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Safe Mechanical Ventilation Treatment Settings for Respiratory Failure Patients

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Abstract: Mechanical ventilation (MV) is a complex support tool for respiratory failure patients. However, MV is easily mismanaged, and the common practice today relies on clinician's experience and intuition. Due to this subjectivity, along with the complex task of managing multiple interdependent MV settings, setting patient-specific optimal MV is a difficult task. This research proposes a model-based method to manage the wide range of possible MV settings while taking patient-specific conditions into consideration. This method makes use of a "VENT" protocol to aid clinicians' decision makings. The model-based method is integrated recommendations based on landmark studies and established guidelines to guide MV settings. Forward simulation results show acceptable results when recreating patient breath waveform from retrospective data. Protocol validation with retrospective patient data shows that actual clinically implemented settings are among the protocol recommendations.

Keywords: *Respiratory failure, Mechanical ventilation, Respiratory mechanics, and Decision making.*

1. INTRODUCTION

Mechanical ventilation (MV) is given to patients who are unable to sustain the minimum blood oxygenation required by the body (Slutsky et al., 2005). These intensive care unit (ICU) patients suffer from respiratory failure, and require artificial breathing support to recover. Modern ventilators enable a range of pressure and volume control to deliver support to the patient (Poor, 2018). However, setting MV parameters is a challenging task with many trade-offs, typically done by experienced clinicians.

Methods of setting MV parameter vary greatly due to inter- and intra-patient variability, clinician experience, and/or clinical evidence-based guidelines based (The Acute Respiratory Distress Syndrome Network, 2000, Brower et al., 2004, Meade et al., 2008, Briel et al., 2010, Amato et al., 2015) (Major et al., 2018). Currently, patient response guides changes in care, leading to a trial and error approach (Esquinas et al., 2018). Several attempts have been made to standardise MV settings, such as the ARDSNet protocol PEEP-FiO2 tables (The Acute Respiratory Distress Syndrome Network, 2000), but cannot account for patient-specific variability, and are less effective (Chase et al., 2014, Fernandez et al., 2015). Suboptimal MV is thus common and can lead to ventilator induced lung injury (VILI) (Alp and Voss, 2006), and increases mortality in acute respiratory distress syndrome (ARDS) to 40-70% (Ranieri et al., 2012).

This research presents a model-based method to provide effective, safe, and patient-specific MV settings. Respiratory mechanics model is used with patient-specific respiratory elastance, airway resistance, and ideal body weight to simulate sets of ventilation settings which can be tested in a virtual trial (Chase et al., 2018). Prior studies have proposed similar computer-based methods to select MV parameters, including using AI and fuzzy logic, targeting arterial CO_2, neural networks, full closed loop automation, and Bayesian forecasting (Lozano-Zahonero et al., 2011, Wysocki et al., 2014, Akbulut et al.). However, these works utilise clinician intuition or sliding scale as the basis of their support systems instead of improving on current standard through incorporating established target ranges (The Acute Respiratory Distress Syndrome Network, 2000, Fan et al., 2017), and there is limited work able to be implemented as an open-source support system to be quickly adapted in a resource-limited setting, such as in the recent COVID-19 pandemic. There is thus a major need to provide an open source, easily adaptable and an economically viable technology solution to this problem.

2. METHODOLOGY

2.1 Model-based Method MV Settings

The model-based MV setting ***VENT*** protocol is conceptually based on: A) **V**irtual-ventilation; B) **E**stimate and eliminate; C) **N**arrowing objectives; and D) **T**abulation. It follows similar concept proposed by Arunachalam et al. (2020).

*A. Virtual-Ventilation (**V** - Stage)*

The first stage of this protocol simulates a virtual patient using a validated respiratory mechanics model (Bates and Suki, 2008, Morton et al., 2019). A single compartment model simulates airway pressure and flow during MV:

$$P_{aw}(t) = E_{rs} \times V(t) + R_{rs} \times Q(t) + P_0 \quad (1)$$

Where patient-specific respiratory elastance (E_{rs}) and resistance (R_{rs}) model airway pressure, $P_{aw}(t)$, tidal volume $V(t)$ and flow rate $Q(t)$ with P_0, a constant offset pressure. *Or* positive end-expiratory pressure (*PEEP*) if there is no auto-*PEEP* (van Drunen et al., 2013). Based on the desired MV

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mode, either volume control (VC) or pressure control (PC), different MV waveforms can be simulated using Eq. (1).

During VC, clinicians set a desired volume and flow, which determines the resulting airway pressure. In PC, the reverse is true. (Major et al., 2018). In VC, the clinician selects target *V(t), Q(t),* and *PEEP,* as well as end of inspiratory time, type of waveform, and breathing frequency. Varying each input parameter results in a different patient response. The results of VC include $P_{aw}(t)$ which consists of plateau pressure (P_{pl}), peak inspiratory pressure (*PIP*) and inspiratory pressure (ΔP). Minute ventilation (*VE*) and inspiration to expiration (*IE*) ratio are computed and finally these combinations of input and output settings are stored.

Conversely, PC mode requires selection of $P_{aw}(t)$ comprising ΔP, *PEEP* and rise percent. Breathing frequency is also pre-set along with controlling either one of three selectable parameters to vary the remaining two dependent variables. At any given selection, either inspiration time, expiration time or I:E ratio can be set. The resulting parameters are tidal volume (V_t), maximum flow rate, minute ventilation and the two remaining time parameters not selected as a control. Similar to VC, a simulated waveform is first generated. To solve for tidal volume, we make use of the relationship of tidal volume and flow rate based on Eq. (1) and solve using Picard iterations. Fig. 1 summarises both the virtual MV patient simulation process for PC and VC mode settings.

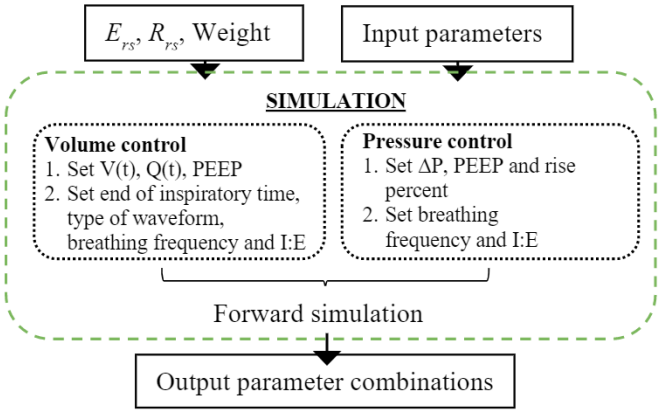

Fig. 1. Implementation of volume control and pressure control in virtual MV patient simulation.

*B. Estimation and Elimination (**E** - Stage)*

From V - stage, various ventilation pressure, flow and volume waveform were simulated using a full range of possible MV setting combination. In this stage, these settings and results are eliminated based on clinical guidelines using estimated airway pressure, flow, and volume. This filtering eliminates unsafe settings. These recommended ventilator settings are summarised in Table 1.

Plateau pressure is static pressure at the end of an inspiratory pause. Recommendations show it should be kept below 30 cmH_2O to avoid barotrauma (Fan et al., 2017). **Plateau time** (t_{pl}) is the length of time the plateau pressure is held.

PEEP is the base pressure at the end of expiration to maintain lung recruitment. However, there is inconclusive evidence for optimal PEEP selection. Current methods make use of either generalised PEEP-FiO2 tables, inflection points, minimising elastance, or general intuition (Pintado et al., 2013, Chiew et al., 2015, Goligher et al., 2021). Generally, PEEP values can vary between 5 – 25 cmH_2O (Gattinoni et al., 2017).

Tidal volume is the amount of air moving into and out of the lungs, normalised to body weight. The recommended range established by the ARDSNet trial is 4 – 8 ml/kg (The Acute Respiratory Distress Syndrome Network, 2000).

I:E ratio is the ratio of inspiration to expiration time and is usually adjusted based on clinician preference with the goal of ensuring adequate ventilation. I:E ratio is closely tied to other time-based settings, such as flow rate, tidal volume, respiratory rate, and minute ventilation. Landmark trials commonly set allowable ranges between 1:1 to 1:3 (The Acute Respiratory Distress Syndrome Network, 2000, Brower et al., 2004, Meade et al., 2008).

Respiratory rate in breaths per minute is commonly 16 – 20, but can vary greatly. While Akoumianaki et al. (2019) highlights possible risks of non-optimal settings, respiratory rates often are in the range from the ARDSNet trial of 6 – 35 (The Acute Respiratory Distress Syndrome Network, 2000).

Minute ventilation is the volume of air displaced into and out of the lungs each minute. It is a product of tidal volume and respiratory rate. Common ventilation goals are between 8 – 10 L/min for adults (Major et al., 2018).

Flow rate is the rate of air entering the lungs to achieve the desired tidal volume. It is generally set between 40–100 L/min. A target at higher levels for patients with COPD is generally administered whereas a maximum value of 60 L/min is typical for ARDS patients (Hasan, 2010).

*C. Narrowing Objectives (**N** - Stage)*

After eliminating harmful sets of MV settings, the remaining settings can be further narrowed based on a clinically desired set of objectives. The specific objectives used in VENT either minimise or maximise ventilator parameters such as driving pressure, minute ventilation, PEEP, Flow rate, I:E ratio, or tidal volume. For example, minimising driving pressure is associated with reduced mortality (Amato et al., 2015, Goligher et al., 2021) Thus, clinicians can target further specific objectives to fine tune ventilator parameters.

*D. Tabulation (**T** - Stage)*

The results are displayed to the clinician in a simple table, showing the remaining possible MV setting combinations. Clinicians can decide which is the best.

Table 1. Recommendation based on literature

Settings	*Range*
Plateau pressure (cmH_2O)	< 30
PEEP (cmH_2O)	Max (P_o) (5 – 25)
Tidal volume (V_t) (mL/Kg)	4 - 8
Minute ventilation (L/min)	8 - 10
I:E	1:1 - 1:5
Max flow rate (L/min)	40 - 100
Respiratory rate (Breath/min)	6 - 35

Table 2. Combination of MV parameter ranges, resolution, and combinations of each setting

	Setting	Full Range	Resolution: Range		No. of Combinations	
			Ventilator	*Adjusted*	*Ventilator*	*Adjusted*
GENERAL	Predicted body weight (kg)	25 – 150	1.0: 25 – 150 [a]	1: 30 – 150	126	121
	Respiratory rate (breath/min)	1.0 – 200	0.1: 1 – <10 1: 10 – 100 [a]	1: 1 – 35	91 + 90	35
	PEEP (cmH_2O)	0 – 45	0.5: 0 – 19.5 1: 20 – 45	1: 0 – 45	40 + 26	46
PRESSURE CONTROL (PC)	I:E ratio	1:299 to 149:1	1: 1:1 – 1:100 [a]	-	N/A[b]	
	Rise time (%)	1 – 100	1: 1 – 100	10: 10 – 100	100	10
	Inspiratory pressure (cmH_2O)	5 – 90 *	1: 5 – 90	5	86	18
	Expiration time (s)	> 0.2	0.01		N/A[b]	
	Inspiration time (s)	0.2 – 8.0	0.01: 0.2 – 8.0	0.2	781	40
VOLUME CONTROL (VC)	Tidal volume (mL)	25 – 2500	1: 25 – 100 [a] 5: 100 – 395 10: 400 – 2500	Changed to tidal volume per body weight (mL/kg) 1: 4 – 8	76 + 60 + 210	5
	Max flow rate (L/min)	3 – 150	0.1: 3 – 20 1: > 20 – 150	5: 5 – 150	198 + 130	30
	Plateau time (s)	0 – 2	0.1	0.1	21	21
	Waveform	Square/Ramp	-	-	2	2
TOTAL NUMBER OF COMBINATIONS PER PATIENT			Ventilator PC = ~ 1.01×10^{13} Ventilator VC = ~ 7.17×10^{12}		Adjusted PC = ~ 1.40×10^{9} Adjusted VC = ~ 1.23×10^{9}	

[a]Adjusted range to include adult patient only.

[b]N/A is based on arbitrarily selecting inspiration time as the controlled variable, varying expiration time to obtain a resulting I:E.

2.2 VENT Protocol Validation

To demonstrate the functionality of the VENT protocol, a case study was conducted and simulated using ventilator settings from a Puritan Bennett 980 ventilator (PB980) as shown in Table 2. Each setting resolution is set to follow the resolution listed in the PB980 operator's manual. The resolution of the MV settings were adjusted in the VENT protocol to reduce the total amount of simulation iterations required to better manage computational resources with no loss of generality.

Validation is used to show the remaining recommendations contains a setting a clinician would indeed select for clinical use. To validate the VENT protocol, recommendations from the VENT protocol are compared against MV settings used for a cohort of ICU patients undergoing MV. The patient airway pressure-flow data comes from a cohort of ICU patients from (Chiew et al., 2018) as part of an observational study under informed consent. Data from 7 of 24 patients were used in this study. The use of this data is approved by the research ethics committee (Ethics Approval Number IREC666).

Patient-specific information such as MV settings and measured outcomes are extracted from breath-by-breath pressure-flow data. These settings are then averaged into hourly settings, which are then compared to VENT protocol recommendations. For validation, MV settings from a single hour from each patient are used to validate the VENT protocol.

The validation procedure is defined:

1. Process patient airway data to extract patient-specific information such as E_{rs} and R_{rs}.
2. Input patient-specific information E_{rs}, R_{rs} and weight along with recommended settings into the VENT protocol.
3. Determine if the remaining setting combinations recommended by the VENT protocol contains the clinically implemented MV settings.

Hence, given a Malaysian cohort, recommendations input into the VENT protocol will be based on Malaysian ICU guidelines (Cawangan Kualiti Penjagaan Kesihatan Bahagian Perkembangan Perubatan Kementerian Kesihatan Malaysia et al., 2012), which are summarised in Table 3. All development, simulation and validation process were performed using MATLAB (Natick, MA, USA).

Table 3. Recommendations based on Malaysian guideline

Settings	*Range*
Plateau pressure (cmH_2O)	< 30
Peak pressure (cmH_2O)	< 45
Tidal volume (V_t) (mL/Kg)	4 – 8
Respiratory rate (Breath/min)	6 – 35

3. RESULTS

As shown in Table 2, the possible MV setting combinations number more than 1.01×10^{13} for PC mode and 7.17×10^{12} for VC mode. With the resolution reduction during simulation, the possible MV settings were still approximately 1.40×10^{9} for PC and 1.23×10^{9} for VC. Clinicians are required to select just one setting from this myriad of combinations. This large number highlights the challenges of selecting patient-specific optimal MV setting if there is no objective, patient-specific guide (Chase et al., 2014). Fig. 2 shows sample of airway pressure, flow and volume waveforms for 3 patients and validated with the clinical findings. The waveforms were generated using the finalised setting output using VENT protocol. Note that only the inspiration phase is analysed as it provides all desired measure outcomes (P_{max}, V_t, etc) whereas expiration phase is a passive process, and it does not affect the inspiration phase and we did not use any information for this research.

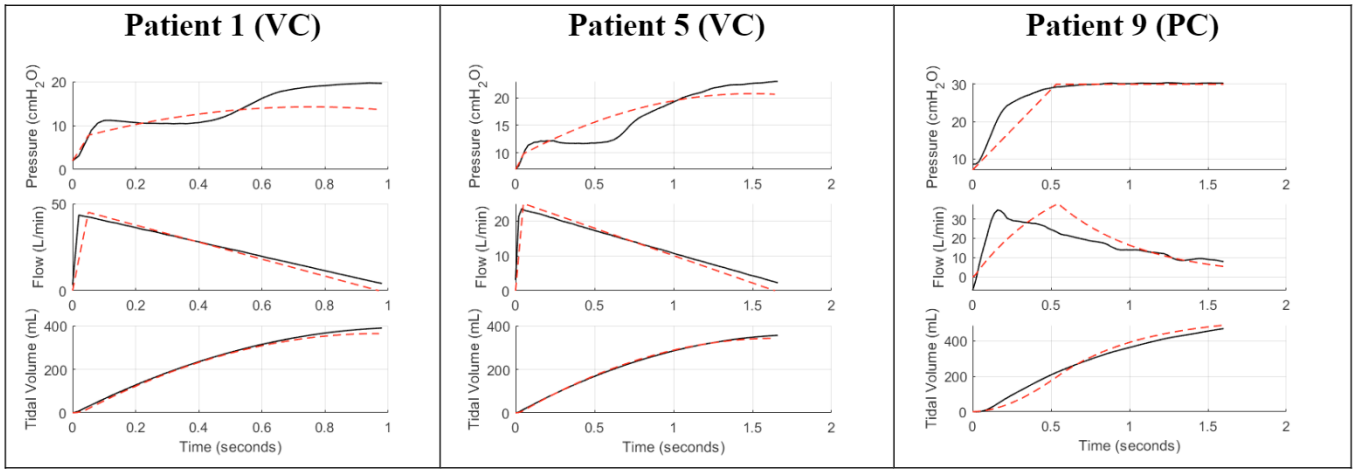

Fig. 2. Comparison between actual measured breath (black solid line) vs simulated breath (red dotted line)

Table 4. Validation of VENT protocol with clinically selected settings

Patient No.	Ventilation Mode	Weight (kg)	E_{rs} (cmH_2O/L)	R_{rs} ($cmH_2O/L/s$)	Number of possible settings	Number of recommendations by VENT	Reduction in combinations (%)	Clinical Setting Within VENT recommendations
1	SIMV/VC	52.0	32.0	6.9	8,694,000	3,181,129	63.4	Yes
2	SIMV/VC	70.2	72.7	2.1	8,694,000	462,460	94.7	Yes
3	SIMV/PC	65.0	42.8	23.2	9,936,000	198,748	98.0	No
4	SIMV/VC	81.0	28.9	6.7	8,694,000	2,342,607	73.1	Yes
5	SIMV/VC	38.0	39.9	5.8	8,694,000	3,409,770	60.8	No
9	SIMV/PC	53.7	42.5	15	9,936,000	201,205	98.0	Yes
23	SIMV/PC	60.0	22.7	14.8	9,936,000	164,469	98.3	Yes

Table 5. Number of VENT recommendations after implementing N-stage

Patient No.	1	2	3	4	5	9	23
Number of recommendations	32,408	31,189	30	30,525	33,353	30	30
Reduction in combinations (%)	99.6	99.6	99.9	99.6	99.6	99.9	99.9

Validations results are presented in Table 4, where the N-stage was not implemented in the validation for a more conservative validation. However, Table 5 shows the possible number of recommendations if the N-stage was implemented with the goals of minimising driving pressure and maximising PEEP.

4. DISCUSSION

As can be observed in Fig. 2, the measured and simulated waveforms are more similar for the input signal. For example, the flow and volume are more similar for Patients 1 and 5 under VC, while the pressure waveform is more similar for Patient 9 under PC. The non-uniformity and fluctuations in the actual measured patient breath waveforms arise from patient effort and are therefore difficult to consider. This issue is more obvious in the pressure waveforms for Patients 1 and 5, where the slight trough in the middle of inspiration indicates patient effort. Note the waveforms only show inspiration.

These non-uniformity and fluctuations in airway waveforms may also be problematic for the application of model-based method MV parameters settings. In particular, patient effort may cause inaccurate patient-specific respiratory mechanics estimation. Respiratory mechanics models used for identifying breath-to-breath respiratory parameters need to capture patient breathing mechanics at any time in different modes of ventilation (Kretschmer et al., 2017), such as when the patient shows spontaneous breathing effort or during asynchrony events (Major et al., 2016, Redmond et al., 2019).

With regards to validation, 5 of 7 clinically implemented settings were among the VENT recommendations. Thus, for these five patient settings, the VENT protocol recommended settings a clinician felt confident enough to set for a patient. As for the remaining two patients, their initial patient settings were not within the recommendations provided by VENT. For Patient 3, the initial settings provided by the clinician caused measured outcomes of V_t below 4 ml/kg and P_{pl} above 30 cmH_2O. The VENT protocol was able to predict this outcome via simulation and this setting was not among its recommendations, as it is outside clinical guidelines. Thus, this outcome does validate the VENT protocol, but shows how clinical choices can be outside accepted clinical guidelines.

The same analysis applies to Patient 5, where the initial settings caused a V_t above 8 ml/kg. Hence, not only was the VENT protocol able to provide recommendations including clinically chosen settings, it also avoided recommending settings outside of recommended MV ranges.

The VENT protocol was also able to reduce the enormous possible setting combinations by at least 60.8% and at most 98.3% for these seven patients, indicating how it can assist in selecting patient settings. If the N-stage was implemented with narrowing objectives of minimum driving pressure and

maximum PEEP, the number of VENT recommendations can be further reduced to a median of 30,525 [30 – 32,103] combinations, showing a possible percentage reduction of 99.6% [99.6 – 99.9]. Although significantly reduced, the remaining number of available recommendations is understandably overwhelming, as shown in Table 5. However, this issue could possibly be overcome by better displaying the possible options in the T stage. For example, presenting that recommended PEEP levels are from 5 – 15 is much easier to read compared to presenting every single setting of PEEP in a table. Equally, many recommendations are "nearby" and effectively offer similar outcomes, so the number could be reduced by grouping, as well. To further reduce combinations, further objectives could be included, such as targets for minute ventilation and maximum flow rate. These targets would need to be set by experienced clinicians as optimal targets for these parameters and others have not been established and therefore cannot be included in this protocol.

Due to this study taking a static-based approach, the following protocol can only be applicable in the initial settings during intubation. Therefore, it is suggested optimal settings are chosen for a frame of time, where an improving lung condition with varying R_{rs} and E_{rs} requires additional intervention. Future work can be implemented in a real-time monitoring system (Szlavecz et al., 2014, Ng et al., 2020, Ng et al., 2021) to incorporate a dynamic and time-varying lung elastance into the protocol for continual monitoring. In addition, the use of this method is required for virtual trials and actual clinical testing for further validation. A condition specific recommendation can be employed and should include other settings such as FiO_2. In addition, with more powerful computing tools, ventilator settings and corresponding resolutions need not be increased in step size to consider all possible settings.

5. CONCLUSIONS

The proposed VENT protocol operates quickly and is suggested to be able to operate in various resource dependent settings. The model-based method provides a guide to better select MV settings which are better designed for each patient. In addition to relieving the mental load of attempting trial and error techniques, VENT protocol potentially saves the patient from experiencing possibly detrimental iterations from those trials. A proposed setting can be first tested before administering on a patient, where safety and ventilation performance can be gauged based on specific physiological data. It shows both experienced and less experienced clinicians can benefit from the proposed system.

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