patient responses to MV were also monitored to ensure they adhere to accepted clinical standards (Table 3).

2.4. Statistical analysis

The cohort values of each virtual trial and the retrospective data were compared across the implemented MV settings and measured patient responses to MV as detailed in Table 2. Pairwise comparisons between the SVP VENT protocol with the Retrospective, VENT, and SiVENT protocols were assessed using the Wilcoxon rank-sum test ($p < 0.05$). To account for multiple comparisons, a Bonferroni correction was applied, yielding a significance threshold of $p < 0.0167$. All statistical analyses was performed with Matlab (R2023a, The Mathworks, Natick, MA, USA).

3. Results

3.1. Virtual trial results

Over 1,229 h of MV data across 8 volume-controlled (VC) and 4 pressure-controlled (PC) MV patients were analysed. Cohort-specific patient demographics are detailed in Table 1. The respiratory elastance, E_{rs} and respiratory resistance, R_{rs} of the VC patient cohort ($N = 8$) are 31.39 [30.33–33.05] cmH_2O/L and 10.53 [9.44–11.43] $cmH_2O/L/s$, respectively; while the E_{rs} and R_{rs} of the PC patient cohort ($N = 4$) are 11.62 [9.31–23.33] cmH_2O/L and 8.50 [7.83–10.20] $cmH_2O/L/s$, respectively. The retrospective temporal E_{rs} profiles for each patient of the VC and PC cohorts are presented in Fig. 2. Each data point consists of breath-to-breath E_{rs} values which are averaged over 30 min intervals.

3.2. Patient responses to MV

The adherence of patient responses to MV to established safety thresholds in Table 3 across the various MV protocols (VENT,

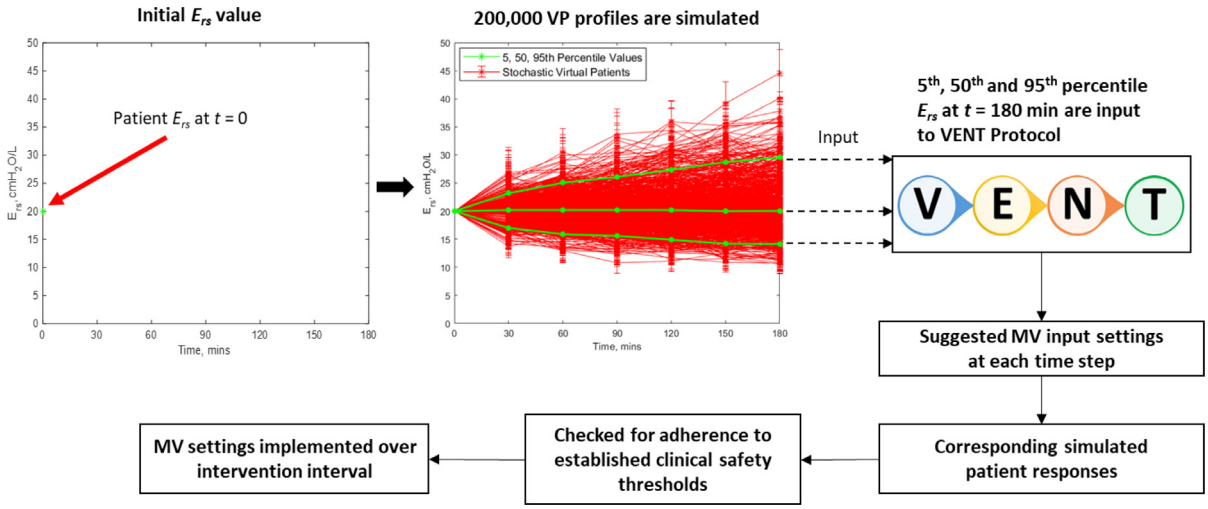

Fig. 1. The general process of the SVP VENT.

Table 4
The adherence of patient responses to MV to accepted clinical standards.

Safety adherence rate (%)	VC MV				PC MV			
	Retro	VENT	SiVENT	SVP VENT	Retro	VENT	SiVENT	SVP VENT
V_T: 4–8 mL/kg	94.92	100.00	100.00	100.00	75.19	73.68	98.35	93.98
P_{PLAT} < 30 cmH_2O	72.89	97.16	97.16	97.21	99.25	99.85	98.50	100.00
MVENT: 5–12 L/min	64.75	99.89	99.89	100.00	86.47	96.09	97.29	99.40
MP <12 J/min	1.90	46.79	46.01	86.61	50.68	99.10	90.98	75.79
ΔP < 14 cmH_2O	32.74	94.48	94.48	80.31	89.32	94.14	93.68	93.23
MP ratio < 4.5	1.28	38.98	38.98	69.83	2.71	78.05	75.19	67.37
Within all safety thresholds	1.23	29.78	29.00	56.83	1.95	68.27	86.47	67.37

SiVENT, and SVP VENT) and retrospective data is summarised in Table 4 for both the VC and PC patient cohort. Patient-specific adherence rates for the VC and PC cohorts are detailed in **Table S2** and **S3** (**Supplementary material - Patient Responses to MV**), respectively.

3.3. Temporal profiles of MV inputs and patient responses

Cohort- and protocol-specific MV settings and patient responses are detailed in Table 5. The *MP* and *MP ratio* were found to be statistically different between the SVP VENT, VENT and SiVENT protocols, and retrospective data ($p < 0.0167$, Bonferroni correction applied). The temporal trends of MV inputs and patient responses for the retrospective, VENT, SiVENT and SVP VENT protocols are presented in Fig. 3 for Patient 4 (VC cohort) and Patient 2 (PC cohort), as examples. Similar plots for all patients of the VC and PC cohorts are presented in the **Supplementary Material (Figures S1–S6)**.

3.4. CDSS intervention intervals

The retrospective VC patients in this study are comprised of 1,785 30 min intervals. The VENT and SiVENT protocols perform an intervention (maintaining or adjustment of MV settings) at the start of each interval, resulting in a total of 1,785 interventions. Implementation of the SVP VENT protocol results in a ∼67% reduction of intervals (597 intervention intervals) for the VC cohort. Similarly, the SVP VENT protocol reduces the total number of intervals for the PC cohort by up to ∼78% with respect to the retrospective, VENT and SiVENT protocols (145 vs 661 intervals). Patient-specific information on the number of intervention intervals for both patient cohorts are detailed in **Tables S4** and **S5** (**Supplementary material – Results**). The SVP VENT intervention intervals for each patient are also illustrated in Fig. 3 for both patient cohorts.

4. Discussion

4.1. Safety of patient care choices and responses to MV

In terms of patient safety, the VC SVP VENT protocol consistently outperformed both retrospective clinical data and alternative protocols (VENT, SiVENT) in achieving adherence of patient MV responses to accepted clinical standards, demonstrating that the inclusion of SVPs lead to improved protocol performance. Overall, all-adherence of the VC SVP VENT was significantly higher at ∼57%, a marked increase compared to the retrospective data (1.23%), VENT (29.78%) and SiVENT protocol (29.00%). Specifically, adherence to maintaining *MP* below 12 J/min was significantly higher with the SVP VENT protocol (∼87%) compared to ∼46% for the VENT and SiVENT protocols, and only ∼2% for the retrospective data. This improvement is likely attributed to the modulation of tidal volume (V_T) in VC MV modes, where V_T has a greater influence on the calculation of *MP* (Gattinoni et al., 2023). Despite this improvement, it is important to note that the relatively poor adherence of the VC protocol compared to the PC protocol is likely due to the higher E_{rs} values of the VC cohort (31.39 [30.33–33.05] cmH_2O/L vs 11.62 [9.31–23.33] cmH_2O/L), which reflects poorer patient conditions. When combined with higher clinically implemented *PEEP* values, these elevated E_{rs} values result in relatively higher *MP* and *MP ratio* values, making it more challenging to maintain adherence to *MP ratio* thresholds compared with the PC cohort.

In the PC cohort, the SVP VENT protocol achieved adherence rates exceeding 67% across all individual safety metrics, with an all-adherence rate of ∼67%, marking a ∼65% improvement on

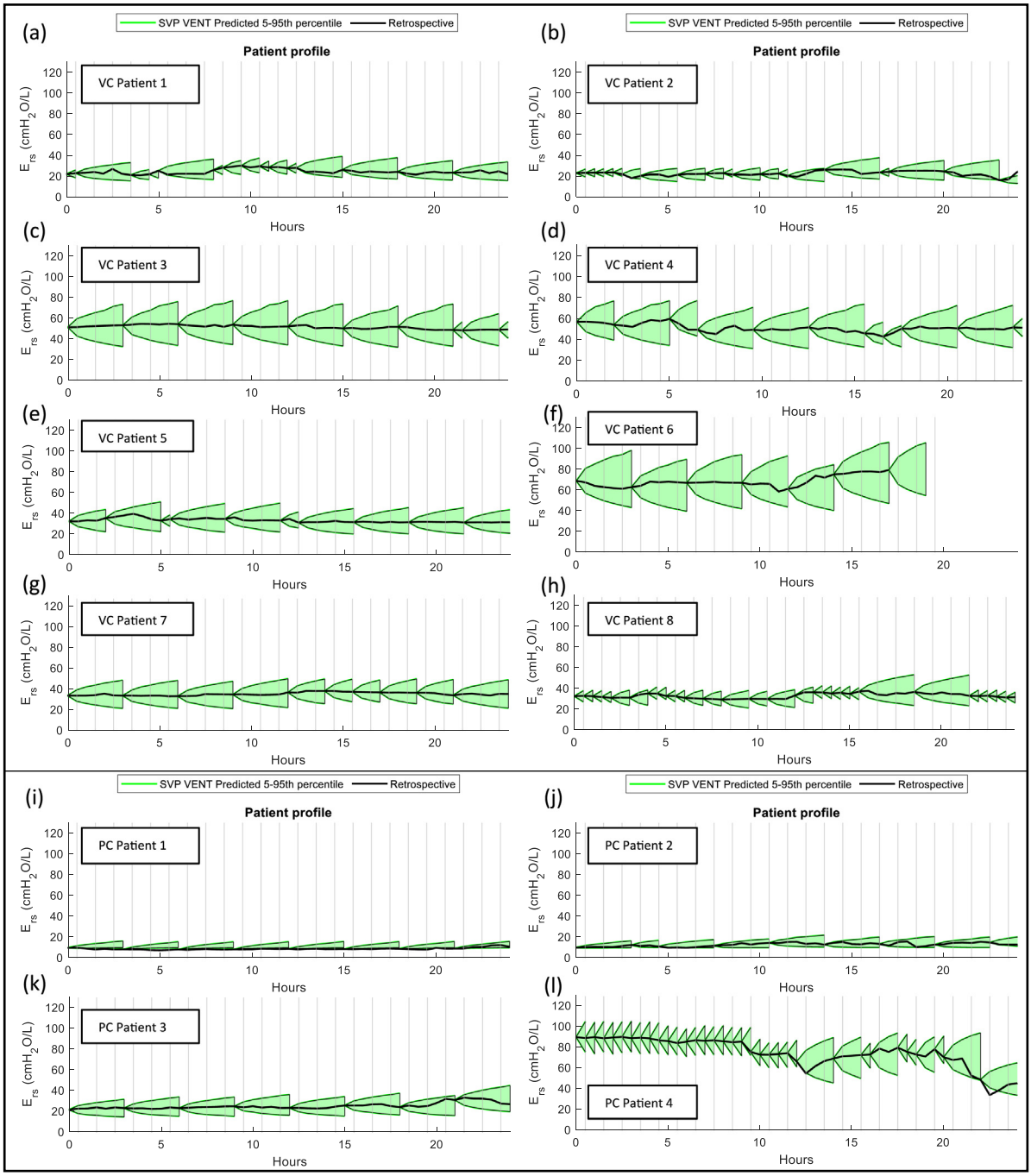

Fig. 2. (a–h) The temporal E_{rs} profiles for Patients 1–8 of the VC cohort. (i–l) The temporal E_{rs} profiles for patients 1–4 of the PC cohort. The length (x-axis) of the SVP VENT predicted 5-95th percentile of E_{rs} also represents the duration of the intervention interval ($t_{compliant}$).

the retrospective patients. However, the SiVENT protocol achieves the highest all-adherence rate of ∼86% out of the 3 protocols for this PC cohort, suggesting that while the SVP VENT protocol effectively ensures adherence to each individual safety parameter, there may be trade-offs between them. Consequently, maintaining adherence across all metrics simultaneously for a particular patient interval can be challenging, leading to a lower overall adherence rate.

The SVP VENT protocol effectively reduced the median *MP ratio* of the VC cohort to 3.32 [2.89–4.74], which is below the safety threshold (*MP ratio* = 4.5) identified in a study on porcine models (D'Albo et al., 2024), and consequently improved the adherence rate of *MP ratio* to ∼70%. For the PC cohort, all three protocols resulted in increased *MP ratio* adherence rates compared to the retrospective patient cohort (Table 4) and resulting in median *MP ratio* values of less than 4.5 (Table 5). The improvement in the VC cohort can be attributed to the SVP VENT protocol's narrowing objective of explicitly minimising *MP ratio*, in contrast to VENT and SiVENT, which only limit absolute *MP* (< 17 J/min) without targeting *MP ratio* directly. This design choice allows SVP VENT to provide tighter control over *MP ratio*, and by extension *MP*, particularly in VC modes of MV, where achieving optimal *MP ratio* values appears to be more challenging without such targeted intervention. This benefit arises because in VC

Table 5
The median [interquartile range, IQR] MV parameters and patient responses of the retrospective clinical data, VENT, SiVENT, and SVP VENT protocol over the entire acquisition period. A significance threshold of $p < 0.0167$ was used after Bonferroni correction was applied.

VC MV	Retro	VENT	SiVENT	SVP VENT
V_T (mL/kg)	6.31 [5.61 – 6.74]	4.00 [4.00 – 4.00]	4.00 [4.00 – 4.00]	4 [4 – 6][a,b,c]
$\dot{V}_{MAX}$ (L/min)	60.32 [56.23 – 67.46]	50.00 [45.00 – 55.00]	50.00 [40.00 – 55.00]	25 [25 – 25][a,b,c]
RR (breaths/min)	25.21 [20.13 – 35.29]	22.00 [20.00 – 28.00]	22.00 [20.00 – 28.00]	18 [11 – 19][a,b,c]
T_{PLAT} (s)	0 [0 – 0]	0.1 [0 – 0.2]	0.1 [0 – 0.1]	0 [0 – 0][b,c]
PEEP (cmH_2O)	9.19 [6.13 – 13.72]	11.00 [6.00 – 14.00]	11.00 [6.00 – 14.00]	9.19 [6.13 – 13.72]
P_{MAX} (cmH_2O)	29.79 [26.60 – 31.74]	24.62 [23.43 – 27.21]	24.53 [23.48 – 27.55]	22.52 [21.16 – 25.85][a,b,c]
P_{PLAT} (cmH_2O)	28.09 [22.75 – 30.22]	21.75 [18.21 – 25.06]	21.75 [18.21 – 25.06]	22.07 [20.49 – 25.28][a,b,c]
MP (J/min)	28.36 [22.51 – 35.60]	12.24 [11.32 – 15.69]	12.39 [11.33 – 15.32]	8.96 [8.29 – 10.92][a,b,c]
ΔP (cmH_2O)	15.54 [13.41 – 19.96]	10.53 [9.40 – 12.83]	10.53 [9.40 – 12.83]	12.30 [10.63 – 13.60][a,b,c]
MVENT (L/min)	10.91 [9.08 – 12.64]	6.85 [5.60 – 7.48]	6.85 [5.60 – 7.48]	5.06 [5.02 – 5.14][a,b,c]
MP ratio	11.83 [8.30 – 15.21]	5.70 [4.00 – 6.25]	5.54 [3.97 – 6.13]	3.32 [2.89 – 4.74][a,b,c]
PC MV	**Retro**	**VENT**	**SiVENT**	**SVP VENT**
P_I (cmH_2O)	8.43 [8.05 – 9.81]	5.00 [5.00 – 10.00]	10.00 [5.00 – 10.00]	10 [10 – 10][a,b,c]
T_I (s)	0.98 [0.90 – 1.07]	0.80 [0.60 – 1.00]	0.60 [0.60 – 1.20]	0.80 [0.60 – 0.96][a,b]
RR (breaths/min)	17.8 [16.25 – 21.90]	25.00 [21.00 – 25.00]	25.00 [21.00 – 25.00]	23 [20 – 25][a,b,c]
RP (%)	26.60 [14.00 – 33.83]	40.00 [10.00 – 70.00]	20.00 [10.00 – 60.00]	20 [10.00– 31.25][a,b,c]
PEEP (cmH_2O)	5.38 [5.22 – 5.56]	5.00 [5.00 – 6.00]	5.00 [5.00 – 6.00]	5.38 [5.22 – 5.56][b,c]
V_T (mL/kg)	6.73 [6.17 – 7.93]	4.05 [3.99 – 4.30]	4.98 [4.72 – 5.24]	5.48 [5.05 – 6.26][a,b,c]
P_{PLAT} (cmH_2O)	13.49 [13.38 – 15.37]	12.43 [12.43 – 12.43]	12.43 [12.43 – 12.43]	10.56 [8.60 – 12.80][a,b,c]
MP (J/min)	11.92 [10.26 – 13.84]	5.73 [5.29 – 7.08]	7.73 [6.55 – 10.87]	10.74 [8.16 – 11.94][a,b,c]
ΔP (cmH_2O)	8.31 [7.95 – 9.72]	7.43 [6.43 – 7.43]	7.43 [6.43 – 7.43]	5.40 [3.43 – 7.37][a,b,c]
MVENT (L/min)	8.80 [7.61 – 10.42]	6.02 [5.56 – 6.35]	7.27 [6.18 – 8.69]	7.91 [6.57 – 9.33][a,b,c]
MP ratio	6.54 [4.37 – 7.84]	2.02 [1.61 – 4.09]	3.27 [2.31 – 4.46]	3.54 [3.14 – 4.92][a,b,c]

[a] The MV parameters and VP responses of the SVP VENT protocol are statistically different to the retrospective data.
[b] The MV parameters and VP responses of the SVP VENT protocol are statistically different to the VENT protocol.
[c] The MV parameters and VP responses of the SVP VENT protocol are statistically different to the SiVENT protocol.

modes, *MP ratio* and actual *MP* can be more effectively modulated through explicit control of tidal volume. Future protocol refinements could also adopt a more targeted optimisation of *MP* and *MP ratio* by focusing on the higher-risk subcomponents of *MP*, as described by Marini *et al.*, recognising that certain portions of *MP* within a breath contribute more significantly to lung injury than others (Marini & Rocco, 2020).

Existing research has demonstrated a correlation between prolonged exposure to *MP* exceeding 18 J/min and extended durations of invasive MV, as well as prolonged intensive care unit length of stay (Manrique et al., 2024). Thus, the implementation of the SVP VENT protocol tracking temporal trends of *MP* and *MP ratio* offers the potential to ensure these metrics are met by consistently maintaining lower *MP* and *MP ratio* levels. Therefore, the overall results show its potential for integration into clinical practice to improve patient safety, where this study justifies moving to initial clinical trials and validation of the approach.

4.2. Temporal profiles of MV inputs and patient responses

In this study, the SVP VENT protocol (Supplementary material – VENT Protocol) features a hierarchical **V-stage** for determining MV settings. In the VC protocol, V_T is first constrained to 6–8 ml/kg. If no suitable MV setting can be determined within this range, the protocol expands the V_T range to 4–8 ml/kg. This adjustment accounts for patients with higher E_{rs} values, where lower tidal volumes may be necessary to prevent barotrauma. In the PC protocol, retrospective clinical settings for the start of each intervention interval are first used to set T_I and *RP*. If the protocol fails to provide a MV setting recommendation, T_I and *RP* are then adjusted by the protocol itself to ensure appropriate ventilation. This hierarchical approach is designed to improve patient-specific adaptability while reducing computational burden.

Temporal trends of MV inputs and patient responses across the retrospective, VENT, SiVENT and SVP VENT protocols are illustrated in Fig. 3 for Patient 4 (VC cohort) and Patient 2 (PC cohort). For Patient 4 (Fig. 3a), the MV input settings recommended by the three protocols were relatively similar, except for a notable difference in $\dot{V}_{MAX}$, where the SVP VENT protocol suggested a setting approximately 15 L/min lower than the VENT and SiVENT protocols (25 L/min vs 40 L/min). Additionally, patient responses to MV including P_{MAX}, P_{PLAT}, ΔP, *MP*, *MVENT* and *MP ratio*, were significantly lower across all three protocols when compared to the retrospective data. Specifically, the *MP* and *MP ratio* achieved by the SVP VENT protocol were slightly lower than those of the VENT and SiVENT protocols, which aligns with its primary goal of minimising the *MP ratio*.

In contrast, for Patient 2 (PC cohort), there was greater temporal variation in MV input settings for the VENT and SiVENT protocols, while the SVP VENT protocol exhibited less variability. This consistency in the SVP VENT protocol could help avoid excessive changes in ventilation settings, minimising patient discomfort and stress. In terms of patient responses to MV and the safety of care choices, most measurements were within a safe range even in the retrospective data, likely due to Patient 2's relatively low E_{rs} (as depicted in Fig. 2j). However, generally, for Patient 2, all three protocols achieved lower P_{PLAT}, ΔP, *MP*, and *MP ratio* compared to the retrospective data.

Across the VC patient cohort (Table 5), the SVP VENT protocol was associated with lower P_{MAX} and *MVENT*, resulting in significantly reduced *MP* and *MP ratio*. Notably, in the PC cohort, the SVP VENT protocol favoured a lower *RR*, but a higher V_T to achieve similar *MVENT* levels. While this approach led to reductions in P_{PLAT} and ΔP, it also resulted in slightly higher *MP* and *MP ratio* values compared to the VENT and SiVENT protocol ($p < 0.0167$, Bonferroni correction applied), though still lower than the values observed in the retrospective data. Importantly, the median [IQR] *MP* of 10.74 [8.16–11.94] J/min remained below the clinically significant threshold of 12 J/min.

In this study, a recruitment and distension basis function respiratory model (Eq. (1)), which effectively simplifies to a single-compartment lung model, SCM (Eq. (2)) was used to determine

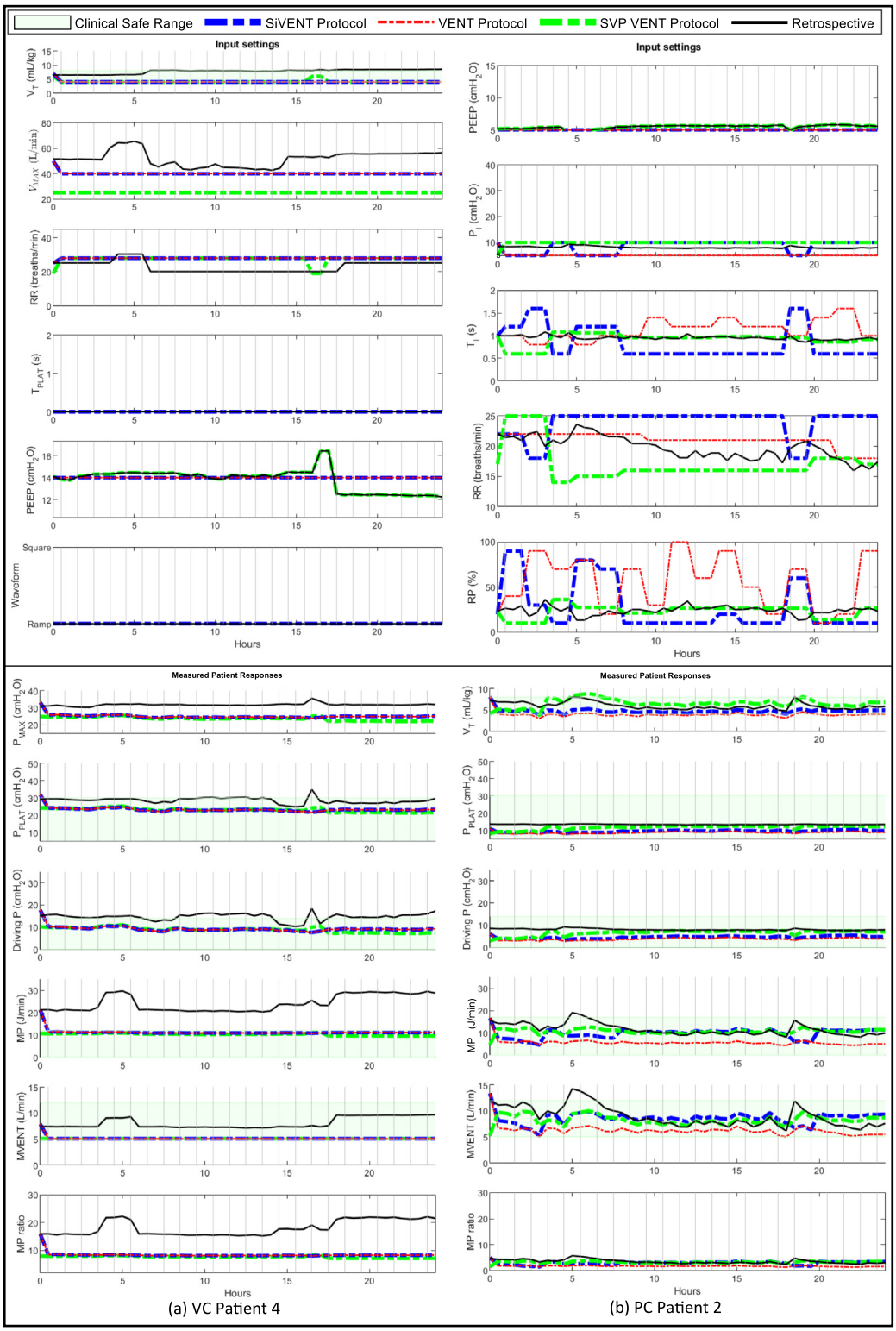

Fig. 3. The MV input settings and patient responses for the retrospective clinical data, VENT protocol, SiVENT protocol and SVP VENT protocol over the first 24 h of MV for (a) Patient 4 (VC cohort) and (b) Patient 2 (PC cohort).

patient-specific trends of respiratory mechanics and MV parameters. The SCM, which has been developed and validated over time, provides an optimal balance between complexity and clinical utility, making it particularly suitable for real-time, bedside personalisation (Warnaar et al., 2023). More complex models can also account for pulmonary gas exchange and respiratory control, and may offer higher precision, but require additional measuring modalities. In contrast, the SCM integrates seamlessly into existing clinical workflows without necessitating extensive modifications (Warnaar et al., 2023).

The SCM relies solely on airway pressure and flow measurements, which are readily obtainable from standard ventilators, making it a more practical and accessible tool for real-time patient-specific adjustments in mechanical ventilation. It is also

important to note the SVP VENT protocol is generalisable and can evolve over time, incorporating different models and new insights on safe ventilator setting ranges as they emerge from ongoing clinical studies. Thus, this model is flexible enough to ensure the approach remains aligned with the latest evidence-based practices concerning mechanical power.

In this study, retrospective *PEEP* values are used throughout the SVP VENT protocol, as the stochastic model and stochastic VPs assume fluctuations in patient E_{rs} occur independently of *PEEP* changes. Essentially, this model attributes shifts in respiratory system condition solely to disease progression and/or other non-*PEEP* related factors. Thus, in clinical practice, the protocol could provide MV setting recommendations based on the *PEEP* levels determined by clinicians, integrating easily with standard *PEEP* adjustments and manoeuvres. Equally, it is flexible enough to react to any changes in E_{rs}, such as in cases of E_{rs}-guided *PEEP* titration (Amato et al., 2015; Chiew, Chase, Shaw, Sundaresan, & Desaive, 2011b; Goligher et al., 2021; Morton et al., 2019).

4.3. CDSS intervention intervals

The findings of this study demonstrate the ability of the SVP VENT protocol in extending the allowable intervention interval to 3 h by incorporating stochastic VP E_{rs} profiles, resulting in up to a 78% reduction in number of intervention intervals. While longer prediction intervals are theoretically possible using stochastic models such as in the SiVENT protocol, they often suffer from wide percentile bounds when data is limited (Ang, Chiew et al., 2023; Ang, Chiew, Wang, et al., 2022; Lee et al., 2021). This greater width can lead to E_{rs} predictions too broad to be clinically useful, as they fail to provide precise guidance for ventilation adjustments.

In contrast, the SVP VENT protocol overcomes this limitation by utilising stochastic VP profiles offering a more reliable prediction window for E_{rs} changes up to 3 h in advance. This feature allows clinicians to adjust MV settings based on anticipated patient-specific trends, rather than reactive adjustments to current conditions. By providing a longer and more accurate intervention interval, SVP VENT has the potential to reduce clinician workload of setting MV while maintaining patient safety and optimising patient responses to MV. It is essentially a dose-to-risk approach where the range of probabilities can also be modified for different protocol approaches (Chase, Shaw, Preiser, Knopp, & Desaive, 2021). Such a dose-to-risk form of care is already used in ICU and NICU glycaemic control (Chase, Benyo, & Desaive, 2019; Le Compte et al., 2010; Stewart et al., 2016). Importantly, the protocol is not intended to totally replace clinical judgement, but to complement it—acting as a supportive tool and safeguard, particularly in settings where clinical experience or specialist knowledge may be limited.

The retrospective E_{rs} profile, along with the predicted 5th–95th percentile ranges of E_{rs} for the SVP VENT protocol, is shown in Fig. 2 for all patients of the VC and PC cohort. These profiles illustrate the variability in retrospective E_{rs} profiles, resulting in variances of recommended MV settings and resulting patient responses between the different protocols. From Fig. 2, width of the SVP VENT predicted 5th–95th percentile range of E_{rs} widens with increasing E_{rs} values, suggesting the protocol accounts for the greater potential temporal variability in respiratory system condition among patients with higher E_{rs}.

Patient 4 (VC) and Patient 2 (PC) were selected to represent patients from different MV modes and varying ranges of E_{rs} (Fig. 3), with Patient 2 exhibiting a lower E_{rs} range. At hour 5 of Patient 4's (VC) ventilation, the SVP VENT protocol opted for a shorter intervention interval (as seen in Fig. 2d). This adjustment likely reflects the protocol's responsiveness to the relatively larger change in patient E_{rs} of $\sim$10 cmH_2O/L. This adaptability allows the SVP VENT to maintain safe MV settings 3 h later, while also accommodating variable intervention intervals based on patient risk, particularly in response to more drastic fluctuations in E_{rs}. Shorter intervention intervals are also selected by the SVP VENT protocol at a time of 15.5 and 16.5 h due to a change in *PEEP* of more than 1 cmH_2O, as illustrated in Fig. 3a. Similarly, for Patient 2 in the PC cohort (Fig. 2l), the SVP VENT protocol selected shorter 30 min intervention intervals to address elevated E_{rs} levels and the increased potential for temporal variability in respiratory mechanics.

4.4. Limitations

In terms of limitations, the SVP VENT protocol was validated using retrospective data from a single-centre patient cohort of only 12 patients on controlled ventilator modes, highlighting the need for broader validation across multicentre settings to establish its efficacy. While the SVP VENT showed effective adherence to individual safety metrics, achieving all adherence over extended intervention intervals remains challenging due to the potential trade-offs between safety metrics, particularly for PC modes of ventilation. Future studies could explore further optimisation of the protocol, including its performance across different patient populations and settings. A key direction for advancement involves refining the balance between minimising *MP* ratio and driving pressure, while ensuring safe ventilation delivery. Achieving this balance may benefit from the integration of more comprehensive physiological models, including more complex respiratory models as well as those describing pulmonary gas exchange, haemodynamics, and metabolic demand (Ma, Fujioka, Halpern, Bates, & Gaver, 2023; Miserocchi et al., 2024; von Platen et al., 2020; Warnaar et al., 2023). Such extensions would better capture the multifactorial goals of MV in the intensive care environment, where oxygenation, carbon dioxide clearance, and systemic perfusion are intricately linked. This multidimensional framework would offer a more holistic, physiology-driven approach to MV management—one that accounts not only for mechanical loading of the lungs, but also for the broader physiological context of critically ill patients. However, it is important to emphasise that this study represents a proof-of-concept framework focused exclusively on respiratory mechanics, and demonstrating how stochastic virtual patients, respiratory mechanics, and clinical safety thresholds can be used to personalise MV. While the current protocol demonstrates the feasibility of integrating stochastic virtual patients into model-based decision support for MV, the intent of this study was not to provide an exhaustive physiological representation, but rather to establish and validate a tractable, modular framework upon which more complex physiological models can be integrated. This layered development approach facilitates progressive refinement—starting from mechanical safety and progressing toward a holistic optimisation of ventilatory care tailored to the individual patient.

Moreover, the maximum intervention interval of the SVP VENT protocol was restricted to 3 h in this preliminary investigation. Future studies should examine the effects of extending these intervals on patient safety and clinical outcomes during MV. Extending the interval duration may help ascertain whether longer, less frequent adjustments can be implemented without compromising safety, akin to strategies implemented in glycaemic control protocols (Uyttendaele, Knopp, Shaw, Desaive, & Chase, 2020). It may also be possible to augment the stochastic model for greater precision by including more temporal values of E_{rs}, which was also done in glycaemic control protocols, where it was found stable patients tended to remain stable and have narrower intervals (Davidson et al., 2019; Uyttendaele et al., 2019). These

outcomes and approaches would also enable an assessment of the protocol's adaptability over prolonged monitoring periods, potentially further alleviating the workload on clinical personnel.

A key limitation of this study is the assumption that changes in E_{rs} are independent of *PEEP* variations. While this assumption is key to developing the E_{rs} stochastic model, it does not fully reflect the complex physiological relationship between *PEEP* and lung mechanics. In clinical settings, *PEEP* adjustments can influence lung recruitment, overdistension, and compliance, thereby affecting E_{rs} (Cove, Pinsky, & Marini, 2022; Gattinoni & Marini, 2022). However, in this study, retrospective *PEEP* values were used consistently across all protocols to maintain comparability with the retrospective trial, minimising the risk of bias introduced by varying *PEEP* strategies. Additionally, intervention intervals were adjusted to exclude periods of significant *PEEP* changes (greater than ± 1 cmH_2O), further isolating the model's performance in predicting E_{rs} trends. Future iterations of the protocol could address this limitation by further extending the stochastic model to account for dynamic E_{rs}-*PEEP* interactions using adaptive modelling techniques (Kim, Knopp, Dixon, & Chase, 2020; Morton et al., 2019, 2020; Sun et al., 2022, 2024; Zhou et al., 2021).

An important factor in the clinical implementation of the SVP VENT protocol is its computational demands, particularly the requirement for 200,000 SVP simulations at every intervention interval. Given the limited processing capabilities of bedside monitoring and ventilator systems, real-time feasibility may be constrained. However, offloading computations to cloud-based systems or dedicated hardware (e.g., edge computing devices) could mitigate this burden. Additionally, algorithmic optimisations such as presimulating the SVP profiles and its corresponding MV protocol suggested settings could further reduce computational overhead. As clinical computing infrastructure continues to evolve, these advancements may enable seamless integration of SVP VENT into ICU workflows. Future work should focus on real-time deployment strategies and computational optimisations to facilitate bedside implementation without compromising protocol effectiveness.

5. Conclusions

The protocol's effectiveness maintains the *MP* below the critical threshold of 12 J/min across the VC cohort and achieves adherence exceeding 67% across all individual safety metrics in the PC cohort. This result underscores the protocol's potential for enhancing patient safety. However, broader validation across multi-centre settings and further optimisation, particularly in addressing trade-offs between safety metrics, are necessary to refine and extend its applicability. The findings of this virtual trial support the need for initial clinical trials to evaluate the protocol's impact on clinical workload and patient safety adaptability over prolonged monitoring periods, facilitating its incorporation into standard clinical procedures.

Further, this study demonstrates the potential of the SVP VENT protocol to enhance MV management by extending the allowable intervention interval to 3 h, while effectively maintaining patient safety. By incorporating stochastic VP E_{rs} profiles, the SVP VENT protocol anticipates patient-specific trends, allowing for proactive adjustments to MV settings rather than reactive responses to immediate conditions. This capability reduces clinician workload and optimises patient responses to MV, as shown by the protocol's success in achieving lower median *MP* and *MP ratio* values compared to traditional and alternative protocols, especially in VC ventilation modes. Overall, the SVP VENT protocol represents a significant step forward in optimising the delivery of MV treatment by maintaining patient safety, reducing *MP* and *MP ratio*, and extending intervention intervals, offering the potential for safer and more efficient ventilation management in critical care settings.

CRediT authorship contribution statement

Christopher Yew Shuen Ang: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Yeong Shiong Chiew:** Writing – review & editing, Supervision, Resources, Conceptualization. **Xin Wang:** Writing – review & editing, Supervision. **Ean Hin Ooi:** Writing – review & editing, Supervision. **Mohd Basri Mat Nor:** Writing – review & editing, Supervision. **Matthew E. Cove:** Writing – review & editing, Data curation. **Cong Zhou:** Writing – review & editing. **J. Geoffrey Chase:** Writing – review & editing, Supervision.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.ifacsc.2025.100334.

Data availability

Data will be made available on request.

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