An Extension to the First Order Model of Pulmonary Mechanics to Capture a Pressure dependent Elastance in the Human Lung

A. Knörzer*. P. D. Docherty**, Y. S. Chiew**,
J. G. Chase**, K. Möller*

*Institute of Technical Medicine, Furtwangen University, Villingen-Schwenningen
Germany (e-mail: andreas.gerhard.werner.knoerzer@hs-furtwangen.de).
**Department of Mechanical Engineering, University of Canterbury, Christchurch 8140,
New Zealand (e-mail:paul.docherty@canterbury.ac.nz)

Mechanical ventilation (MV) is a lifesaving therapy for patients with the acute respiratory distress syndrome. However, selecting the optimal MV settings is a difficult process as setting a high positive end-expiratory pressure (PEEP) value will improve oxygenation, but can produce ventilator induced lung injuries (VILI). To find a suitable value is patient specific and depends on different things like the underlying illness and the current state. In this study, a respiratory model that defined constant bronchial resistance and pressure-dependent variable elastance was fitted to pressure volume (PV) responses for 12 datasets of 10 acute respiratory distress syndrome (ARDS) patients which underwent a recruitment maneuver (RM) to open previous collapsed alveoli. We believe that the range of minimal elastance represents that range in which oxygenation can be improved by recruitment with reducing the risk of VILI.

The first order model with a variable elastance (E_{drs}) described by Chiew *et al.* (2011) was modified with a factor α to express added end-expiratory volume due to an increased PEEP. Model parameters were identified using a nonlinear least square method that optimized E_{drs} agreement across PEEP-levels.

The model yielded an increase in overlapping quality of pressure dependent E_{drs}-curves. A best pressure range for PEEP could be identified in 9 of 12 datasets. The model could potentially provide a simple method of decision support at the bedside for clinicians and could prospectively an automated extend in mechanical ventilation devices.

Keywords: , Physiological Models, Gradient methods, Least-squares problems, Linear equation, Medical application, Optimization problems.

1. INTRODUCTION

Mechanical ventilation (MV) is a lifesaving therapy in intensive care units (ICU). Especially for those who suffer from acute respiratory distress syndrome (ARDS). Such patients have fluid filled, stiffer lung units and possibly concurrent partial collapsed regions of the lung (Slutsky and Ranieri, 2000). ARDS by nature is heterogeneous, and varies across patients. This variability severely hampers standardising and optimizing MV treatment. In addition, Dreyfuss *et al.* (1998) and Ricard *et al.* (2002) reported that MV itself has the possible risk to induce ventilator induced lung injuries (VILI). Different approaches such as computer tomography (CT), electrical impedance tomography (EIT) and mathematical models are employed in research to find a singular method for determining optimal patient-specific ventilator settings to improve care and outcomes (Ranieri *et al.* 2012, Bikker *et al. 2010*).

Recent studies have showed that mathematical models are capable of patient bedside application to guide MV without any additional invasive protocols and added workload (Chiew et *al.*, 2011) to the ICU clinicians. Furthermore, models can be combined with existing models currently used in related fields such as oxygen-replacement (Kretschmer *et al.*, 2013). However, the concomitant identification of complex models can impose limitations on their accuracy, identifiability and feasibility in a clinical setting. In contrast, oversimplified models cannot capture all clinically relevant behaviour.

The simplest model to describe the human lung is the first order model (FOM). The FOM simplifies the lung as being one compartment with constant airway resistance and lung compliance (Bates, 2009). However, due to the simple structure of the FOM, pathophysiology of a severely diseased lung such as cyclic opening and collapsing of alveoli during MV in ARDS patients cannot be described. Hence, a variable elastance model (E_{drs}-model) was proposed by Chiew *et al.* (2011) to visualize these clinically important mechanical properties of ARDS patients. This model captures patient-specific respiratory mechanics dynamically. However, it is limited by assuming a constant physiological airway resistance in all patients that is not realistic.

This study extends the time-varying elastance model from Chiew *et al.* in two ways: 1. By applying a fitting parameter capturing additional end-expiratory lung volume resulted by reopened alveoli as described by Stahl *et al.*, (2006) and Dellamonica *et al.*, (2011). 2. By a patient-specific, pressure independent resistance, whichaffords consistent E_{drs} as a function of pressure across all different PEEP levels. It is hypothesised that alveoli recruitment and the avoidance of VILI could be achieved by locating the pressure at which the minimal elastance is found. The minimal pressure can thus potentially be used to set the optimal patient-specific positive end-expiratory pressure (PEEP) during MV to improve care and outcome.

2. METHODS

2.1 First Order Model (FOM)

The model used in this analysis is based on the simple FOM. The FOM can be represented in electrical analogy as a series circuit of a resistor and a capacitor (Fig. 1). In this analogy, airway pressure is represented as voltage and air flow by current. The resistor describes the airway resistance R_{FOM} that is mainly due to the trachea or in case of mechanical ventilation mainly due to the endotracheal tube. The capacitor represents the inverse of respiratory elastance, E_{FOM}, which involves all active forces against inhaled volume. Such forces are the sum of the alveoli state (open, closed or distended), as well as the counterforce of the ribcage. The FOM is defined as:

$$P_{aw} = R_{FOM}\dot{V} + E_{FOM}V + P_0 \qquad (1)$$

where P_{aw} is the airway pressure, $\dot{V}$ is the volume flow rate, V represents the tidal volume and P_0 is the PEEP.
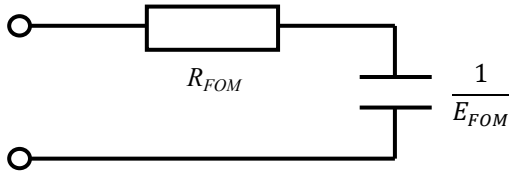

Fig. 1. Electrical analogy of the first order model.

A healthy lung would exhibit a linear pressure volume for a period before and exponential rise in pressure with respect to volume once overdistension occurs. ARDS lungs often exhibit the same behaviour, at a lower volume, with an added effect of low gains at lower pressure (sigmoidal in shape). This change at low pressure is due to the recruitment of collapsed alveoli. Thus, in both of these cases, the linear elastance of the FOM does not conform to the known patient behaviour. Hence, a dynamic elastance term that varies with pressure (E_{drs}) was developed by Chiew *et al.* (2011):

$$P_{aw} = R\dot{V} + E_{drs}(P_{aw})V + P_0 \qquad (2)$$

The Navier-Stokes equation of flow implies that the resistance of the bronchial path will change during inspiration due to its increasing diameters. Hence, a pressure dependent resistance would also be a reasonable assumption. However, this proposal lacks structural identifiability. Thus, only one pressure dependent term can be evaluated for a given data set. Furthermore, during mechanical ventilation, the endotracheal tube as well as the small bronchioles do not stretch much and their resistance can be modelled as a constant value (Guttmann *et al.*, 1995).

At higher PEEP-levels, it can be reasonably assumed that in some cases, alveolar recruitment has taken place. Hence, while the elastance of the individual alveoli are exponential (Salazar and Knowles, 1963), the number of available alveoli is increased. Thus, (2) can be modified according to each PEEP by adding a parameter α_x (with x equal to the index of the applied PEEP starting at x=0 for e.g. an applied PEEP of 5 cmH_2O) that modulates E_{drs} as a function of available alveoli due to the effect of elevated airway pressure by PEEP increase. In effect, if $\alpha_1 > \alpha_2$ recruitment can be inferred, $\alpha_1 < \alpha_2$ derecruitment could be detected.

$$P_{aw} = R_\alpha\dot{V} + \alpha_x E_\alpha(P_{aw})V + P_{0,x} \qquad (3)$$

Whereas E_α and R_α represent the E_{drs} and R_{Edrs} influence by factor α in the later identification process.

2.2 Patients and Data Acquisition

Twelve retrospective datasets from 10 ARDS patients were analysed. Full patient details and recruitment criteria can be found in Sundaresan *et al.* (2011). Every patient underwent a recruitment-manoeuvre with three or four incremental PEEP-levels over a period of 30 minutes. The five breaths prior to each PEEP change were used in this study.

The FOM parameters of each patient are calculated by linear regression using the mean breath from each PEEP. To identify parameters of the time-varying elastance model ($x = [R_\alpha, \alpha_1, \alpha_2, \alpha_3]^T$) a nonlinear gradient descent method was applied in Matlab (lsqnonlin.m, MathWorks, Natick, MA). The objective function ensured that the same E_α values could be used across all breaths for various pressure levels and multiple PEEP levels:

$$x = \operatorname{argmin}_x \sum_{i=1}^{n} \sum_{j=i+1}^{n} \sum_{P_{aw}=0.5}^{50} \left(E_{\alpha,i}(P_{aw}) - E_{\alpha,j}(P_{aw}) \right)^2 \qquad (4)$$

where there are *n* available breaths and $E_{\alpha,i}$ is defined via rearranging (3):

$$E_{\alpha,i} = \frac{P_{aw,i} - P_{0,x} - R_\alpha\dot{V}_i}{\alpha_x V_i} \qquad (5)$$

The α value at minimal clinically acceptable PEEP (α_0) was fixed to 1 and represents a datum value for α_{1-3}. Wide bounds covering realistic α values were placed on the identifiable parameter range:

$$x = \begin{bmatrix} 0.25 < R_\alpha < 30 \\ 0.5 < \alpha_1 < 1.5 \\ 0.25 < \alpha_2 < 2.5 \\ 0.25 < \alpha_3 < 2.5 \end{bmatrix} \qquad (6)$$

All other settings used during parameter identification were set to the default lsqnonlin.m values. Identifying the minimal range of E_α during a recruitment manoeuvre allows a model based optimal PEEP ($PEEP_{OPT}$) to be selected. $PEEP_{OPT}$ can be identified corresponding to the tidal pressure (TP).

However, this is only attempted when there is sufficient E_α curve overlapping, which is defined over the pressure range from 5 cmH$_2$O up to the maximal pressure available in the data (e.g. 50 cmH$_2$O) as:

$$PEEP_{OPT} = \begin{cases} PEEP: E_\alpha(PEEP) = E_\alpha(PEEP + TP), & \sqrt{\sum_{i=1}^{n}\sum_{j=i+1}^{n}\sum_{P_{aw}=5}^{50}\left(E_{\alpha,i}(P_{aw}) - E_{\alpha,j}(P_{aw})\right)^2} < 5000 \\[4mm] \text{undefined}, & \sqrt{\sum_{i=1}^{n}\sum_{j=i+1}^{n}\sum_{P_{aw}=5}^{50}\left(E_{\alpha,i}(P_{aw}) - E_{\alpha,j}(P_{aw})\right)^2} \geq 5000 \end{cases} \quad (7)$$
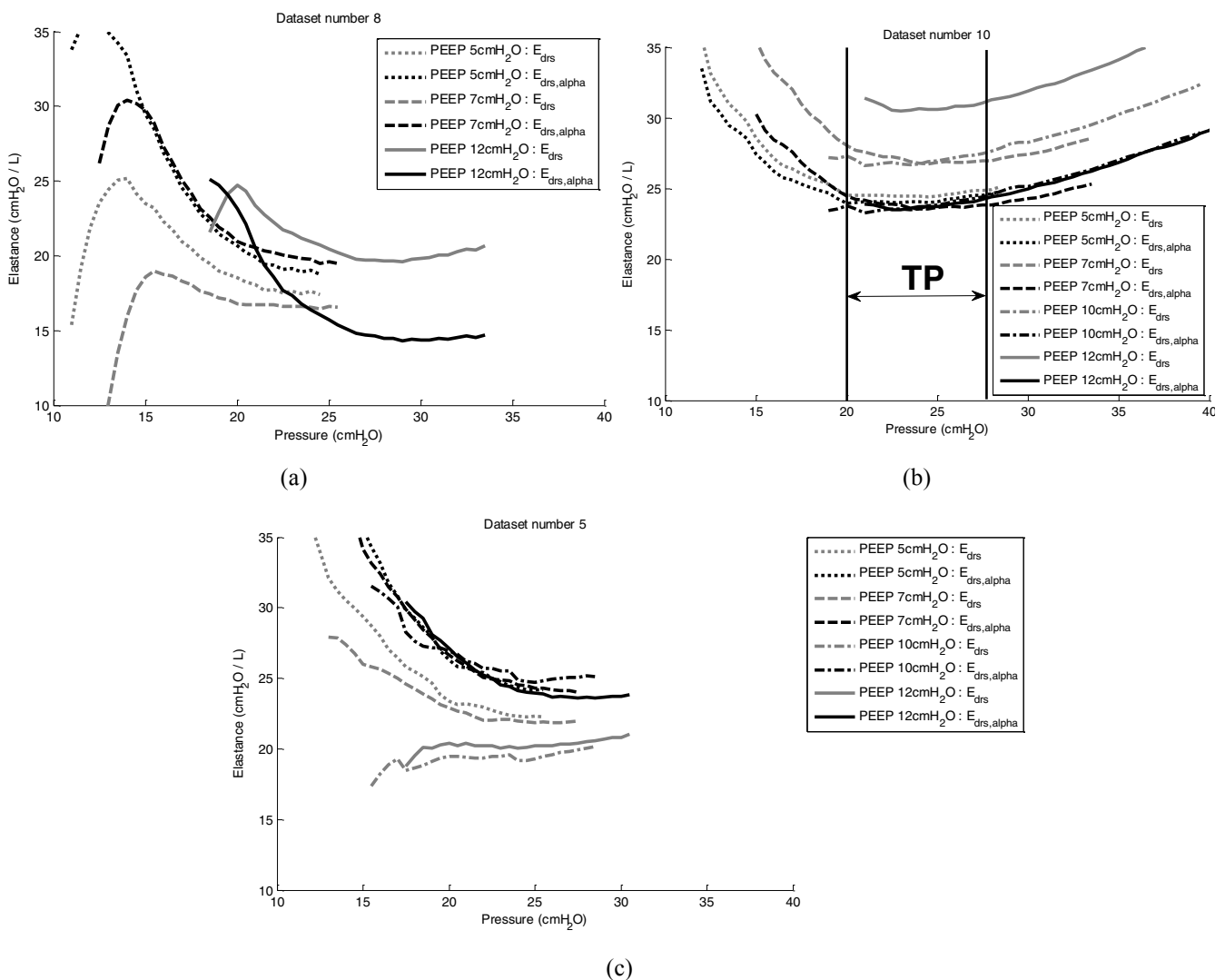
(a)

(b)

(c)

Fig. 2: E_{drs} and E_α plotted against airway pressure. The grey lines indicate the original E_{drs} curves identified with using R_{FOM}, while the black lines show the E_α curves developed using (5). Dataset 10 (b) exhibits an apparent region of minimum elastance whereas dataset 5 (c) exhibits consistently decreasing E_α without evidence of over distension at the pressures encountered. Dataset 8 (a) shows in increase in overlapping quality but without an obvious minimal elastance due to the different shape of the E_α curve of the PEEP 12 cmH$_2$O.

3. RESULTS

Overall, the algorithm performs well and shows a significant increase in overlapping of the $E_\alpha(P_{aw})$ curves compared to $E_{drs}(P_{aw})$ in all datasets. Such issue makes it possible to identify a minimum E_α across the whole pressure range. An example between the initial value using R_{FOM} for calculating E_{drs} (2) compared to the modified (3) can be seen in Fig. 2.

Tab. 1 summarises the results of the FOM identified R_{FOM} compared to identified R_α with declaration of recommended PEEP where appropriate. Tab. 1 shows that in 7 of 12 datasets E_α does not rise at the highest pressures and thus, the E_α values imply that higher pressure could be applied in such patients. All such datasets show a drop in R_α compared to R_{FOM}. Conversely, in the other 5 datasets, showing a rise in E_α at higher pressures, R_α is larger than R_{FOM}. In 3 datasets, the optimal PEEP ($PEEP_{OPT}$) is undefined, as there was insufficient E_α overlapping, and the model assumptions failed. The recruitment parameters, α_{1-3} show no particular trend when overlapping increases.

Only 5 of 12 datasets showing a consistent increase in α at higher pressure ranges. $\alpha_{1,2,3}$ did not change significantly in one direction in any case. Dataset 4 resulted in reaching the upper boundary of α_1 and showed no additional improvement in overlapping.

Patients of dataset 5 and 10 were both ventilated with a tidal range 800 ml/min equivalent to a minute ventilation of 9.6 L/min. An example of a recommended PEEP, as well as tidal pressure-range for ventilation in the lowest elastance parts can be seen in Fig. 2.

4. DISCUSSION

The pulmonary model proposed in this article is based on the assumption of intra-patient consistency in elastance at equivalent pressure levels and across different PEEP levels. Hence the model was identified in such a manner to allow an overall airway resistance and a pressure dependent elastance. The results showed that the α-modified model partially captures the effects of additional end-expiratory lung volume due to PEEP. However, dataset 7 shows a minimal in α_2 (PEEP 10 cmH$_2$O) and a decrease in α_3 (PEEP 12 cmH$_2$O) compared to α_1 (PEEP 7 cmH$_2$O), but showing a minimal E_α-range starting at a PEEP of 14 cmH$_2$O. This inconsistent suggests that α_x captures more effects than the volume distribution due to recruitment. So the initial definition for α is just wrong, but still increasing the system performance.

Given the recruitment and distension effects of the ARDS lung, the pressure dependent elastance is a more physiologically realistic term for the application of model-based ventilation than the fixed value used by the FOM. In particular, Stahl *et al.* (2006) found similar end-expiratory shifts in their work by using an interval based least square fitting method.

Low respiratory elastance values suggests region of efficiency in terms of the amount of pressure required to achieve a volume change. Hence, this model may be useful for finding the optimal PEEP and tidal pressure range settings for ARDS patients while maintaining sufficient ventilation. In particular, dataset 10 showed a minimal elastance in the range of 20 cmH$_2$O up to 27 cmH$_2$O. For this individual, setting PEEP to 20 cmH$_2$O and ventilating with a tidal pressure of 7 cmH$_2$O could enhance the trade-off between recruitment and distension by pressure controlled ventilation resulting in an improvement of oxygenation. Equally, using this method, the tidal volume (or minute ventilation) can be estimated. In contrast, Patient 5 shows a minimum E_α at 25 cmH$_2$O in the present data. Hence, this let assume that the patient could be ventilated with even higher PEEP levels as used in the recruitment manoeuvre. This is then valid if such higher pressures showing as well a later increase in E_α. On the hand, a pure asymptotical behaviour is physiologically implausible and such results have to be taken carefully. However, further retrospective studies and validation with more datasets including an examination to the underlying disease are needed to be conducted on the robustness and clinical applicability of this model.

Table 1: Identification results

Dataset	R_{FOM}	R_α	α_1	α_2	α_3	Recommended PEEP	E_{drs} minimum found
1	6.64	7.30	1.11	1.23	-	20	Yes
2	6.47	5.19	1.27	1.44	-	undefined	No
3	12.25	0.68	1.01	1.04	-	25	No
4	9.35	1.63	1.50	0.59	-	undefined	No
5	6.53	3.97	0.99	0.87	0.96	25	No
6	7.68	0.25	0.98	0.47	0.79	25	No
7	3.5	4.29	1.09	0.91	0.97	14	Yes
8	10.83	9.16	0.20	1.49	-	undefined	No
9	7.59	9.77	1.17	1.12	-	25	Yes
10	6.08	6.54	1.12	1.11	1.26	20	Yes
11	2.67	4.0	1.01	0.92	-	14	Yes
12	10.3	3.55	0.85	0.78	-	30	No

Tab. 1. Comparison between the resistance from the first order model (RFOM) to the resistance of the Edrs,α-model (REdrs,α). α0 was hold to 1 and is not represented. Further recommended PEEPs based on the Edrs,α-model are listed and information of obvious minimal Edrs can be identified.

The recommended PEEP levels are generally high and mostly in the range of the recommended ARDSNet trials of maximal 30 cmH$_2$O, excluding dataset 12. (Slutsky and Ranieri, 2000). This PEEP range of 14 cmH$_2$O up to 30 cmH$_2$O also coincides with the findings of Zick *et al.* (2013) and Caironi *et al.* (2010). Zick *et al.* argued in their works that a relatively high PEEP of 21 cmH$_2$O could have a benefit for the patients. Caironi *et al.* suggested the same for a PEEP of 15 cmH$_2$O to 20 cmH$_2$O with plateau pressure up to 28 cmH$_2$O. Both believe that higher PEEP can avoid unnecessary recruitment and collapse of alveoli.

Using pressures in the range of minimal elastance could generally improve ventilation in a way of balancing stress between healthy and early recruitable alveoli to later recruitable in the overall lung tissue. Lionetti *et al.* (2005) showed that distension of pulmonary tissue in ARDS can lead to released inflation mediators which again lead to organ failure (the main reason for the high mortality in ARDS). Real acting stress on lung tissue could not be captured in the model. The specific time-varying elastance within the tidal pressure range, the tidal volume delivered can be estimated, and thus do not lose the ability to maintain a sufficient minute ventilation. This information of the tidal pressure and tidal volume can be used in mechanical ventilation on pressure control modes.

In this study, the E_α model assumes a static resistance throughout the whole range of airway pressure, which could potentially be incorrect. In particular, van Drunen *et al.* (2013) described a potential collapse of respiratory airway systems and resulting a variable resistance at different underlying PEEP levels. The model showed a trend in the identified resistance compared to the FOM due to an E_α rise at higher pressures. However, this outcome may have been coincidental.

The possibility of identifying an overall E_α-curve over pressure and finding the minimal elastance range can be used to set pressure- or volume-controlled ventilation as well as PEEP. If further studies show an increase in patients outcome, treated with such recommended PEEP, this method can then be an automated process in coming mechanical ventilator devices. As a summary, the α-model has the potential to support clinicians in setting best patient-specific ventilator settings to improve patient care and outcome in the ICU.

5. CONCLUSIONS

In this study, we developed a bedside usable algorithm to find the minimal lung elastance range of patient from a routine clinical procedure and simple parameter identification process. The model was able to identify a minimal E_α range that can be used to improve the ventilation strategy by recognising the optimum range of elastance, and thus leading clinicians in setting ventilation parameters in each patient according to their specific respiratory mechanics. This model has the potential to improve patient ventilation therapy.

However, the model requires further investigation for validation, and confirmation of interpretation.

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