Preprints of the 19th World Congress
The International Federation of Automatic Control
Cape Town, South Africa. August 24-29, 2014

Relation of Respiratory System Elastance and Expiratory Time Constant: Are They From the Same Lung?

Nor Salwa Damanhuri*, Paul D. Docherty*, Yeong Shiong Chiew*, Erwin J. van Drunen*, Nor Azlan Othman*, Thomas Desaive, J. Geoffrey Chase***

**Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand (e-mail: nor.damanhuri@pg.canterbury.ac.nz).*
***GIGA Cardiovascular Science, University of Liege, Liege, Belgium (email: Tdesaive@ulg.ac.be)*

Abstract: Modeling the respiratory system can aid clinical decision making during mechanical ventilation (MV) in the intensive care. However, most lung models only use airway pressure and flow data during inspiration phase of the breathing, and the data from expiration are often neglected. In this study, we hypothesized that the airway pressure and flow data during expiration have equal important information as the inspiratory data for respiratory mechanics modeling. In particular, expiratory time constant parameter, *K*, can provide unique information and relation with respiratory system elastance in MV patients. Two different respiratory models were investigated, with one model focusing on data from inspiratory cycle (Single compartment model) and the other focusing on expiratory cycle (Time constant model). The expiratory time constant model and single compartment model were evaluated based on 22 retrospective datasets of acute respiratory distress syndrome (ARDS) patients from two different cohorts. The expiration time constant model captured a moderate correlation with the lung elastance with R^2= 0.568 in Cohort 1 and weak correlation with R^2= 0.184 in Cohort 2, resulting in an overall of R2 = 0.435. Significant variations in lung resistance may lead to a poor correlation between *K* and lung elastance, E_{lung}. Thus, the application of *K* as a surrogate to the respiratory elastance warrants further investigation.

1. INTRODUCTION

Patients with Acute Respiratory Distress Syndrome (ARDS) experience severe widespread lung injury that leads to inability of gas exchange and breathing problem. ARDS patients admitted to the intensive care unit (ICU) are mechanically ventilated (MV) for breathing support. However, conventional MV does not provide enough real-time information to guide therapy, and suboptimal MV settings increase the risk of further lung injury and complications (Dreyfuss *et al.*, 1998, Slutsky, 1999).

Positive end expiratory pressure (PEEP) is applied during MV to prevent de-recruitment at the end of expiration by keeping unstable lung units open, and to recruit the new lung units. It has also been shown to greatly improve oxygenation in ARDS patients (Meade *et al.*, 2008, Amato *et al.*, 1998). However, selection of patient-specific, optimal PEEP remains widely debatable (Halter *et al.*, 2003, Puybasset *et al.*, 2000). In addition, there are limited non-invasive methods that can provide real time information on the patient's lung condition and disease state (Sundaresan *et al.*, 2011b, Carvalho *et al.*, 2007). Thus, clinicians often resort to generalised approaches (Kallet *et al.*, 2007) or experience and intuition to select PEEP, increasing the variability and risk of suboptimal care. Mathematical lung models can be used to better identify patient-specific response to MV to aid selecting of PEEP and MV settings.

In particular, respiratory system modelling can provide real-time information on the patient condition and response based on MV airway pressure, (P_{aw}) and flow, (Q_{aw}) data. However, most studies show that these models require specific data profiles and specialised protocols for model identification (Oostveen *et al.*, 2003, Ben-Tal, 2006). These models also focus only on data collected during inspiration, and data during expiration are neglected. However, recent research by Al Rawas *et al.*(2013) and van Drunen *et al.* (2013) studied expiratory data phase and found high correlation between the expiratory time constant and respiratory system elastance in clinical and experimental trials. This finding has led to a potential to use of the expiratory or perhaps the 'forgotten twin' during clinical respiratory mechanics monitoring to guide MV.

This study extends the investigation on the relation of expiratory time constant with respiratory system elastance in retrospective clinical cohorts. These data comprise of patients undergoing a recruitment manoeuvres (RM) with step PEEP changes. These data provide a variation of respiratory system elastance at different PEEP levels (Chiew *et al.*, 2011). These respiratory system elastance variations thus provide a unique platform to investigate the relation of expiratory time constant with inspiratory respiratory system elastance. More importantly, information on respiratory system elastance response to PEEP has shown clinical potential for guiding PEEP titration. Thus, a good correlation between these metrics will imply that the expiratory time constant can also be used to titrate PEEP under similar assumptions (van Drunen *et al.*, 2013).

2. METHODOLOGY

2.1 Patients Data and Analysis

Data from two retrospective ARDS cohorts were used for this study, consisting of 10 patient-datasets from Sundaresan *et.al* (2011a) and 12 patient-datasets from Bersten *et al.* (1998) (Cohort 1 and 2, respectively). In particular, patients in Cohort 1 underwent a modified protocol-based RM. These patients were ventilated with 5-8 different PEEP levels using a decreasing inspiratory flow profile (Sundaresan *et al.*, 2011a). All patients in Cohort 1 were fully sedated and ventilated using Puritan Bennett PB840 ventilators (Covedin, Boulder, CO, USA) with volume control (tidal volume = 6-8 mL/kg). The clinical trials and the use of this data has been reviewed and approved by the New Zealand, South Island Regional Ethics Committee. Further details on clinical protocols are in Chiew *et al* (2011).

Patients in Cohort 2 were fully sedated and ventilated using Puritan Bennett 7200ae ventilators (Carlsbad, CA, USA) under volume control mode (tidal volume = 8-10 mL/kg) and a square-wave inspiratory flow. Patients in Cohort 2 were tested in 3-4 different PEEP levels. PEEP trials were at baseline and then repeated at 30 min intervals following PEEP changes between 5 and 15 cmH_2O. These clinical trials were approved by the Committee for Clinical Investigation at Flinders Medical Centre.

2.2 Lung Elastance Model

The lung elastance model is derived from the single compartment lung model.

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

where P_{aw} is the airway pressure, t is time, R_{lung} is the respiratory airway resistance, $\dot{V}$ is the flow, E_{lung} is the lung elastance, V is the lung volume and P_0 is the offset pressure.

However, this model focuses on inspiration. Using an integral-based method (Hann *et al.*, 2005), the lung elastance (E_{lung}) and respiratory resistance (R_{lung}) are estimated.

$$\int P_{aw}(t) = R_{lung} \times \int \dot{V}(t) + E_{lung} \times \int V(t) + \int P_0 \quad (2)$$

R_{lung} consists of the resistance in endotracheal tube and airway branching respiratory system. With the data from the measured inspiratory pressure (P_{aw}) and flow ($\dot{V}$) for each breathing cycle, the best values that fit the single compartment lung model as defined in Equation (1) are determined.

2.3 Expiratory Time Constant Model

The expiratory time constant model is also derived from the single compartment lung model, but focuses on expiration. van Drunen *et. al* (2013) proposed a method of calculating the time constant (K), during the expiration time cycle. The expiratory time constant model derived from the single compartment lung model is defined:

$$\dot{V}(t) = \dot{V}_0 e^{t/\tau} = \dot{V}_0 e^{-Kt} \quad (3)$$

where $\dot{V}$ is the value of maximum expiratory flow and $\tau = 1/K = R_{lung}/E_{lung}$ is the time constant for this model during expiratory time. The details on how Equation (3) is developed can be found in van Drunen *et. al* (2013).

It is important to note that expiration is a passive process that unloads the inspired tidal volume over a resistance at a constant ventilator applied end expiratory pressure.

2.4 Analysis

Inspiration and expiration in the respiratory system are two different physiological processes. The expiratory time-constant model parameter, K, is calculated continuously for each PEEP level for both cohorts. The trend for the estimated K values are compared with the inspiration derived values E_{lung}/R_{lung} and E_{lung}. Performance was assessed by trend correlation coefficient (R^2) where comparisons between the estimated K for expiration, and both E_{lung}/R_{lung} and E_{lung} for inspiration were made.

3. RESULTS

Figures 1 and 2 compare the correlation between K and inspiration derived E_{lung}, and between K and inspiration derived E_{lung}/R_{lung} for both Cohorts 1 and 2. The Pearson correlation for K- E_{lung} for Cohort 1 is $R^2 = 0.568$, Cohort 2- $R^2 = 0.184$ and the overall value is $R^2 = 0.435$. The correlation K- E_{lung}/R_{lung} is $R^2 = 0.340$ for Cohort 1 and $R^2 = 0.002$ for Cohort 2 and $R^2 = 0.078$ all together. The median and inter-quartile range (IQR) of E_{lung}, R_{lung}, E_{lung}/R_{lung} and K for each data set are reported in Tables 1 (Cohort 1) and 2 (Cohort 2).

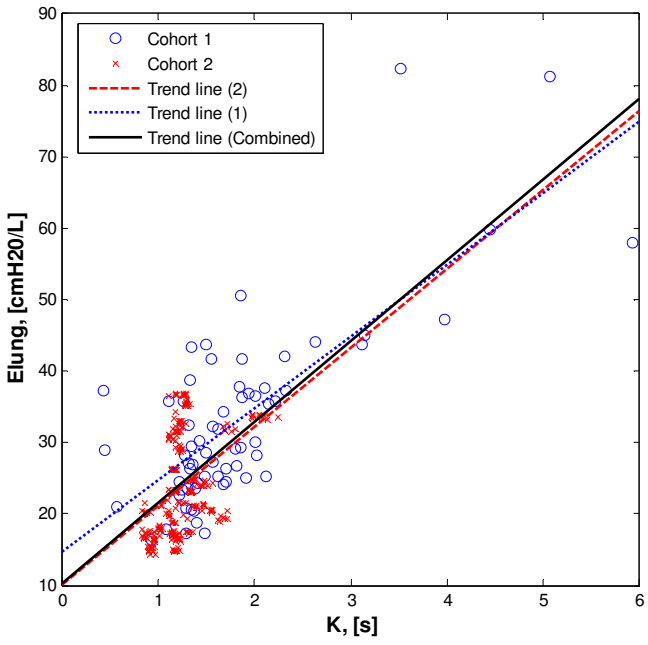

Fig. 1. Correlation plots of K vs E_{lung} for both data sets with with $R^2 = 0.568$ for Cohort 1 and $R^2 = 0.184$ for Cohort 2 and $R^2 = 0.435$ for both Cohorts at all PEEP levels.

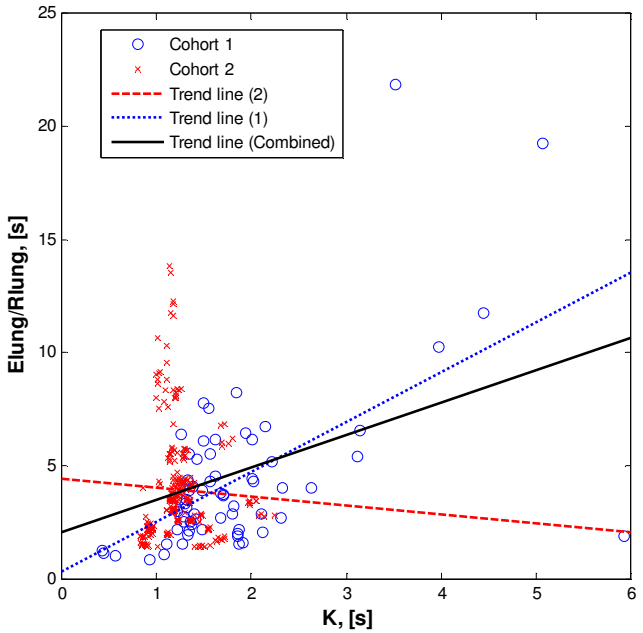

Fig. 2. Correlation plots of K vs E_{lung}/R_{lung} for both data sets with R^2 = 0.340 for Cohort 1 and R^2 = 0.002 for Cohort 2 and R^2 = 0.078 for both Cohorts at all PEEP levels.

Table 1. Median and IQR E_{lung}, R_{lung}, E_{lung}/R_{lung} and K of each dataset from Cohort 1.

Dataset	Median [IQR]			
	E_{lung}	R_{lung}	E_{lung}/R_{lung}	K
S1	32.54 [27.51-37.24]	10.65 [9.59-15.87]	2.53 [1.74-3.76]	1.33 [1.30-1.34]
S2	23.13 [21.31-26.17]	7.66 [7.55-8.25]	3.03 [2.50-3.46]	1.31 [1.29-1.34]
S3	20.70 [18.05- 26.81]	6.70 [6.17-7.45]	2.86 [2.33-4.37]	1.34 [1.27-1.41]
S4	25.04 [19.38-27.04]	19.68 [16.10-23.07]	1.15 [1.04-1.42]	0.93 [0.51-1.50]
S5	44.54 [42.32-49.21]	16.11 [11.54-23.98]	2.52 [2.03-3.72]	2.37 [1.93-3.01]
S6	24.84 [24.49-30.22]	5.65 [5.26-6.40]	4.32 [3.80-5.77]	1.62 [1.44-1.68]
S7	59.70 [47.16-81.18]	4.59 [4.22-5.09]	11.74 [10.27-19.25]	3.98 [3.52-4.44]
S8	29.11 [27.51-32.20]	7.24 [6.66-9.25]	3.65 [3.03-4.37]	1.81 [1.76-2.01]
S9	27.97 [25.07-30.09]	6.45 [6.21-10.86]	3.83 [2.44-4.62]	1.57 [1.49-1.72]
S10	37.18 [36.36-41.86]	5.75 [5.57-8.06]	6.42 [4.61-7.11]	2.15 [1.75-2.27]
Median [IQR]	**29.40 [24.63-37.47]**	**7.78 [6.02-12.72]**	**3.50 [2.18-5.37]**	**1.57 [1.33-1.99]**

Figure 3 compares the trend of R_{lung} between a patient with Chronic Obstructive Pulmonary Disease (COPD) and a non COPD patient for all PEEP levels. Figure 4 shows the trend comparison of expiration time constant, K, inspiration E_{lung} and inspiration E_{lung}/R_{lung} between patient S1 from Cohort 1 and patient B10 in Cohort 2 for all PEEP levels at every breathing cycle. The model-fitting for airway flow and pressure between measured and calculated values for dataset S3 are depicted in Figure 5.

Table 2. Median and IQR E_{lung}, R_{lung}, E_{lung}/R_{lung} and K of each dataset from Cohort 2.

Dataset	Median [IQR]			
	E_{lung}	R_{lung}	E_{lung}/R_{lung}	K
B1	26.23 [23.47-36.62]	7.67 [7.61-7.82]	3.06 [2.99-3.43]	1.18 [1.14-1.21]
B2	15.32 [15.034-16.28]	7.09 [6.27-7.59]	2.18 [2.15-2.34]	0.94 [0.91-0.95]
B3	32.76 [30.99-36.63]	12.69 [8.83-15.43]	2.59 [2.02-4.18]	1.22 [1.13-1.26]
B4	18.27 [17.478-19.29]	7.48 [4.04-11.02]	3.04 [1.75-4.32]	1.49 [1.31-1.67]
B5	21.12 [20.54-21.36]	7.09 [5.24-8.33]	2.86 [2.47-4.09]	1.39 [1.27-1.49]
B6	33.46 [32.39-33.70]	9.95 [5.33-11.82]	3.39 [2.85-5.94]	1.98 [1.77-2.10]
B7	17.18 [16.26-18.67]	3.71 [2.23-4.70]	5.32 [3.41-8.68]	1.16 [1.07-1.19]
B8	17.40 [16.98-20.14]	11.02 [10.88-11.30]	1.55 [1.50-1.84]	0.86 [0.85-0.89]
B9	32.23 [29.53-35.21]	6.69 [6.49-8.35]	4.39 [3.93-5.39]	1.24 [1.19-1.28]
B10	28.90 [25.43-32.91]	5.68 [3.78-7.61]	5.78 [3.34-8.71]	1.20 [1.17-1.25]
B11	17.40 [17.18-18.75]	3.04 [1.60-3.15]	5.64 [5.49-11.70]	1.16 [1.14-1.17]
B12	24.03 [23.29-24.77]	9.70 [6.80-16.57]	2.55 [1.46-3.40]	1.36 [1.35-1.45]
Median [IQR]	**23.10 [17.59-31.48]**	**7.43 [4.88-9.40]**	**3.42 [2.48-4.40]**	**1.20 [1.13-1.34]**

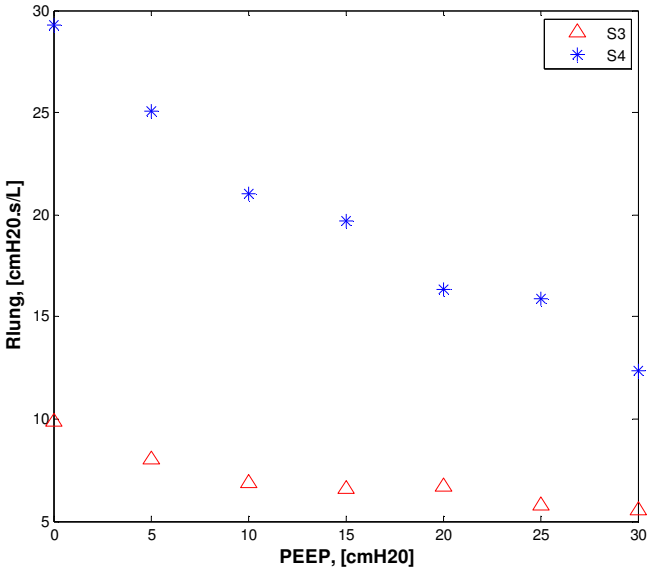

Fig 3. Comparison of R_{lung} between data set S3 which is a non COPD patient with data set S4, COPD patient for all PEEP levels.

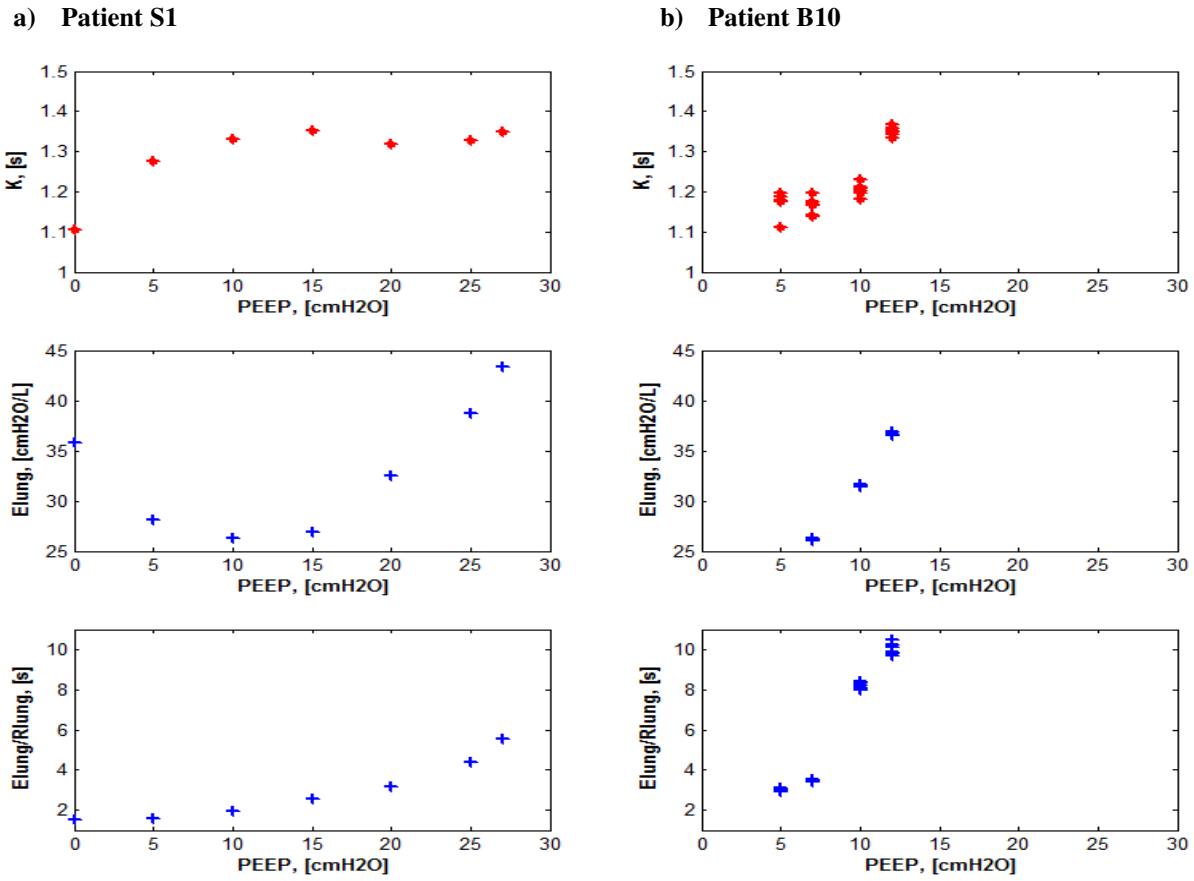

Fig. 4. a) Trend comparison of expiration time constant, K, inspiration E_{lung} and inspiration E_{lung} / R_{lung} for one breathing cycle for patient S1 from Cohort 1 for all PEEP levels. b) Trend comparison of expiration time constant, K, inspiration E_{lung} and inspiration E_{lung} / R_{lung} for seven breathing cycle for patient B10 from Cohort 2 for all PEEP levels

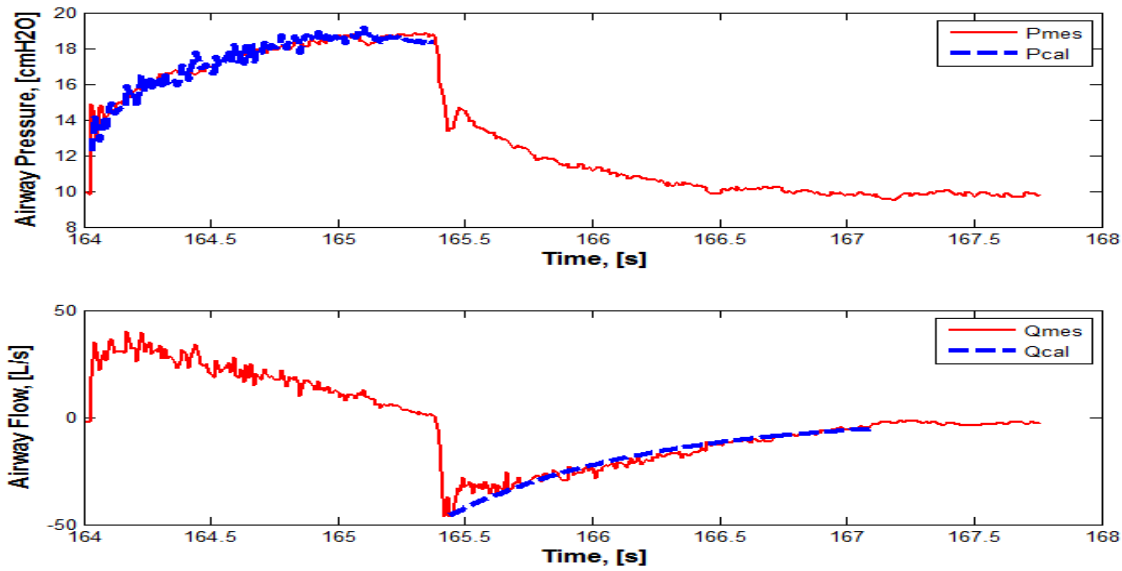

Fig. 5. (Top) Model-fitting between measured airway pressure, P_{mes} and calculated airway pressure, P_{cal} based on the lung elastance model for data set S3 at PEEP = 10 cmH_2O one breathing cycle . (Bottom) Model-fitting between measured airway flow, Qmes and calculated airway flow, Qcal for data set S3 at PEEP = 10 cmH_2O for one breathing cycle.

4. DISCUSSION

In this study, the time constant K has shown moderate correlation with E_{lung} with R^2= 0.568 in Cohort 1 and weak correlation with R^2= 0.184 in Cohort 2, as shown in Figure 1. Comparatively, the correlation of K with the inspiration E_{lung}/R_{lung} shows a weak correlation of R^2= 0.340 for Cohort 1 and R^2= 0.002 for Cohort 2, as depicted in Figure 2. These results contradict to findings by Al Rawas *et. al* (2013) and van Drunen *et. al* (2013) where the time constant estimated using expiratory data has good correlation with the estimated respiratory elastance using inspiratory data.

In this study, Cohort 1 includes of Chronic Obstructive Pulmonary Disease (COPD) patients (datasets S1, S4, S5, S9, S10) which had higher resistance in the lung (R_{lung}) compared to other non-COPD, as shown in Table 1. Furthermore, it can be seen in COPD patient (S4) in Figure 3 that higher R_{lung} exists due to the obstructed airways at lower pressures and PEEP, as compared to the non-COPD patient (S3). Since K= E_{lung}/R_{lung}, an increasing airway resistance would result in a low value of K as compared to E_{lung}. Significant variations in R_{lung} may lead to poor correlation between K and E_{lung} (van Drunen *et al.*, 2013). Equally, these patients were found to have decreased K, with every increase in resistance. Clinically, a patient with COPD requires more time for expiration, which will lead to an increased expiratory time constant (~ 1/K) (Lourens *et al.*, 2000).

Patients in Cohort 1 and Cohort 2 are fundamentally different because the flow profiles are different with a decreasing flow profile in Cohort 1 and a square wave profile in Cohort 2. For some cases, K were relatively unchanged with PEEP, as shown in Figure 4 compared to the value for E_{lung} and E_{lung}/R_{lung} for dataset S1 and dataset B10. Similarly, the median and interquartile range [IQR] of K for Cohort 1 is 1.57[1.33-1.99] while Cohort 2 is 1.20[1.13-1.34]. These results may be due to that the same expiration flow pattern exists in both cohorts thus resulting in relatively constant values of K. In addition, the trend of K does not follow either E_{lung} or E_{lung}/R_{lung} for both cohorts. This lack of correlation may be a subject-specific response due to the increasing severity of ARDS collapsing airways within the lungs, thereby increasing the resistance of the conducting airways (R_{lung}) as mentioned previously in (Gattinoni *et al.*, 2005).

Figure 4 is a patient example where, E_{lung} changed as PEEP changed. With the increasing E_{lung}, it shows that the lung becomes stiffer, thus no further recruitment happened in the lung. Monitoring patient-specific E_{lung} during PEEP changes has the potential to be used in optimum PEEP titration for the ARDS patients (Chiew *et al.*, 2011). Thus, if K had high positive correlation with E_{lung}, it could potentially be used to titrated PEEP. However, in this study, only Cohort 1 shows useful correlation and for Cohort 2, there is almost no correlation. This result indicates that, although K is defined as E_{lung}/R_{lung} from inspiration for expiration, it does not deliver the same result as those same values in inspiration because each expiration and inspiration must be considered separately when determining lung mechanics properties (Möller *et al.*, 2010).

For the result shown in Figure 5, the calculated airway pressure using the inspiration lung elastance model has resulted in a good fitting with the measured airway pressure from the ventilator for data set S3 from Cohort 1 which the median and IQR 1.74[0.79 - 2.79]. This low fitting error is also found in the calculated airway flow versus measured airway flow in this patient data set. This result shows that by using the lung elastance model, it follows the same trend as the measured data.

Study by van Drunen *et al* (2013) showed that K has a similar trend with E_{lung} in experimental ARDS animal trials (van Drunen *et al.*, 2013). However, this study using human data showed otherwise. The animal cohort by van Drunen *et al* (2013) had higher tidal volume (V_t) (10-12 mL/kg) during MV. Higher V_t during ventilation allows more air to enter into the lung. . Higher V_t during ventilation allows more air to enter into the lung, thus allowing the elastic properties to be identified. Equally, higher V_t will thus provide better flow data resolution during expiration cycle.

Compared to the animal study, both human patient cohorts used in this study have lower tidal volume limiting the data available during expiration (6-8 mL/kg). This V_t was found to be less injurious and thus often used as a safety threshold (Brochard *et al.*, 1998, Parsons *et al.*, 2005, The Acute Respiratory Distress Syndrome Network, 2000). Thus, it is not clinically feasible to use higher tidal volume in humans, and an alternate approach, such as the controlled expiration would be required to get the best resolution and value of K that better reflects and correlates with E_{lung} (Möller *et al.*, 2010).

Furthermore, this different in result may also be due to the different protocols applied in these two studies. A better relationship and correlation between K and PEEP might be obtained by designing a clinical protocol where V_t is varied between low and high values at constant PEEP. Equally, controlled expiration cycle might be considered.

Although K has shown a poor correlation for Cohort 2, it still delivered a good indication for COPD patients in Cohort 1 due to the higher airway resistance in the lung. Thus, the potential application for K remains in diagnosing and provide further insight lung condition in COPD patients. Furthermore, with specific ventilation profile and clinical protocol, K can be extended to determine real-time lung parameters using only expiration data. In particular, this application can be important in spontaneously breathing (SB) patient, where these patients have individual breathing effort that alters the lung mechanics, and cannot be estimated with additional invasive tools. However, the results and implications that were derived from this study, shows otherwise. Thus, the application of expiratory time constant in SB patients warrants further investigations.

5. CONCLUSIONS

In this research, it has shown that variations in lung resistance may lead to a lower correlation between K and E_{lung}. However, there is a relation exists between K and the lung resistance, (R_{lung}) especially for COPD patients. Time constant K may have potential in tracking the changes in

disease state for MV patients in real-time, but it warrants further investigation with specific clinical protocol and ventilation practice.

6. CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

REFERENCES

Al-Rawas, N., Banner, M. J., Euliano, N. R., Tams, C. G., Brown, J., et al. (2013). Expiratory time constant for determinations of plateau pressure, respiratory system compliance, and total resistance. *Crit Care,* 17**,** 1**,** R23.

Amato, M. B. P., Barbas, C. S. V., Medeiros, D. M., Magaldi, R. B., Schettino, G. P., et al. (1998). Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *New England Journal of Medicine,* 338**,** 6**,** 347-354.

Ben-Tal, A. (2006). Simplified models for gas exchange in the human lungs. *Journal of Theoretical Biology,* 238**,** 474 - 495.

Bersten, A. D. (1998). Measurement of overinflation by multiple linear regression analysis in patients with acute lung injury. *Eur Respir J,* 12**,** 3**,** 526-532.

Brochard, L., Roudot-Thoraval, F., Roupie, E., Delclaux, C., Chastre, J., et al. (1998). Tidal Volume Reduction for Prevention of Ventilator-induced Lung Injury in Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med,* 158**,** 6**,** 1831-1838.

Carvalho, A., Jandre, F., Pino, A., Bozza, F., Salluh, J., et al. (2007). Positive end-expiratory pressure at minimal respiratory elastance represents the best compromise between mechanical stress and lung aeration in oleic acid induced lung injury. *Critical Care,* 11**,** 4**,** R86.

Chiew, Y. S., Chase, J. G., Shaw, G., Sundaresan, A. & Desaive, T. (2011). Model-based PEEP Optimisation in Mechanical Ventilation. *BioMedical Engineering OnLine,* 10**,** 1**,** 111.

Dreyfuss, D. & Saumon, G. (1998). Ventilator-induced lung injury: lessons from experimental studies. *Am J Resp Crit Care Med,* 157**,** 294 - 323.

Gattinoni, L. & Pesenti, A. (2005). The concept of "baby lung". *Intensive Care Medicine,* 31**,** 6**,** 776 - 784.

Halter, J. M., Steinberg, J. M., Schiller, H. J., Dasilva, M., Gatto, L. A., et al. (2003). Positive End-Expiratory Pressure after a Recruitment Maneuver Prevents Both Alveolar Collapse and Recruitment/Derecruitment. *Am J Respir Crit Care Med,* 167**,** 12**,** 1620-1626.

Hann, C. E., Chase, J. G., Lin, J., Lotz, T., Doran, C. V., et al. (2005). Integral-based parameter identification for long-term dynamic verification of a glucose-insulin system model. *Computer Methods and Programs in Biomedicine,* 77**,** 3**,** 259-270.

Kallet, R. & Branson, R. (2007). Respiratory controversies in the critical care setting. Do the NIH ARDS Clinical Trials Network PEEP/FIO2 tables provide the best evidence-based guide to balancing PEEP and FIO2 settings in adults? *Respiratory care,* 52**,** 4**,** 461.

Lourens, M. S., Van Den Berg, B., Aerts, J. G., Verbraak, A. F., Hoogsteden, H. C., et al. (2000). Expiratory time constants in mechanically ventilated patients with and without COPD. *Intensive Care Med,* 26**,** 11**,** 1612-8.

Meade, M. O., Cook, D. J., Guyatt, G. H., Slutsky, A. S., Arabi, Y. M., et al. (2008). Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome. *JAMA: the journal of the American Medical Association,* 299**,** 6**,** 637-645.

Möller, K., Zhao, Z., Stahl, C.and Guttmann, J. Year. On the analysis of dynamic lung mechanics separately in ins- and expiration. *In:* XII Mediterranean Conference on Medical and Biological Engineering and Computing 2010, 2010. Springer, 164-167.

Oostveen, E., Macleod, D., Lorino, H., Farre, R., Hantos, Z., et al. (2003). The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *European Respiratory Journal,* 22**,** 6**,** 1026-1041.

Parsons, P. E., Eisner, M. D., Thompson, B. T., Matthay, M. A., Ancukiewicz, M., et al. (2005). Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. *Crit Care Med,* 33**,** 1**,** 1-6.

Puybasset, L., Gusman, P., Muller, J.-C., Cluzel, P., Coriat, P., et al. (2000). Regional distribution of gas and tissue in acute respiratory distress syndrome. III. Consequences for the effects of positive end-expiratory pressure. *Intensive Care Medicine,* 26**,** 9**,** 1215-1227.

Slutsky, A. S. (1999). Lung Injury Caused by Mechanical Ventilation*. *Chest,* 116**,** suppl 1**,** 9S-15S.

Sundaresan, A., Chase, J., Shaw, G., Chiew, Y. S. & Desaive, T. (2011a). Model-based optimal PEEP in mechanically ventilated ARDS patients in the Intensive Care Unit. *BioMedical Engineering OnLine,* 10**,** 1**,** 64.

Sundaresan, A. & Chase, J. G. (2011b). Positive end expiratory pressure in patients with acute respiratory distress syndrome - The past, present and future. *Biomedical Signal Processing and Control,* In Press, Corrected Proof.

The Acute Respiratory Distress Syndrome Network (2000). Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. *N Engl J Med,* 342**,** 18**,** 1301-1308.

Van Drunen, E. J., Chiew, Y. S., Chase, J. G., Shaw, G. M., Lambermont, B., et al. (2013). Expiratory model-based method to monitor ARDS disease state. *Biomed Eng Online,* 12**,** 57.