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Model-based PEEP optimisation in mechanical ventilation

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Abstract

Background: Acute Respiratory Distress Syndrome (ARDS) patients require mechanical ventilation (MV) for breathing support. Patient-specific PEEP is encouraged for treating different patients but there is no well established method in optimal PEEP selection.

Methods: A study of 10 patients diagnosed with ALI/ARDS whom underwent recruitment manoeuvre is carried out. Airway pressure and flow data are used to identify patient-specific constant lung elastance (E_{lung}) and time-variant dynamic lung elastance (E_{drs}) at each PEEP level (increments of $5cmH_2O$), for a single compartment linear lung model using integral-based methods. Optimal PEEP is estimated using E_{lung} versus PEEP, E_{drs}-Pressure curve and E_{drs} Area at minimum elastance (maximum compliance) and the inflection of the curves (diminishing return). Results are compared to clinically selected PEEP values. The trials and use of the data were approved by the New Zealand South Island Regional Ethics Committee.

Results: Median absolute percentage fitting error to the data when estimating time-variant E_{drs} is 0.9% (IQR = 0.5-2.4) and 5.6% [IQR: 1.8-11.3] when estimating constant E_{lung}. Both E_{lung} and E_{drs} decrease with PEEP to a minimum, before rising, and indicating potential over-inflation. Median E_{drs} over all patients across all PEEP values was 32.2 cmH_2O/l [IQR: 26.1-46.6], reflecting the heterogeneity of ALI/ARDS patients, and their response to PEEP, that complicates standard approaches to PEEP selection. All E_{drs}-Pressure curves have a clear inflection point before minimum E_{drs}, making PEEP selection straightforward. Model-based selected PEEP using the proposed metrics were higher than clinically selected values in 7/10 cases.

Conclusion: Continuous monitoring of the patient-specific E_{lung} and E_{drs} and minimally invasive PEEP titration provide a unique, patient-specific and physiologically relevant metric to optimize PEEP selection with minimal disruption of MV therapy.

Keywords: ARDS, ALI, Elastance, Compliance, PEEP, Critical care, Mechanical Ventilation

1 Introductions

Acute respiratory distress syndrome (ARDS) and acute lung injury (ALI), occurs due to severe inflammatory response of the lung, resulting in direct alveolar injury, pulmonary oedema and alveolar collapse [1,2]. The lung injury greatly impairs the patients breathing, reducing alveolar gas exchange, resulting in possible mortality and morbidity if not given a proper treatment. ALI/ARDS patients are associated with high morbidity, mortality up to 60% [3] and significant medical cost [4].

Patients diagnosed with ALI/ARDS are mechanically ventilated for breathing support [5,6]. Various mechanical ventilation (MV) modes have been introduced to clinicians for the support of patients with ALI/ARDS [7]. However, the fundamentals of MV remains in selecting an optimal positive end-expiratory pressure (PEEP) to maximise patients' lung recruitment, prevent alveoli collapse, and avoid ventilator induced lung injury (VILI) [8]. The heterogeneity of the disease and patients' variable response to MV, encourages PEEP treatment to be patient-specific and individualised. However, there is no gold standard method in PEEP selection; consequently, optimising patient-specific PEEP in MV remains a challenge for clinicians [9-11].

Model-based and patient-specific approaches offer the ability to identify intra- and inter-patients variability and thus, potential to guide MV therapy based on patient's condition and needs [12,13]. This approach provides the opportunity to balance risk of lung injury and lung function support and reduce work of breathing [14] during MV. However, to date, only a few have been tested [15-17] and their potential in critical care is not yet validated.

This research presents several model-based approaches to identify patient-specific disease state and patient-specific response to MV therapy using patient-specific, constant lung elastance (E_{lung}) [16,18] with comparison of dynamic lung elastance (E_{drs}) in ALI/ARDS. Dynamic lung elastance (E_{drs}) is a time-variant lung elastance during each breath in MV. E_{lung} and E_{drs} are thus proposed for guiding PEEP selection. By monitoring both the identified parameters (Elastance = 1/Compliance) through limited PEEP titration, it is possible to identify PEEP settings that maximize recruitment, minimize work of breathing without inducing lung injury.

2 Methods

2.1 Study Design

Ten patients in the Intensive Care Unit (ICU), Christchurch Hospital, New Zealand, diagnosed with ALI or ARDS (PaO_2/FiO_2 (PF ratio) between 150-300 mmHg), underwent a modified protocol-based recruitment manoeuvre (RM) [17]. PEEP is increased with increments of $5cmH_2O$ from zero PEEP (ZEEP) until peak airway pressure reaches a limit of $45cmH_2O$ [19]. Patients were sedated and paralyzed with muscle relaxants to prevent spontaneous breathing efforts. All patients were ventilated using Puritan Bennett PB840 ventilators (Covidien, Boulder, CO, USA) with volume control (tidal volume, V_t = 400~600ml), synchronized intermittent mandatory ventilation (SIMV) mode, throughout the trial. The clinical trials and the use of the data were approved by the New Zealand, South Island Regional Ethics Committee.

A heated-pneumotachometer with Hamilton Medical flow sensor (Hamilton Medical, Switzerland) connected to the ventilator circuit Y-piece is used to record patient's airway pressure and flow data. A Dell™ (Dell, Austin, TX, USA) laptop was used in conjunction with National Instruments USB6009 and Labview Signal Express (National Instruments, Austin, TX, USA) to obtain measurements at a sampling rate of 100 Hz. Analysis was performed using MATLAB (The Mathworks, Natick, Massachusetts, USA).

2.2 Model-based Analysis

The model-based approach incorporates a physiologically relevant and validated recruitment model [17,20] with the use of a single compartment linear lung model

that captures fundamental lung mechanics and properties in real-time to identify patient-specific constant lung elastance (E_{lung}) and dynamic lung elastance (E_{drs}) during MV. The model uses transpulmonary pressure (P_{tp}), volume (V) and flow (Q) and off-set pressure (P_0), to identify lung elastance (E_{lung}) and resistance (R_{lung}). Patient-specific lung elastance, E_{lung} reflects the lung stiffness (1/Compliance). Therefore, a lower E_{lung} is a more compliant lung. E_{lung} is identified from measured data using an integral-based method [21]. The model is defined:

$$P_{tp} = E_{lung}V + R_{lung}Q + P_0 \tag{1}$$

Airway pressure is related to transpulmonary pressure (P_{tp}) and pleural pressure (P_{pl}) by:

$$P_{tp} = P_{aw} - P_{pl} \tag{2}$$

When the patient is sedated and fully dependant on the ventilator to breathe, it can be assumed that there is no chest wall activity, allowing P_{pl} to be omitted in this case. Equation 1 is then further modified to eliminate P_{pl}, yielding:

$$P_{aw} = E_{lung}V + R_{lung}Q + P_0 \tag{3}$$

Patient-specific dynamic lung elastance, E_{drs}, is identified as a time-variant lung elastance and Equation (3) is defined:

$$P_{aw}(t) = E_{drs}(t)V(t) + R_{lung}Q(t) + P_0 \tag{4}$$

To ensure that the identified parameters of constant E_{lung} and time-variant E_{drs} ($E_{drs}(t)$) are valid, the absolute percentage error between the identified model and measured clinical pressure data is reported.

2.3 Model-Based PEEP Selection

During each breathing cycle, as PEEP rises, lung elastance (E_{lung}) falls as new lung volume is recruited faster than the pressure build-ups in the lung. If little or no recruitment occurs, E_{lung} rises with PEEP indicating that pressure above that PEEP level was unable to recruit significant new lung volume and is, instead, beginning to stretch already recruited lung [22]. Hence, recruitment and potential lung injury can be balanced by selecting PEEP at minimum E_{lung}.

Compared to a single, constant E_{lung} value at each PEEP, identifying time-variant E_{drs} allows this change to be seen dynamically within each breath as pressure increases thus allowing a more detail view of patient's lung physiological condition. Three model-based approaches based on patient-specific E_{lung} and E_{drs} trajectory in a patient's breath at different PEEP levels are used to optimize PEEP selection.

Minimum E_{drs} and E_{lung}: locates the point where minimum E_{drs} *or* E_{lung} occurs over all PEEP values (and pressure for E_{drs}) during the recruitment manoeuvre.

Minimum E_{drs} Area: E_{drs} Area is obtained by integrating E_{drs} over time during the patient's breathing cycle at each PEEP. E_{drs} Area is more clinically relevant than median or mean E_{drs} throughout each breath and can be shown to be proportional to patient-specific work of breathing.

Inflection Method: This method detects the inflection in the E_{drs} Area-PEEP and E_{lung}-PEEP curves. Inflection is defined here at the PEEP value with E_{drs} value 5-10%

above (before) minimum E_{drs} Area or E_{lung} (105~110% of minimum E_{drs} Area or E_{lung}). PEEP is selected where inflection occurs, as a point of diminishing returns.

The overall approach implies that as long as E_{drs} falls during each breath, as PEEP level increases, that recruitment of new volume outweighs lung stretching as flow and volume follow a path of lesser or least resistance. These methods are thus attempts to maximize recruitment (Minimum E_{drs} and Minimum E_{drs} Area) and also ensure safety from excessive pressure (Inflection Method). These metrics are three of many possibilities to demonstrate the concept.

2.4 Edrs Area and Work of Breathing

These approaches were also compared with selecting PEEP using the identified minimum or inflection of constant E_{lung}, for comparison to other similar work [23]. Patient-specific E_{lung} and E_{drs} are only analyzed during inspiration and not during the expiratory cycle. This choice was made because increases in pressure induce lung damage as it passes a limit and thus expiration (decreasing pressure) should not be used to guide PEEP selection.

A higher resolution of the trend changes in E_{drs} can be observed using E_{drs} Area. E_{drs} Area is obtained through integration of E_{drs} with time. It is also known that the work of breathing (WOB) [24,25] for a patient is proportional to lung elastance. In general, more work is required to fill a given lung volume with higher elastance. WOB is defined:

$$WOB = P_{aw} \times V \tag{5}$$

Substituting P_{aw} from Equation (3) into Equation (5) and using $P_0 = 0$, (atmospheric).

$$\begin{aligned} WOB &= (E_{lung}V + R_{lung}Q) \times V \\ &= E_{lung}V^2 + R_{lung}QV \end{aligned} \tag{6}$$

From Equation (6), work of breathing can be divided into work to overcome lung elastance ($WOB_E = E_{lung}V^2$) and work to overcome airway resistance ($WOB_R = R_{lung}QV$). Substitution of dynamic lung elastance, E_{drs}, for constant E_{lung} enables a derivation for WOB_E:

$$E_{drs} = WOB_E(t)/V(t)^2 \tag{7}$$

E_{drs} Area in Equation (8) is the integral of Equation (7), yielding the relation of E_{drs} to the work of breathing required to overcome lung elastance at a given level of PEEP and mode of MV.

$$E_{drs}Area = \int E_{drs}(t)dt \tag{8}$$

2.5 Analysis and Comparisons

In this study, E_{lung} and median E_{drs} are compared using Pearson's linear correlation coefficients to relate these metrics. E_{lung} and E_{drs} Area are also compared to median E_{drs} and WOB_E to ensure there was no loss of information for each patient at different PEEP values, and to show the validity of Equation (7) and using E_{drs} Area. Finally,

clinically selected PEEP is compared to the value determined by proposed model-based metrics.

3 Results

Table 1 shows the clinical details of the 10 patients recruited with their clinical diagnostics, and PF ratios. Table 2 shows the median [Inter-quartile Range (IQR)] E_{drs} for each patient and PEEP, and absolute percentage fitting error. Median absolute percentage fitting error ($APE_{Edrs(t)}$) across all patients and PEEP is 0.9% [IQR: 0.5-2.4]. Median E_{drs} at each PEEP is 32.2cmH_2O/l [IQR: 26.1-46.6]. Median [IQR] E_{drs} decreases with increasing PEEP until the minimum E_{drs}. Patients who suffer from COPD (Patients 1, 4, 5, 9 and 10) have significantly higher E_{drs} than others ($P < 0.0001$), as expected clinically. Table 3 shows the constant lung elastance (E_{lung}) at each PEEP with median = 32.2cmH_2O/l [IQR: 25.0-45.9], and absolute percentage fitting ($APE_{E\text{-}lung}$) at 5.6% [IQR: 1.8-11.3]. Table 4 shows the E_{drs} Area at each PEEP with median [IQR] of 34.0cmH_2Os/l [IQR: 24.7-48.5].

Figure 1 shows patient-specific time-varying E_{drs} at each PEEP level for Patients 2, 6, 8 and 10. E_{drs} decreases as pressure increases at each PEEP. However, at higher PEEP, this trend can reverse indicating stretching exceeding recruitment of new lung volume. The optimal PEEP derived by minimum E_{drs} is indicated.

Figure 2 shows patient-specific E_{drs} Area for Patients 2, 6, 8 and 10 with PEEP. The optimal PEEP is derived using minimum E_{drs} Area and Inflection method with the band of 5-10% above minimum E_{drs} Area shown by the dashed-lines.

Figure 3 shows patient-specific constant lung elastance (E_{lung}) with increasing PEEP for Patients 2, 6, 8 and 10. E_{lung} decreases with PEEP and the trend is similar to the E_{drs} Area-PEEP plot of Figure 2, as expected from the high correlation. The optimal PEEP using minimum E_{lung} and Inflection E_{lung} (Dashed-lines) are also indicated.

Across all 10 patients, patient-specific constant lung elastance (E_{lung}) can be represented by the median of dynamic lung elastance (E_{drs}) with correlation R = 0.987. Correlation of E_{lung} and WOB_E is R = 0.815. E_{drs} Area and median E_{drs} are also closely correlated with R = 0.896. Hence, E_{drs} can be represented with E_{drs} Area, where E_{drs} Area captures all E_{drs} values in a given breath and thus, is a more physiologically representative metric. Finally, validating Equation (2), E_{drs} Area is correlated to the work to overcome lung elastance, WOB_E, as expected, with R = 0.936. The correlations are shown in Figure 4.

Table 1 Patient demography.

Patients	*Sex*	*Age (year)*	*Clinical Diagnostic*	*PF Ratio*
1	F	61	Peritonitis, COPD	214
2	M	22	Trauma	180
3	M	55	Aspiration	222
4	M	88	Pneumonia, COPD	165
5	M	59	Pneumonia, COPD	285
6	M	69	Trauma	280
7	M	56	Legionnaires	265
8	F	54	Aspiration	302
9	M	37	H1N1, COPD*	182
10	M	56	Legionnaires, COPD	237

*Chronic Obstructive Pulmonary Disease

Table 2 Patient-specific dynamic lung elastance (E_{drs}) at each PEEP level.

Patient	Dynamic Lung Elastance, E_{drs} (cmH_2O/l) Median [IQR]							E_{drs} (cmH_2O/l) Median [IQR]	APE* (%) Median [IQR]
	PEEP (cmH_2O)								
	0	5	10	15	20	25	30		
1	63.1 [46.9-114.9]	53.8 [43.0-80.2]	43.6 [38.4-54.5]	35.0 [33.3-39.4]	33.4 [32.0-34.2]	31.1 [32.0-32.4]	PEEP 27 32.2 [31.9-32.6]	35.0 [32.5-51.2]	1.1 [0.5-4.1]
2	30.8 [26.3-45.1]	26.4 [23.7-31.4]	23.1 [22.0-24.3]	22.1 [22.0-22.6]	22.5 [22.4-22.6]	PEEP 22 23.1 [22.9-23.2]		23.1 [22.5-26.4]	0.7 [0.6-2.4]
3	26.9 [22.6-36.9]	22.1 [20.2-25.6]	18.3 [18.0-19.0]	17.3 [17.2-17.4]	17.5 [17.1-17.5]	17.8 [17.4-18.7]	PEEP 28 19.2 [17.9-19.7]	18.3 [17.6-21.4]	0.6 [0.5-1.3]
4	73.2 [50.4-144.4]	70.4 [49.9-126.9]	54.5 [41.7-82.3]	36.8 [30.6-43.9]	28.5 [25.6-31.4]	25.9 [21.6-28.4]	23.1 [19.4-25.5]	36.8 [26.6-66.4]	3.4 [0.9-5.4]
5	105.7 [80.6-199.8]	97.8 [77.5-166.8]	89.3 [74.3-143.4]	79.4 [68.6-107.3]	67.3 [61.4-79.4]	52.3 [52.0-55.8]		84.4 [67.3-97.8]	3.2 [0.9-6.0]
6	30.4 [25.9-39.1]	26.2 [25.5-27.2]	23.3 [22.4-23.5]	21.6 [21.5-21.8]	21.8 [21.3-22.5]	23.3 [22.6-23.9]		23.3 [21.8-26.2]	0.8 [0.6-1.2]
7	49.3 [46.1-62.4]	42.2 [41.5-43.1]	44.3 [41.8-47.7]	53.6 [48.8-59.7]	PEEP 16 52.4 [50.3-57.6]			49.3 [43.8-52.7]	1.6 [1.3-2.0]
8	45.7 [37.9-67.8]	37.2 [32.9-43.0]	31.8 [29.9-33.5]	28.8 [28.0-29.8]	27.4 [27.1-27.9]	26.8 [26.3-27.0]	27.0 [26.8-27.5]	28.8 [27.1-35.9]	0.8 [0.5-2.2]
9	58.1 [47.1-100.8]	40.5 [36.4-52.8]	39.9 [35.8-48.7]	31.2 [30.2-33.6]	28.3 [27.9-29.0]	26.3 [26.3-26.5]	26.2 [25.8-26.5]	31.2 [26.8-40.4]	0.8 [0.4-2.1]
10	54.4 [48.1-76.2]	45.2 [41.9-51.8]	39.4 [38.4-41.7]	35.9 [35.7-36.0]	33.9 [33.7-34.1]	33.9 [33.4-34.6]	PEEP 27 33.9 [33.2-34.8]	35.9 [33.9-43.8]	0.4 [0.4-0.9]
Median [IQR]	51.9 [30.8-63.1]	41.4 [26.4-53.8]	39.7 [23.3-44.3]	33.1 [22.1-36.8]	28.4* [22.5-33.9]	26.3* [23.1-32.2]	26.6* [23.1-32.2]	32.2 [26.1-46.6]	0.9 [0.5-2.4]

*APE - Absolute Percentage Fitting Error (%)

*Values presented include value from different PEEP.

Table 3 Patient-specific constant lung elastance (E_{lung}) at different PEEP.

Patient	Constant Lung Elastance, E_{lung} (cmH_2O/l)							E_{lung} (cmH_2O/l) Median [IQR]	APE (%) Median [IQR]
	PEEP (cmH_2O)								
	0	5	10	15	20	25	30		
1	53.8	47.0	41.2	32.8	32.8	32.1	PEEP 27 32.2	34.7 [32.4-45.5]	7.2 [1.7-19.0]
2	27.7	25.3	22.8	22.3	22.6	PEEP 22 23.1		23.0 [22.6-25.3]	2.5 [1.1-7.7]
3	24.0	21.6	18.3	17.3	17.4	18.1	PEEP 28 19.1	18.3 [17.6-20.9]	4.2 [1.6-6.6]
4	60.2	59.7	50.1	35.1	27.8	25.3	22.5	35.1 [25.9-57.3]	17.7 [15.4-32.1]
5	87.4	84.0	81.2	74.3	65.7	53.1		77.8 [65.7-84.0]	15.7 [9.2-19.8]
6	27.1	25.5	22.8	21.6	21.8	23.4		23.1 [21.8-25.5]	2.7 [2.2-4.2]
7	47.7	42.5	45.5	55.7	PEEP 16 55.3			47.7 [44.8-55.4]	6.2 [5.0-7.7]
8	41.7	35.5	31.2	28.7	27.5	26.6	27.0	28.7 [27.2-34.4]	2.9 [1.3-8.7]
9	51.3	39.1	38.2	31.1	28.2	26.2	26.1	29.7 [26.2-38.7]	3.1 [1.0-10.8]
10	51.0	44.1	39.2	35.8	33.9	34.0	PEEP 27 34.2	35.8 [34.1-42.9]	2.0 [1.0-5.6]
Median [IQR]	49.4 [27.7-53.8]	40.8 [25.5-47.0]	38.7 [22.8-45.5]	31.9 [22.3-35.5]	28.0* [22.6-33.9]	26.2* [23.3-32.6]	26.6* [22.5-32.2]	32.2 [25.0-45.9]	5.6 [1.8-11.3]

Eg. PEEP 16 is included in PEEP 20 Median [IQR]

*Values presented include value from different PEEP. Eg. PEEP 16 is included in PEEP 20 Median [IQR]

Table 5 compares clinically selected PEEP during MV therapy with PEEP selected using Minimum E_{drs}, and Minimum E_{drs} Area and the Inflection method. The clinical values are set over a much narrower range, both higher and lower than those selected using E_{drs}. Minimum E_{drs} Area always selects a higher PEEP, by definition, than the Inflection method. However, Minimum E_{drs} Area selects PEEP similar to or higher than Minimum E_{drs}, where it also thus adds consideration of the reduction in overall WOB_E in selecting PEEP. PEEP derived from minimum E_{lung} and Inflection E_{lung} are also indicated.

4 Discussion

4.1 Model-based PEEP Selection

Median fitting error for time-variant E_{drs} in Table 2 is less than 1%, showing that a single compartment lung model can be used for time-varying E_{drs} estimation. The wide range of patient-specific E_{drs} across all patients and PEEP shown in Table 2 reflects the heterogeneity of ALI/ARDS patient condition and response to PEEP that makes standardising and PEEP selection difficult [26]. Compared to the estimation of E_{lung} in Table 3, median fitting error is 5.6% and in specific cases, fitting error can be as high as 15.7-17.7% (Patients 4 and 5). This latter result indicates that a first order model can be used to estimate most patient-specific constant E_{lung}, but, in several cases, the model may not accurately represent patients' physiological condition. Time-varying

Table 4 Patient-specific E_{drs} Area at different PEEP.

Patient	E_{drs} Area (mH_2Os/l)							E_{drs} Area (cmH_2Os/l) Median [IQR]
	PEEP (cmH_2O)							
	0	5	10	15	20	25	30	
1	84.6	49.5	37.1	28.9	26.6	25.7	PEEP 27 25.7	28.9 [25.9-46.4]
2	34.0	24.8	21.0	20.2	20.3	PEEP 22 20.7		20.9 [20.3-24.8]
3	37.7	27.6	22.2	20.8	19.1	19.7	PEEP 28 18.9	20.8 [19.3-26.3]
4	102.2	91.2	61.7	37.9	31.7	48.1	47.5	48.1 [40.3-83.8]
5	118.7	99.9	89.1	70.6	75.7	42.9		82.4 [70.6-99.9]
6	29.4	23.8	20.8	21.6	19.5	20.8		21.2 [20.8-23.8]
7	37.6	33.8	31.3	37.9	PEEP 16 32.1			33.8 [31.9-37.7]
8	55.1	38.5	32.0	29.0	27.5	24.1	24.3	29.0 [25.1-36.9]
9	106.5	55.2	51.3	38.3	34.1	31.6	31.3	38.4 [32.2-54.2]
10	74.7	52.6	44.0	39.5	37.3	37.2	PEEP 27 37.3	39.5 [37.3-50.5]
Median [IQR]	64.9 [37.6-102.2]	44.0 [27.6-55.2]	34.6 [22.2-51.3]	33.5 [21.6-38.4]	29.6* [20.3-34.1]	25.7* [20.8-38.6]	28.5* [24.3-37.3]	34.0 [24.7-48.5]

*Values presented include value from different PEEP. Eg. PEEP 16 is included in PEEP 20 Median [IQR]

E_{drs} provides a better model fit across all patients and also provides a clearer insight into the patient's physiological condition, and is thus the better model-based metric.

Figures 1 and Figure 2 shows E_{drs}-Pressure-PEEP curves and E_{drs} Area decrease with increasing PEEP, lung pressure, and volume over each breath. In the beginning of the recruitment manoeuvre, at zero end-expiratory pressure (ZEEP), E_{drs} is relatively very high for all patients with median $51.9 cmH_2O/l$ [IQR: 30.8-63.1]. In particular, chronic obstructive pulmonary disease (COPD) patients or patients with similar clinical features [27] (Patients 1, 4, 5, 9 and 10) have initially the highest E_{drs} median, as expected, from $63.1 cmH_2O/l$ [IQR: 57.2-81.3] versus $30.8 cmH_2O/l$ [IQR: 29.5-46.6] for the other patients ($p = 0.0079$). As PEEP rises, it is observed that E_{drs} curves drop at patient-specific rates. High constant lung elastance, E_{lung} at ZEEP and decreasing elastance as PEEP increments are also observed in Figure 3 for Patient 10.

In all cases, patient-specific E_{drs} and E_{lung} decrease to a patient-specific minimum before increasing at higher PEEP. Minimum E_{drs} and E_{lung} suggest the point where the lung is most compliant, if ventilated at that PEEP level. Further increases in PEEP and pressure thus lead to increased E_{lung} or E_{drs}, and thus increase detrimental effects. In particular, increases in E_{lung} or E_{drs} can be associated with overstretching of the patient's lung [16,28]. However, the heterogeneity of ALI/ARDS means there is a possibility of overstretching of healthy lung units even at low PEEP and airway pressures [10]. Thus, Minimum or, perhaps preferably, Inflection E_{drs} and E_{lung} can provide a potentially higher resolution metric.

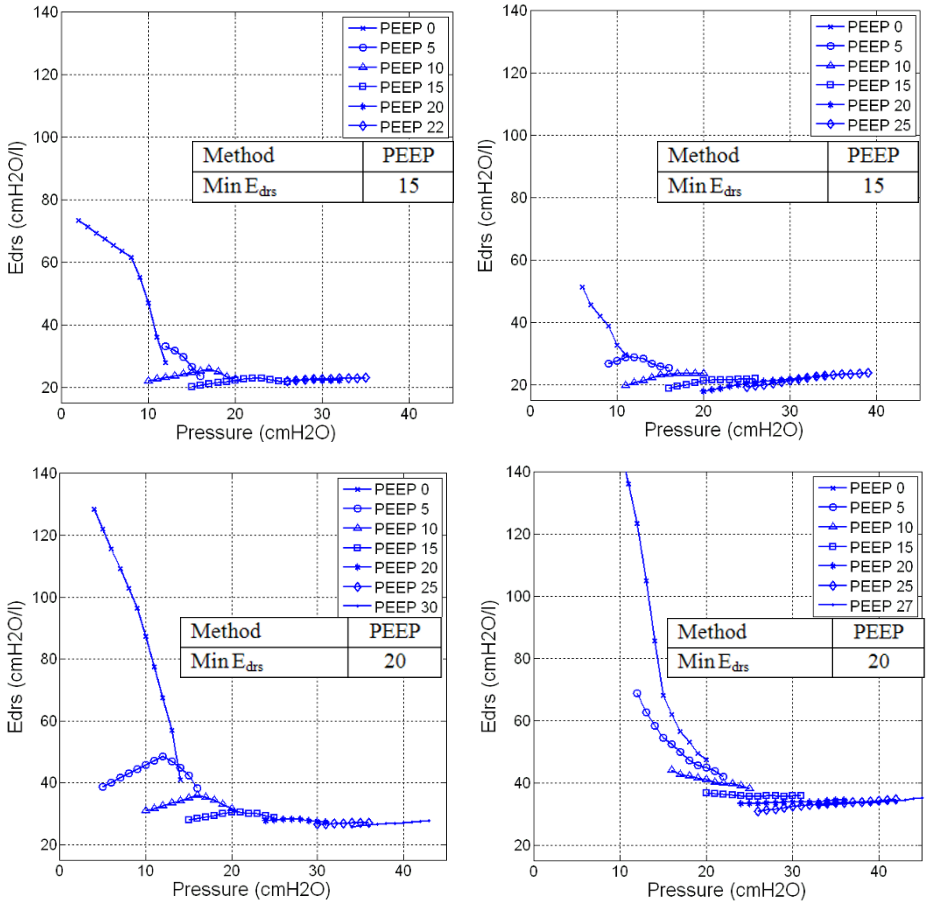


Figure 1 Dynamic lung elastance (E_{drs})-Pressure-PEEP plot. Top Left Panel: Patient 2, Top Right Panel: Patient 6. Both patients show significant E_{drs} drop from lower zero PEEP to PEEP 15cmH_2O. Further increase of PEEP to 20cmH_2O shows increase of overall E_{drs}. Bottom Left Panel: Patient 8, Bottom Right Panel: Patient 10. Both patients show a consistent drop in overall E_{drs} with increasing of PEEP and overall E_{drs} did not rise with PEEP for the entire ranged considered.

Patients 2 and 6 (Figure 1, 2, 3: Top panels) are examples where patient-specific E_{drs}, E_{drs} Area and E_{lung} increase after descending to a minimum. Results suggest that further increases of PEEP and inflation pressures will stretch lung units causing possible damage, as seen by increasing E_{drs} at higher PEEP. The rise of E_{drs} occurs at relatively low PEEP and pressure 15-20cmH_2O in these two patients.

In contrast, Patients 8 and 10 (Figure 1, 2, 3: Bottom panels) never see E_{drs} or E_{lung} rising even at the maximum PEEP used in this study. However, the E_{drs} range at higher PEEP for Patients 8 and 10 (PEEP 15~30cmH_2O) is relatively small with median E_{drs} = 31.3cmH_2O/l, [IQR = 27.2-33.9]. This outcome indicates that further increases of PEEP from 15 to 30cmH_2O has no added advantage in reducing E_{drs}, suggesting PEEP selection should be made at using the Inflection method.

Table 2 shows median [IQR] E_{drs} for every patient and PEEP. The IQR range drops significantly for every patient as PEEP increases. This range also indicates lung status or condition with the influence of pressure. A small IQR range indicates that the lung is ventilated at a PEEP level where maximal lung recruitment occurs over a narrow pressure range as tidal volume, V_t is fixed in the MV mode used. A high IQR range

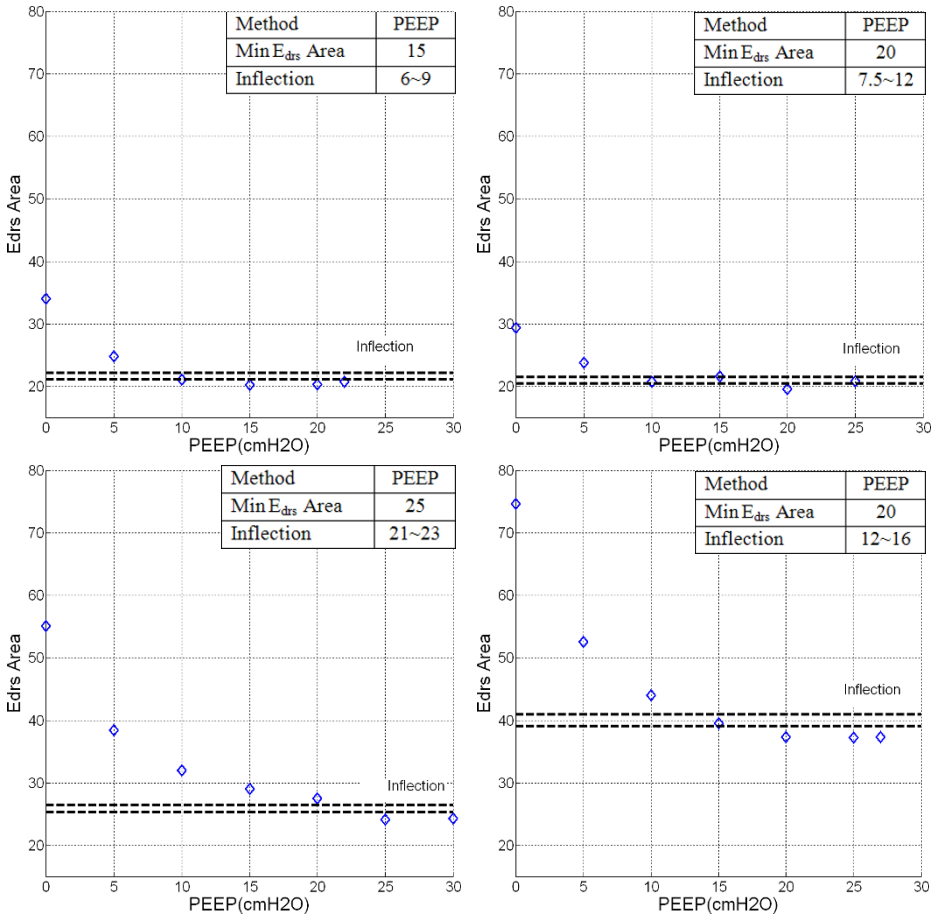


Figure 2 E_{drs} Area-PEEP plot. Top Left Panel: Patient 2, Top Right Panel: Patient 6. Bottom Left Panel: Patient 8, Bottom Right Panel: Patient 10. Severe COPD or patients with similar clinical features (e.g. Patient 10) showed significantly higher E_{drs} Area compared to other patients. PEEP selection is based on minimum E_{drs}-Area and the inflection method with PEEP increase.

shows the opposite. Hence, the lengths along pressure in Figure 1 also indicate how readily the patient was recruited and that easiest recruitment occurs at minimum E_{drs} [29].

Table 4 shows the patient-specific E_{drs} Area at each PEEP. It is found that E_{drs} Area is closely related to median E_{drs}, as shown in Figure 4. E_{drs} Area at lower PEEP with median 64.9 cmH2Os/l [IQR: 37.6-102.2] is observed and as PEEP increases, E_{drs} Area decreases. Upon reaching minimum E_{drs} Area, patient-specific E_{drs} Area increase with PEEP (Patients 2, 4, 6, 7 and 10). This trend is similar to the trend observed in patient-specific dynamic E_{drs} (Table 2) and constant E_{lung} (Table 3). Optimal PEEP derived using minimum or inflection method in E_{drs} Area is similar to minimum patient-specific E_{drs} but different as E_{drs} Area considers the whole inspiration and the effect of WOB_E. It is also found that E_{drs} Area is closely correlated to work in overcoming the lung elastic properties (WOB_E). This means that E_{drs} Area provides combined information of patients-specific lung physiological conditions as well as work of breathing.

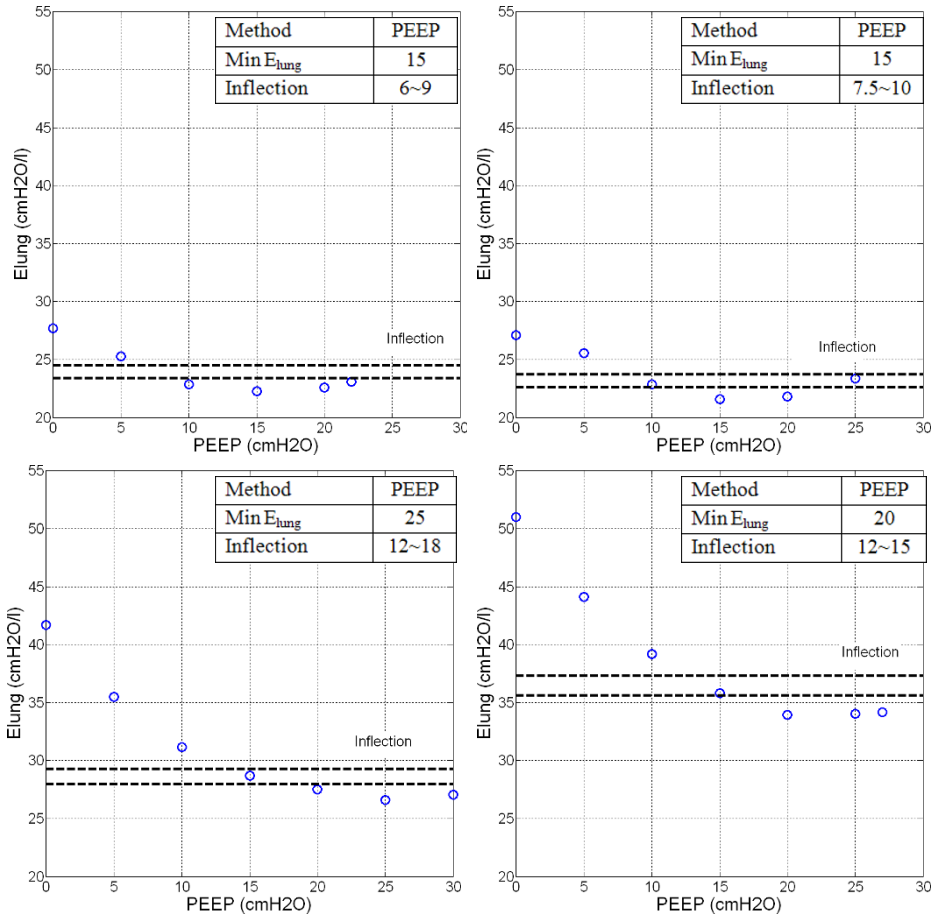


Figure 3 E_{lung}-PEEP plot. Top Left Panel: Patient 2, Top Right Panel: Patient 6. Bottom Left Panel: Patient 8, Bottom Right Panel: Patient 10. PEEP derived from Minimum E_{lung} and Inflection method are as indicated.

Table 5 shows the model-based approaches to PEEP selection compared to clinically selected PEEP. For 9 of 10 patients, the PEEP value selected using Minimum E_{drs} and E_{drs} Area results in a value higher than the clinically selected PEEP. This latter result suggests that these patients could be treated at PEEP levels higher than clinically selected PEEP. When Minimum E_{drs} or E_{drs} Area metrics are compared with Minimum E_{lung} [16], they result in selecting similar PEEP. However, selecting PEEP is a trade off in minimizing lung pressure and potential damage, versus maximizing recruitment. Hence, the Inflection method offers similar recruitment at a lower PEEP and may be a safer choice, although its selected values are still higher than clinically selected in 7 of 10 cases. Overall, these results reflect the heterogeneity of the ALI/ARDS lung and the need for patient-specific approaches to select PEEP.

Patient 9 is an interesting case which illustrates the model's potential to capture unique patient-specific lung recruitment and condition as it occurs in a clinically and physiologically relevant manner. When the patient is ventilated from PEEP of 5 to $10cmH_2O$, median E_{drs} only decreases by less than $1.0cmH_2O/l$. However, when PEEP is increased to $15cmH_2O$, the median E_{drs} drops significantly, as shown in Figure 5. This smaller E_{drs} drop suggests that only minimal lung volume is recruited from PEEP

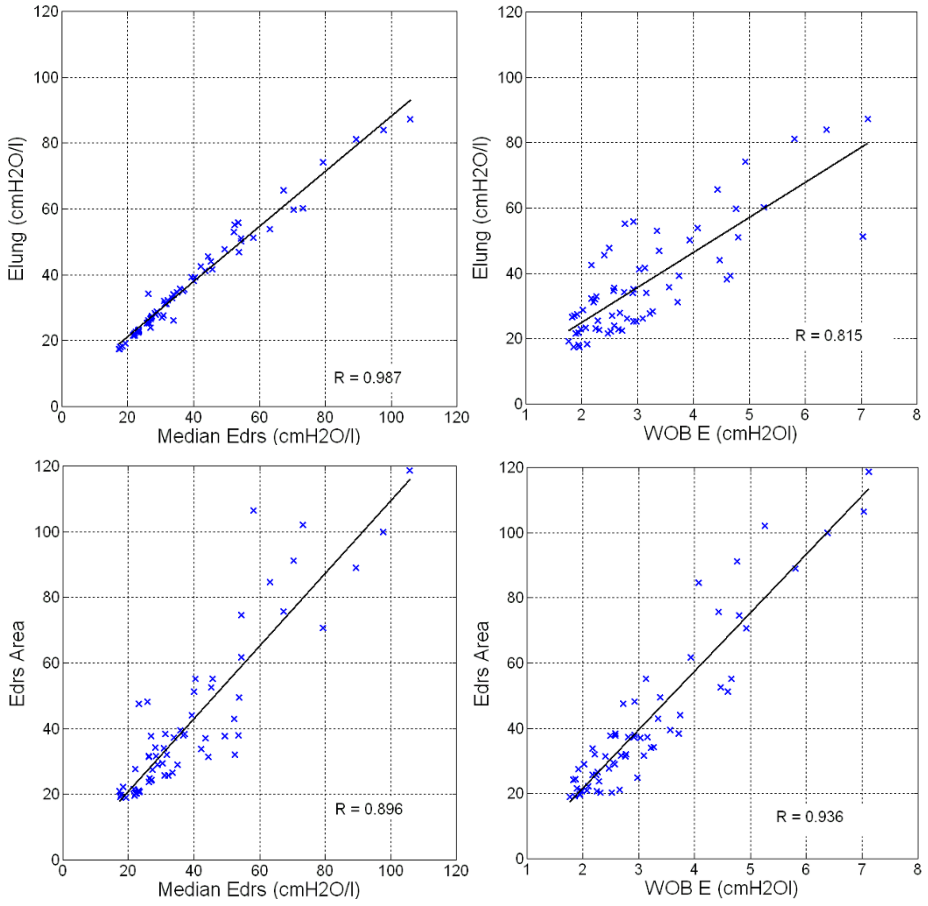
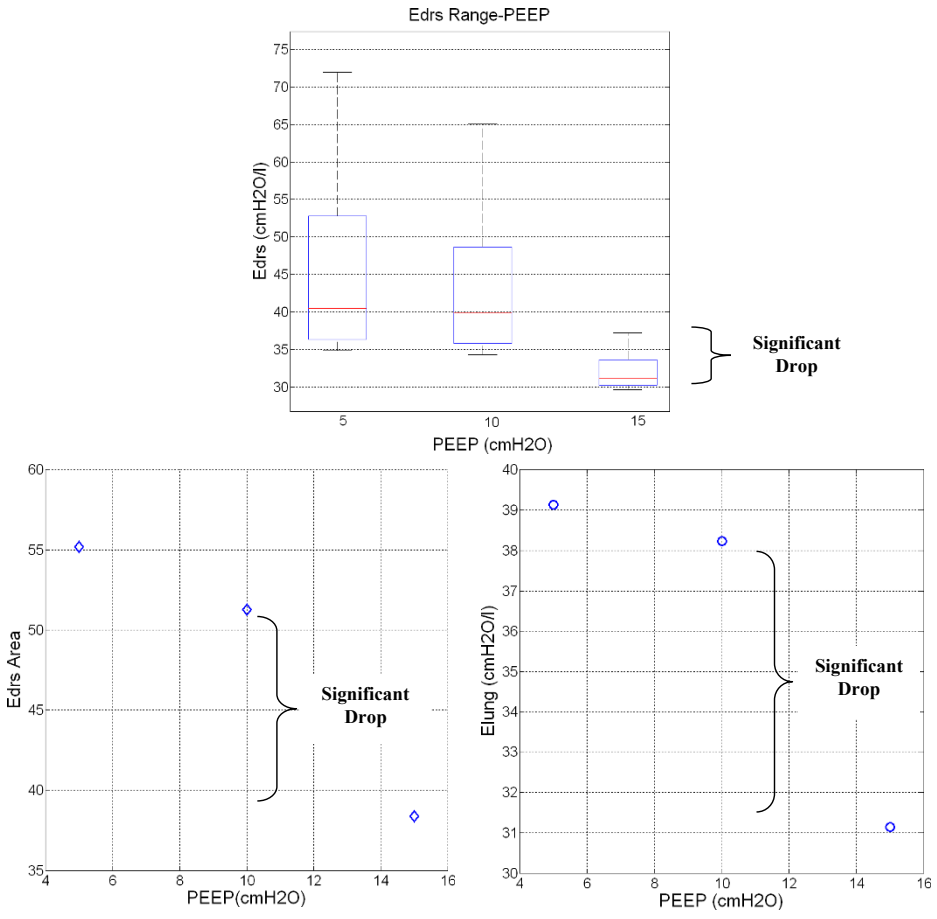


Figure 4 Pearson's Correlation. Top Left Panel: E_{lung}-Median E_{drs}, R = 0.987. Top Right Panel: E_{lung}-WOB_E, R = 0.815. Bottom Left Panel: E_{drs} Area-Median E_{drs}, R = 0.896. Bottom Right Panel: E_{drs} Area-WOB_E, R = 0.936.

of 5 to 10 cmH_2O. The significant drop in E_{drs} at PEEP 15cmH_2O indicates that PEEP *15* cmH_2O has overcome recruitment resistance and additional new lung volume is recruited. Patient 9 was diagnosed with H1N1 and high PEEP for lung recruitment has proven to be beneficial for these patients [30]. Similar trends can be observed in Figure 5 bottom panels with the E_{drs} Area-PEEP plot and E_{lung}-PEEP-plot.

Table 5 PEEP (cmH_2O) selection in clinical and model-based approach.

	Patients									
Selection Methods	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Clinical	10	12	10	10	12	11	7.5	12	10	10
Minimum E_{drs}	20	15	15	25	25	15	5	20	15	20
Minimum E_{drs} Area	25	15	20	20	25	20	10	25	25	20
Inflection E_{drs} Area	14~16	6~9	15~17	16~18	22~24	7.5~12	5~7.5	21~23	20~23	12~16
Minimum E_{lung}	25	15	15	30	25	15	5	25	30	20
Inflection E_{lung}	13~17	6~9	8~10	26~27	21~24	7.5~10	5	12~18	19~22	12 ~15



PEEP (cmH_2O)	5	10	15
E_{drs} ($cmH2O/l$) Median [IQR]	40.5 [36.4-52.8]	39.9 [35.8-48.7]	31.2 [30.2-33.6]
E_{drs} Area (cmH_2Os/l)	55.2	51.3	38.3
E_{lung} (cmH_2O/l)	39.1	38.2	31.1

Figure 5 Patient 9 E_{drs}, E_{drs} Area and E_{lung} change with PEEP. Top Panel: Box-and-whisker diagram for Patient 9 E_{drs} when PEEP increase from 5 to 10cmH_2O. The E_{drs} drops significantly when PEEP is increase from 10 to 15cmH_2O. Bottom Left Panel: E_{drs} Area-PEEP plot for Patient 9. Bottom Right Panel: E_{lung}-PEEP for Patient 9.

4.2 Limitations

In this research, the lung model used to identify patient-specific E_{drs} comprised a single compartment lung model. It was initially proposed for simple computational analysis and neglects the effect of nonlinear flow [31]. However, this analysis is based predominantly on trend comparisons, where the patient is their own reference. In addition, the model is simple and capable of capturing the fundamental lung mechanics, which varies intra- and inter- patients. Hence, this limitation should be minimal in this case, but should be confirmed with direct prospective clinical studies.

During the clinical trials, the patients were sedated and paralyzed using muscle relaxants. It is assumed that after sedation, the patient will be fully dependant on mechanical ventilation and not have spontaneous breathing effort. This assumption thus assumes the patient's pleural pressure (P_{pl}) after sedation is zero and allows P_{pl} in Equation (3) to be omitted, which may not be entirely valid [32]. However, this assumption is made for the first step study to prove the concept within a simpler situation. Otherwise, the terms E_{lung} and E_{drs} would represent a respiratory system elastance [31] and time-variant dynamic respiratory system elastance. However, given the low fitting errors observed, this issue should have little impact in this research.

During the course of estimating patient-specific E_{lung} or E_{drs}, respiratory system resistance, R, is assumed overall constant within a physiological range [33] as PEEP increases. This assumption may not be entirely valid in some cases [33,34]. However, continuous measurements of respiratory resistance are not typically available and the effect of this resistive term is limited mathematically in its impact. Equally, trend comparison, as used here, across PEEP values will reduce the impact.

The identification of E_{lung}, E_{drs} and E_{drs} Area during MV is presented as a method to select PEEP, but there is currently no conclusive, optimum overall E_{drs} or E_{drs} Area in patients. E_{drs} range varies depending on patient disease state and thus will also change over time. However, this trial includes only 10 patients, and there is not yet enough clinical data to indicate an optimum E_{lung}, E_{drs} or E_{drs} Area value for a specific patient or group. On-going, prospective trials with more specific patient groups should develop more conclusive outcomes, relating specific set values of E_{drs} metrics to effective patient-specific treatments and clinical outcome.

In particular, the time-varying E_{drs} value and its change over a given breathing cycle, provides additional insight to guide ventilation that is not investigated here. For example, changes in ventilator pattern or mode to modify the E_{drs} trajectory could also be used with this data to guide therapy choice. However, this study does not have the numbers or design to provide that advice, or specific E_{drs} values associated with specific decrease state or lung damage.

5 Conclusions

The model-based approach presented provides patient-specific, physiological insight not directly measurable without additional invasive, disruptive and clinically intensive test manoeuvres. This method can be directly implemented using modern ventilators with minimal, limited PEEP titrations, and thus without significant interruption to ongoing therapy. In particular, the full manoeuvres used here would not be required for clinical use, and only modest PEEP changes (3-8cmH_2O) would be required to determine if E_{drs} was decreasing at a different PEEP. E_{drs} offers higher resolution in patients' response to change of pressure and PEEP, which is potentially, a better metric compared to existing constant lung elastance estimation. Thus, the overall method is readily generalisable and clinical practicable. It is able to capture patient-specific condition and responsiveness to PEEP and recruitment accurately, and as clinically expected. Hence, the approach presented offers significant potential to improve clinical insight and delivery of mechanical ventilation, and should be prospectively tested.

6 List of Abbreviations

ALI: Acute lung injury; APE: Absolute percentage error; ARDS: Acute respiratory distress syndrome; COPD: Chronic Obstructive Pulmonary Disease; E_{lung}: Patient-specific constant lung elastance; E_{drs}: Patient-specific dynamic lung elastance; FiO_2: Fraction of Inspired Oxygen; ICU: Intensive care unit; IQR: Interquartile Range; MV: Mechanical ventilation; PaO_2: Partial pressure of oxygen in arterial blood; P_{aw}: Airway pressure; P_{pl}: Pleural pressure; P_{tp}: Transpulmonary pressure; PEEP: Positive end expiratory pressure; PF Ratio: PaO_2/FiO_2; P_0: Offset pressure; Q: Flow; RM: Recruitment manoeuvre; R_{lung}: Resistance; SIMV: Synchronized intermittent mandatory ventilation; t: Time; V: Volume; VILI: Ventilation induced lung injury; V_t: Tidal volume; WOB: Work of Breathing; WOB_E: Work to overcome respiratory system elastance; WOB_R: Work to overcome airway resistance; ZEEP: Zero PEEP

7 Competing Interests

The authors declare that they have no competing interests.

8 Authors Contribution

YSC, JGC, GMS created and defined the model. YSC, JGC and TD had input to analysis of results. GMS, AS implemented trials clinically with input from all others. All authors had input in writing and revising the manuscript. All authors have read and approved the final manuscript.

9 Consent

Written informed consent was obtained from the participant and or relative/friends/family of this study. A copy of written consent is available for review by the Editor-in-Chief of this journal.

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