

Virtual Mechanical Ventilation Protocol – A Model-based Method To determine MV Settings

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Abstract: Intensive care mechanical ventilation (MV) therapy is a lifesaving intervention for a patient with respiratory failure. MV supports patients breathing by maintaining positive airway pressure and airflow to the lung. However, there is currently little clinical consensus protocol to set the best MV setting. Hence, it is important to provide an objective and patient-specific MV settings to support patient recovery. This study presents a model-based method to find optimal MV settings using clinical bedside data. A mathematical model of the respiratory system is first used to estimate patient-specific respiratory mechanics. These mechanics are then incorporated with significant clinical findings from the literature to simulate a series of MV settings. The simulation of MV settings is performed using the single compartment lung model using the MATLAB software. From this series of simulated MV settings, optimal MV settings can be determined objectively by the clinician. This model-based method potentially provides decision support for the clinician to set optimal MV settings.

Keywords: Model-based Methods, Respiratory Mechanics, Mechanical Ventilation Settings

1. INTRODUCTION

Setting mechanical ventilation (MV) treatment for respiratory failure patients is a challenging task. In particular, it requires an in-depth assessment of patient-specific physiological conditions and their cause-and-effect relationships with the MV settings. It is often only performed by trained clinicians due to elaborated MV setting. Consequently, clinicians adjust the ventilator setting manually based on their intuition and clinical experience (Chase et al., 2014). In the past decades, numerous studies were researching into MV setting recommendations. The ARDS network study in 2000, recommended the low tidal volume to improve patients outcomes (The Acute Respiratory Distress Syndrome Network, 2000). The effect of positive end-expiratory pressure (PEEP) is also investigated in-detail, and it has been advocated to maintain PEEP at a higher level to maintain recruitment, while not inducing barotrauma (Lucangelo et al, 2008). These patient-specific settings involve multiple controls of ventilation variables, and for most of the settings, they have a coupled effect towards patients response and outcome. Hence, there is a need to provide a standardised guideline to set MV.

Computer-based control of ventilator parameter setting has already been proposed by several researchers. Lozano et al. introduced fuzzy logic to achieve desired ventilator status by controlling arterial CO₂ partial pressure (Lozano-Zahonero et al., 2010). Burns et al. studied extensively about the application of advance closed loop systems to gradually withdraw ventilator from patient to reduce the duration of MV (Burns et al., 2008). Wysocki et al. re-examined terms such as decision support, computerised protocol and closed-loop systems to make ventilation therapy safer and more efficient (Wysocki et al., 2013). However, the available methods are currently

limited to specific type and ventilator models. Similarly, Wysocki et al. study is patented to IntelliVent™ which is a product of Hamilton Medical. While these ventilators are able to show potential in guiding better therapy, they may not be accessible for some resource limited clinical environment. Thus, an open-source, generalised MV selection guiding method will be beneficial for resource limited environment in improving MV care.

Generally, intensive care clinicians are capable of selecting general mechanical ventilator settings as per their training and experience. The proposed method is a supporting tool for the general practitioners or nurses to provide recommendation of MV settings objectively similar to a trained specialist. This method may potentially help to automate MV setting determination which may reduce clinical burden and resources. In this study, we present a model-based method to deduce patient-specific optimal MV settings from a myriad of possible settings. In this method, a set of virtual MV protocols can be simulated by integrating literature findings into the patient's respiratory mechanics model. The method first estimates the patient-specific respiratory mechanics using a clinically validated single compartment lung model. The estimated respiratory mechanics are then used to simulate possible MV settings, and finally filtered down to settings that meet literature requirements.

2. METHOD

2.1 Mechanical ventilator settings based on literature recommendations

The virtual MV protocol developed in this study is a static approach and designed to incorporate patient conditions and literature findings. There are several notable literatures that

provided recommendation on MV settings. The outcomes from the literatures can be translated into MV targets to maximise patient outcomes and prevent any forms of injury.

- A. *Plateau pressure* (P_{plat}) is the airway pressure measured during the end of inspiratory pause in volume control modes. This pressure is lower than peak airway pressure, is a measure of static pressure in the lung or alveoli pressure. MV is set where P_{plat} is less than 35 cmH₂O to avoid pressure-induced lung injury, barotrauma (Gattinoni et al., 2006).
- B. *Driving pressure* (ΔP) is the pressure difference added above PEEP to P_{plat} . Amato et al. published a meta-analysis, suggesting that controlling ΔP may be more important compared to other MV parameters (Amato et al., 2015). Higher ΔP during MV is associated with increased mortality (Aoyama et al., 2018). Thus, ΔP is recommended to be as low as possible.
- C. *Positive end-expiratory pressure* (PEEP) is a setting of elevated airway pressure at the end of expiration. Titrating optimal PEEP is often a topic of debate, with some advocating higher levels, and some lower levels. It can be set at a level where minimum elastance occur during PEEP titration practice. The recommended range is 5 to 25cmH₂O (Gattinoni et al., 2017).
- D. *Tidal volume* (V_t) is the amount of air entering and exiting the lungs during each MV breath. Higher tidal volume can assist with the removal of carbon dioxide from the lung in patients. However, excessive volumes can also overinflate and stretch lung tissue causing injury. V_t is usually set at 6-8 mL/kg using predicted body weight (Fan et al., 2018).
- E. *Minute ventilation*: In addition to V_t , maintaining a sufficient level of *minute ventilation* 5-8 l/min is crucial for patient care. Aside from the setting of V_t , maintaining the minute ventilation level can be achieved by controlling respiratory rate (RR) and inspiration to expiration ($I:E$) ratio. RR during MV is the number of breaths per minute, commonly around 12 to 20 breaths per minute (O'Driscoll, 2017). As for I:E ratio, it is typically around 1:2 to 1:5 to avoid auto-PEEP and potential hypercapnia.

From the literature, there are various forms of MV protocol are seen. These settings are summarised in Table 1.

Table 1. Recommended criteria in Literature

Ventilation Settings	Criteria	Relation to Equation
Plateau pressure (P_{plat})	< 35 cmH ₂ O	$P_{plat} = EV(t) + PEEP$
Driving pressure (ΔP)	min(ΔP)	$\Delta P = P_{plat} - PEEP$
Positive End Expiratory Pressure (PEEP)	max(P_o)	$P_{aw}(t) = E_{rs}V(t) + R_{rs}Q(t) + PEEP$
Alveoli pressure ($P_{alveoli}$)	< 35 cmH ₂ O	$P_{alveoli} = EV(t)$
Tidal volume (V_t)	6< V_t <8ml/kg	$V_t = \max(V(t))$
Minute ventilation (Min_Vent)	5L< Min_Vent < 8L	$Min_Vent = \max(\dot{V}(t)) \times RR$

2.2 Single Compartment Linear Lung Model

The recommendations of past-randomised controlled trials, notable clinical trial findings are integrated with a respiratory mechanics model to offer all possible MV settings. The targets in Table 1 are incorporated into a single compartment linear lung model for simulating of potential virtual mechanical ventilation settings. The single compartment linear lung model is the most commonly used model to describe patient-specific respiratory mechanics. This model is shown in Eq. (1).

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

Where, P_{aw} is the airway pressure, t is time, E_{rs} is the respiratory system elastance, V is the air volume, R_{rs} is the respiratory system resistance, Q is the airway flow, and P_o is the offset pressure or PEEP if there is little or no patient intrinsic PEEP. Using inspiratory airway pressure and flow data, E_{rs} and R_{rs} can be estimated using linear regression. The model is fitted to bedside measured airway pressure, flow rate and volume from the ventilator to determine the patients' respiratory system elastance (E_{rs}) and airway resistance (R_{rs}). The elastance provides insight towards the patient's lung stiffness. A stiffer lung requires a higher pressure to deliver a set amount of air into the lung. A lower elastance indicates a more compliant lung. With the E_{rs} and R_{rs} information, a set of MV protocols can be simulated to determine all possible MV settings.

2.3 Simulation of Virtual MV Protocol

In this study, the elastance (E_{rs}) and resistance (R_{rs}) values of the patient are then used for forward simulation to obtain the myriad of airway pressure by setting a range of safe PEEPs, tidal volumes, IE ratio and flow type. Table 2 shows the range of the parameters fixed in this study based on literature recommendations.

Table 2. Range of MV settings

Ventilation Settings	References	Range	Increment	No. of possibility
Vt (ml/kg)	Fan et al.	4 – 10	1	7
RR (bpm)	O'Driscoll et	12 – 20	1	9
IE Ratio, I:E	Poor et al.	1:2–1:5	0.1	4
PEEP (cmH ₂ O)	Pintado et al.	5 – 30	5	6
Flow Type	Poor et al.	R,S	-	2
Total possible settings (7 x 9 x 4 x 6 x 2)				3024

R - Ramp, S - Square.

Based on Table 2, there are total of 3024 possible combinations of MV settings. From these myriads of settings, the virtual protocol can be narrow down to a smaller range of MV possibilities based on a specific MV objective. The sequence can be divided into 5 different stages with each stage having different roles. The 5 stages are Estimation, Initiation, Simulation, Elimination, and finally, Formulation, abbreviated as 'EISEF'. Figure 1 illustrates the sequence of narrowing possible MV settings to attain achieve a set of MV objective.

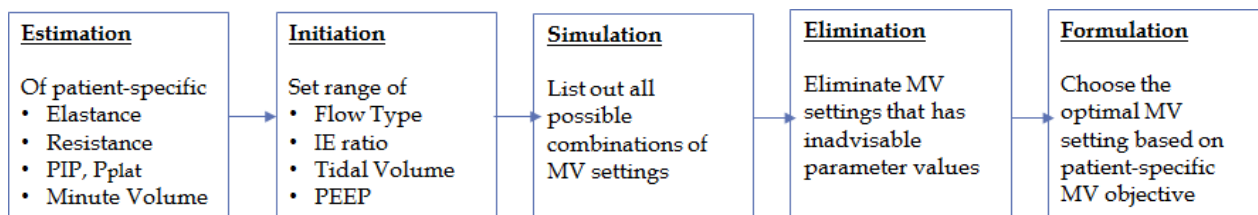


Fig.1. EISEF Steps to determine optimal MV setting

In the estimation stage, patient-specific respiratory system elastance (E_{rs}) and resistance (R_{rs}) are estimated to determine the patient's lung condition. These are used to regulate the possible MV settings. In the initiation stage, the ranges of tidal volume (V_t), respiratory rate (RR), IE ratio, PEEP and flow type are selected.

During volume control mode, MV inspiration flow support can be divided by either the ramp and square wave profile (Poor, 2018). After initiating with a flow profile, V_t can be fixed based on predicted patient ideal body weight (Linares-Perdomo et al., 2015) and Inspiratory expiratory (I:E) ratio (Poor, 2018). In the simulation stage, all possible MV combinations can be simulated. Volume profiles can then be calculated by integrating flow profiles with respect to time. Then, patient-specific parameters such as V_t , Min_Vol, P_{plat} , PIP, and ΔP are calculated for the complete range of MV setting combinations as per relation shown in TABLE 1. In the elimination stage, we can start to eliminate combinations that are not within literature recommendations. Finally, in the formulation stage, clinicians can formulate a set of strategies with the remaining MV combinations to obtain an optimal MV setting.

In this study, 3 virtual patients with different sets of patient-specific respiratory mechanics were simulated to investigate the feasibility of the developed MV virtual protocol. The virtual patient parameters were fixed based on ARDS subjects respiratory mechanics parameters specified by Arnal et al. (Jean-Michel Arnal MD, 2018) as shown in Table 3. After estimating the range of E_{rs} and R_{rs} for each patient using bedside airway pressure data, the average, standard deviations, median and confidence interval values of the respiratory mechanics can be used to simulate all possible MV combinations, providing the lower and upper boundary of the possible MV settings.

Table 3. Sample of virtual patient

Patient	Sample description	Wt (kg)	Elastance (cmH ₂ O/l)	Resistance (cmH ₂ O/s/l)
A	Mild ARDS	70	22 [18 – 27]	11 [9 – 14]
B	Obese, Moderate ARDS	90	25 [20 – 32]	12 [10 – 14]
C	Severe ARDS	75	26 [22 – 33]	12 [9 – 14]

Values in median [IQR], IQR – Inter Quartile Range.

All simulations were performed using MATLAB R2018b (The Mathworks, Natick, Massachusetts, USA). In this study, minimal driving pressure and higher PEEP is taken as ventilation objective to formulate the optimal setting.

3. RESULT

Based on the combinations provided in Table 2, 3024 MV setting combinations can be simulated for each virtual patient. The Median E_{rs} and R_{rs} values in Table 3 are used as virtual patient respiratory mechanics. Table 4 shows number of possible combinations for virtual patients after EISEF stages. Table 5 shows the potential MV parameter setting combination after formulation.

Table 4. Remaining MV settings after EISEF

Patient	Total MV Setting	Objective		Possible Settings	Percent
		PEEP (cmH ₂ O)	ΔP (cmH ₂ O)		
A	3024	10	<15	84	2.78%
B	3024	10	<17	12	0.40%
C	3024	15	<15	24	0.79%

Table 5. Potential optimal MV setting

Patient	Formulation					
	Flow	Vt	RR	IE	PEEP	ΔP
		ml/Kg	bpm	Ratio	(cmH ₂ O)	(cmH ₂ O)
A	Ramp	7	13	0.33	10	<15
B	Ramp	6	12	0.5	10	<17
C	Ramp	6	14	0.33	15	<15

Table 6 shows some samples of MV parameter combinations of Patient A. The red color shaded boxes are parameters that exceed the thresholds and the green shaded boxes are some of the remaining potential setting parameter combinations. The inspiratory profiles of airway pressure, flow, volume, airway pressure drop due to resistance, alveoli pressure and, plateau pressure during inspiration are shown in Figure 2 for Patients A. Figure 3 shows a sample of utilising the virtual protocol sequencing for Patient B. As the literature recommendations are applied to the virtual protocol, the number of possibilities is reduced by 95% to 48 combinations after eliminating non-viable settings. Further formulation of ventilator strategy will see a reduction to 12 combinations which is less than 1% of the initial total possible settings.

Table 6: List of some parameter combination of MV setting (15 of 3024) of Patient A

S.No	FLOW	Vt (ml/Kg)	VT (l/breath)	RR (BPM)	IE ratio	t _{breath} (sec)	PEEP (cmH ₂ O)	Min. Vol. (l/min)	E (cmH ₂ O/l)	R (cmH ₂ O/s/l)	PIP (cmH ₂ O)	ΔP (cmH ₂ O)	P _{alveoli} (cmH ₂ O)	P _{plateau} (cmH ₂ O)
1	'Ramp'	4	0.28	12	1:5	5.0	5	3.4	22	11	12.87	7.87	6.16	11.16
2	'Ramp'	5	0.35	12	1:5	5.0	5	4.2	22	11	14.84	9.84	7.7	12.7
3	'Ramp'	6	0.42	12	1:5	5.0	5	5.0	22	11	16.81	11.81	9.24	14.24
4	'Ramp'	6	0.42	12	1:2	5.0	30	5.0	22	11	41.81	11.81	9.24	39.24
5	'Ramp'	6	0.42	20	1:2	3.0	10	8.4	22	11	21.81	11.81	9.24	19.24
6	'Ramp'	7	0.49	12	1:3	5.0	30	5.9	22	11	43.77	13.77	10.78	40.78
7	'Ramp'	7	0.49	13	1:3	4.6	10	6.4	22	11	23.77	13.77	10.78	20.78
8	'Ramp'	7	0.49	20	1:2	3.0	10	9.8	22	11	23.77	13.77	10.78	20.78
9	'Ramp'	8	0.56	12	1:5	5.0	5	6.7	22	11	20.74	15.74	12.32	17.32
10	'Ramp'	9	0.63	12	1:5	5.0	5	7.6	22	11	22.71	17.71	13.86	18.86
...
3020	'Square'	6	0.42	20	1:2	3.0	30	8.4	22	11	43.86	13.86	9.24	39.24
3021	'Square'	7	0.49	20	1:2	3.0	30	9.8	22	11	46.17	16.17	10.78	40.78
3022	'Square'	8	0.56	20	1:2	3.0	30	11.2	22	11	48.48	18.48	12.32	42.32
3023	'Square'	9	0.63	20	1:2	3.0	30	12.6	22	11	50.79	20.79	13.86	43.86
3024	'Square'	10	0.7	20	1:2	3.0	30	14.0	22	11	53.10	23.10	15.4	45.4

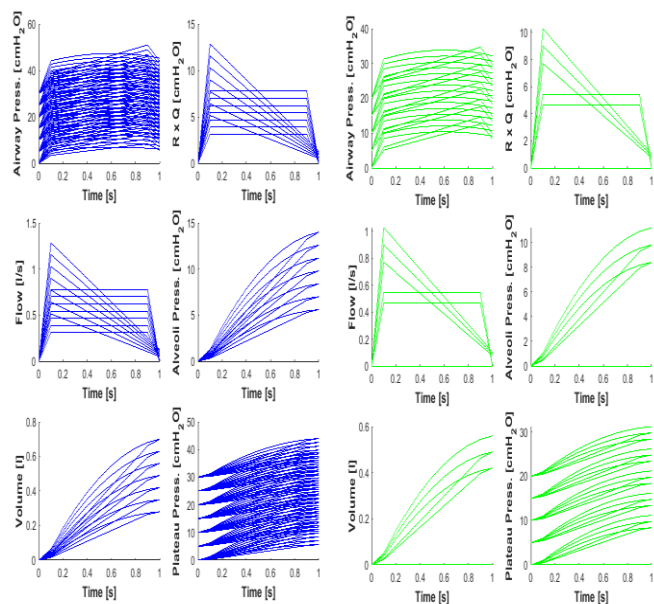


Fig.2. Patient-A MV setting all combination (Left) and possible settings after elimination & formulation (Right)

4. DISCUSSION

A generalised model-based method to determine the optimal MV parameter combinations is proposed in this study. The proposed method is capable to determine a range of patient-specific optimal MV settings using model-based method combine with literature studies. The proposed method follows a 5-stages EISEF process, from estimation of patient condition to formulation of MV protocol based on objectives. It is clear

that using literature recommendation elimination process alone will not be sufficient to titrate patient-specific MV settings. Formulation of ventilation strategy is required to obtain one set of optimal MV settings. As shown in Table 6, 3024 MV parameter combinations were simulated for each virtual patient. Using the 5-Stages MV protocol selection process proposed in this study, the combinations were narrowed down to 84, 12, 24 preferred combinations for Patients A, B and C as shown in Table 4.

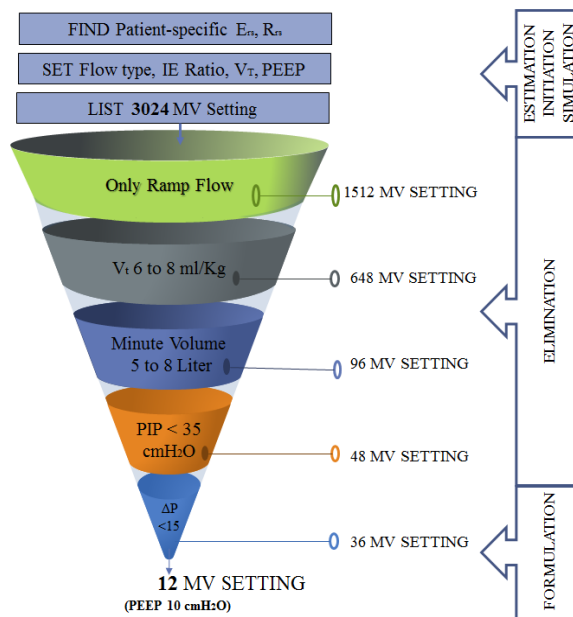


Fig.3. EISEF process of MV settings to obtain the optimal setting as per ventilator objective of Patient-B.

Based on patient condition, the number of the possible optimal setting derived from the method varies. Comparatively, Patient-A had more possible MV setting options with 84 combinations. The result is as expected as Patient-A had an overall lower E_{rs} , indicating that the patient had a more compliant lung than other patients. Comparatively, only 12 MV setting combinations are available for Patient-B whose weight is higher with moderate ARDS. In patient with higher weight, increase in weight increases the V_t , which affects the minute volume. Further, increase in V_t will also result in increased of the PIP and P_{plat} . This increment leads to reduction in number of possible MV settings. In order to compensate the higher oxygen requirement of obese patients while maintaining lower PIP & P_{plat} , higher RR is normally recommended which lead to increased work of breathing (De Jong et al., 2017). Thus, setting optimal MV setting for obese patient is more challenging than average weight patient (De Jong et al., 2017).

In recent research, high PEEP and low driving pressure are recommended ventilation strategy for ARDS patients to increase lung recruitment with minimal lung injury. Similarly, respiratory failure patient with hypoxemia can be treated with high volume-targeted mode (Mosier et al., 2015). After elimination stage of the EISEF protocol, the clinicians can formulate the ventilation strategy based on patient underlying disease and lung condition. For the 3 patients used in this study, the potential MV settings based on a specific ventilation strategy formulation is shown in Table 5. Literature suggests that a driving pressure of less than 15cmH₂O is preferable (Chiumello et al., 2016). However, in case of Patient-B, none of the simulated MV settings combinations had driving pressure <15cmH₂O. In such cases, the least driving pressure can be chosen to determine the optimal setting. In case of Patient-C, PEEP 15cmH₂O was taken as ventilation objective as Patient-C was affected by severe ARDS. This setting was formulated as higher PEEP may be beneficial for severe ARDS patient to maintain lung recruitment (Y. Chiew et al., 2015).

For all 3 patients, V_t of 6 to 8ml/kg is preferable during MV therapy (Fan et al., 2017). Equally, RR of 12 to 20 breaths per minute (O'Driscoll, 2017), IE ratios of 1:2-1:4 (Poor, 2018) and the minute volume of ventilation to maintain healthy oxygenation within 5 to 8 litre are some preferred MV settings to ensure sufficient oxygenation. It is however, setting these MV settings is a challenging task as they are interrelated and may have coupled effect. For example in Table 4 Patient-A, S.No. 5 case, the parameter combination of 6ml/kg tidal volume, 1:2 IE ratio with 20bpm respiratory rate lead to 8.4L of minute volume. Though other parameters were within the prescribed range, the minute volume exceeds the preferred limit. High minute ventilation has reported to associate with acidosis (Poor, 2018) and cause insufficient expiration which may result in auto-PEEP and hyperinflation (Poor, 2018) and thus, is not recommended for setting. Hence, it is very important to study the joint and coupled effect of each parameter before deciding on the MV settings.

The proposed EISEF protocol can be applied to different patients and the settings suggested by the protocol can be patient-specific. The EISEF is developed based on 2 criteria. 1. The ventilator target and 2. The respiratory model. Ventilator targets are derived from literature findings, where in-depth and

comprehensive clinical trials were carried out to investigate the outcomes of these ventilator targets. Thus, by incorporating these findings, MV protocol that was generated theoretically will be beneficial for the patient. As for the respiratory mechanics of the patient, it depends on the respiratory models that are used. In this study, single compartment model was used as it is a clinically validated model (U. Lucangelo et al., 2007). More complex models and control methods (Arunachalam et al., 2020; Chan et al., 2019) may have different settings with different theoretical benefits in MV. It is noted that the methodology presented in this study is currently limited to volume-control ventilation mode. Similar concept can be adapted to pressure-control mode as well to determine the patient-specific possible setting. In future, study on the impact of respiratory models to determine the optimal setting is required. The current model and proposed algorithm only focuses on ventilation. Additional model on perfusion is required to fully capture the effects of mechanical ventilation. Also, the proposed method needs to be studied with real patient data (Y. S. Chiew et al., 2018; Davidson et al., 2014) to understand the method compliance. This study will helps to comprehend the application of EISEF protocol in clinical environment.

There are a number of significant researches investigating into patient-specific optimal MV settings. However, incorporating these findings clinically is challenging as patient conditions are heterogeneous in nature. Thus, having virtual MV protocol that is formulated from literatures can be useful for bedside clinicians in setting MV. The methodology presented in this study is generalisable and can be adapted with new, data-driven clinical findings.

5. CONCLUSION

Control of mechanical ventilation is a complex decision making process. There are various settings and new technologies incorporated to aid patient treatment and optimise therapy. The virtual MV protocol proposed in this study shows the potential application of an objective and patient-specific protocol. Further investigation is required to test its performance, clinical compliance and effects on patient's recovery.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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