How hard is it to breathe? Quantification of lung elastance and inspiratory work of breathing in healthy and COPD patients.

Theodore Lerios * **Jennifer L. Knopp** * **Lui Holder-Pearson** **
Ella F. S. Guy * **J. Geoffrey Chase** *

* *Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand (e-mail: ted.lerios@pg.canterbury.ac.nz).*
** *Department of Electrical and Computer Engineering, University of Canterbury, Christchurch, New Zealand.*

Abstract: Chronic Obstructive Pulmonary Disease (COPD) covers a range of underlying lung conditions. Lung mechanics, particularly airway resistance, are altered, increasing the work of breathing (WOB). Model-based methods to estimate lung parameters may help reduce the clinical burden of diagnosis and monitoring. This analysis presents a modified single compartment model describing lung mechanics and WOB. Plethesmographic data, including derived alveolar pressure, is used to identify inspiratory airway resistance (R_{insp}), lung elastance (E), and inspiratory effort (P_{eff}, cmH_2O). Four (n=10 each) clinical cohorts comprise subjects who are healthy (young and old) and with COPD (with (FL) and without (NFL) expiratory flow limitation). E and R are correlated ($R^2 = 0.73$) and within the normal range in healthy cohorts (R_{insp} <5 $cmH_2O/L/s$, E = 0-6 cmH_2O/L), but elevated to R = 5-15 $cmH_2O/L/s$ and E = 5 - 12 cmH_2O/L in patients with COPD. The peak negative P_{eff} was highest in FL COPD patients, reflecting higher WOB required to overcome E and R_{insp} dynamics. Increased R_{insp} was more dominant than changes in E in COPD patients. Overall, the modelled P_{eff} match pleural and esophageal pressure measurements in literature. The model presented appears to capture key inspiratory effort dynamics, and is a first step towards a more generalised model for non-invasive clinical diagnosis and monitoring of COPD lung conditions.

Keywords: Physiological Modelling, Lung Mechanics, COPD, work of breathing.

1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a group of progressive lung diseases characterised by airway resistance and increased WOB of breathing, where severe COPD significantly impacts gas exchange resulting in 'air hunger' (Loring et al., 2009). COPD is prevalent, and an increasingly significant global cause of death and disability (Vogelmeier et al., 2017). In the United States an estimated US$72 billion/annum is spent on COPD-related healthcare (Khakban et al., 2017), and this will increase with COPD's projected overtaking of ischemic heart disease by 2025. Despite being treatable (Osthoff et al., 2013), it is largely overlooked in policy, healthcare, and the pharmaceutical industry. Emphysema and chronic bronchitis are two common COPD lung conditions. While inflammation in the airways and alveoli can affect the mechanical properties of the lungs, such as airway resistance and lung elastance (Loring et al., 2009), another common characteristic of COPD is expiratory flow resistance and eventual flow limitation (FL). FL is a mechanical-pathophysiological condition characterised by constant flow, despite increased pressure gradient across the airways, and is a well defined (Koulouris et al., 1995; Dellaca et al., 2004; Diaz et al., 2000). Thus, COPD includes a wide range of underlying lung conditions that affect underlying lung mechanics. Identification of patient-specific breathing issues is necessary for effective treatments.

Current methods for assessment of COPD lung mechanics include spirometry and full body plethysmography. Negative expiratory pressure, which applies an additional negative pressure at the mouth during expiration to increase the pressure gradient across the airways. All these methods are currently clinically burdensome, requiring specialist equipment and personnel.

Model-based methods can provide patient-specific insight into pulmonary mechanics from a minimum of easily accessible pressure-flow data, and have been shown useful at the intensive care bedside (Kim et al., 2019; Knopp et al., 2021; Chiew, 2013; Chase et al., 2021). Such methods have the potential to capture the different disease states and lung conditions within COPD, and can provide a less-invasive and less clinically burdensome method for COPD diagnosis and monitoring.

This study fits a simple single compartment model plethesmographic data in subjects who are healthy and those diagnosed with COPD, to identify airway resistance, lung elastance, and overall work of breathing (WOB). The aim is to test and validate models in plethesmographic data, as

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a first step towards a low clinical burden tool for at-home or general clinical COPD diagnosis and monitoring.

2. METHODS

2.1 Model

The difference between pressure measured at the airway (P_{atm}) and alveoli (P_{alv}) give a measure of the resistive pressure across the airways alone (Bates, 2009).

$$P_{atm}(t) - P_{alv}(t) = RQ(t) \tag{1}$$

where R ($cmH_2O/L/s$) is airway resistance and Q (L/s) is flow. The equation of motion describing the elastic tissue dynamics is:

$$P_{alv}(t) - P_{pl} = EV(t) \tag{2}$$

where P_{pl} is the pressure in the pleural cavity. If the pleural pressure is used as a surrogate for inspiratory effort, Equation 2 can be rewritten:

$$P_{alv}(t) = EV(t) + P_{eff} \tag{3}$$

where P_{eff} is the pressure dynamic in the pleural cavity representing breathing effort, and E (cmH_2O/L) is tissue elastance. The modelled atmospheric pressure is therefore described in Equation 4:

$$P_{atm}(t) = RQ(t) + EV(t) + P_{eff} \tag{4}$$

where an electrical analogy is also shown in Figure 1. Equation 4 reflects the single-compartment model formed with an additional breathing effort term. The P_{eff} term is modelled using b-spline basis functions (Langdon et al., 2016; Docherty et al., 2020):

$$P_{eff}(t) = \sum_{i=1}^{M=10} P_{c,i}\Phi_{i,d=2}(t) \tag{6}$$

with $M = 10$ second order ($d = 2$) b-spline functions to fit the unknown shape function (Guy et al., 2022; Knopp et al., 2021; Sun et al., 2022), with P_c the spline coefficients, capturing any nonlinear, time-varying dynamics during expiration for all patients. The second order splines are defined over time with T equally spaced time points:

$$\Phi_{i,0}(t) = \begin{cases} 1 & T_i \leq t \leq T_{i+1} \\ 0 & otherwise \end{cases}$$

$$\Phi_{i,d}(t) = \frac{t - T_i}{T_{i+d} - T_i}\Phi_{i,d-1}(t) + \frac{T_{i+d+1} - t}{T_{i+d+1} - T_{i+1}}\Phi_{i+1,d-1}(t) \quad for\ d \geq 1 \tag{7}$$

Where T_i are $M + 1$ "knots" which define basis function spacing.

2.2 Model Identification

This analysis focuses on inspiratory lung mechanics and breathing effort. Measurement of alveolar pressure decouples E and R in Equations 2 and 3, enabling separate identification of both of these from the alveolar pressure data. Thus, inspiratory resistance is identified from inspiratory pressure-flow data:

$$-P_{alv} = R_{1,insp}Q(t) \tag{8}$$

Inspiratory breathing effort (P_{eff}) and E trade off parametrically in Equation 3. Thus, E is identified from expiration data under the assumption of passive expiration. Expiration is generally passive, driven by the elastic recoil of the lung, diaphragm, and chest wall. However, in COPD patients, particularly those with FL at end-expiration, there can be end-expiratory forced breathing effort to assist in tidal volume clearance and to avoid gas trapping. During inspiration, the relaxation time constant for muscles involved in breathing effort causes negative P_{eff} generated during inspiration to decay. Thus, E is estimated from the middle portion of expiration, defined as 5 points either side of peak expiratory flow (T_{Qpeak}).

$$EV(T_{Qpeak}-5 : T_{Qpeak}+5) = P_{alv}(T_{Qpeak}-5 : T_{Qpeak}+5) \tag{9}$$

Work of breathing (WOB) is calculated as the integral of pressure volume:

$$WOB = \int_{insp} -P_{eff}\, dV \tag{10}$$

For ease of interpretation and presentation, in Equation 10, the WOB is now defined as positive. WOB breathing to overcome the elastic and resistive dynamics respectively are defined:

$$WOB = \int_{insp} RQ\, dV \tag{11}$$

$$WOB = \int_{insp} EV\, dV \tag{12}$$

Results are presented as median [IQR] where relevant.

2.3 Patient Data

Alveolar pressure and airflow measurements obtained during plethysmography (Radovanovic et al., 2018; Zilianti et al., 2021; Radovanovic et al., 2018; Pecchiari et al., 2020) were obtained from 40 subjects with COPD that were separated into four cohorts of 10 patients each: young, old, NFL, and FL. Patient demographics are summarised in Table 1. Pressure-flow data was recorded at a frequency of 66Hz. Data for a single breath is included.

Table 1. Patient information.

	Young	Old	NFL	FL
No. of Patients	10	10	10	10
Age M/F	7/3	8/2	7/3	6/4
BMI MED [IQR]	2.9 [0.7]	4.6 [2.5]	3.4 [2.2]	2.8 [2.3]
FRC MED [IQR]	6.9 [4.0]	20.4 [12.7]	6.1 [4.8]	9.1 [2.2]
VT MED [IQR]	0.8 [0.9]	0.6 [0.7]	0.9 [1.1]	0.4 [0.5]

$$\underbrace{\begin{bmatrix} V(T_{Qpeak}-5) & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots \\ V(T_{Qpeak}-5) & 0 & \dots & 0 \\ V_{insp} & \Phi_1 & \dots & \Phi_M \end{bmatrix} \begin{bmatrix} E \\ P_{(c1)} \\ \vdots \\ P_{(cM)} \end{bmatrix}}_{\mathbf{Ax}} = \underbrace{\begin{bmatrix} -P_{alv(T_{Qpeak}-5)} \\ \vdots \\ -P_{alv(T_{Qpeak}+5)} \\ -P_{alv,insp} \end{bmatrix}}_{\mathbf{b}} \tag{5}$$

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Table 2. Median [IQR] of model parameters and WOB results for all four cohorts.

	$R_{1,insp}$ MED [IQR] $[cmH_2O/L/s]$	RMSE MED [IQR] $[cmH_2O]$	E MED [IQR] $[cmH_2O/L]$	$P_{eff,min}$ MED [IQR] $[cmH_2O]$	WOB P_{eff} MED [IQR] $[cmH_2O.L]$	WOB RQ MED [IQR] $[cmH_2O.L]$	WOB EV MED [IQR] $[cmH_2O.L]$
Y	1.3 [1.1-1.6]	0.3 [0.2-0.4]	1.2 [0.9-2.6]	-1.9 [-3.1- -1.4]	46.4 [27.4-49.8]	0.8 [0.7-1.0]	0.6 [0.4-0.9]
O	2.0 [1.6-2.3]	0.3 [0.3-0.4]	2.2 [1.6-3.0]	-2.4 [-3.5- -2.3]	47.0 [38.7-59.5]	0.9 [0.7-1.4]	0.6 [0.4-0.8]
NFL	2.9 [2.8-3.5]	0.5 [0.4-0.7]	3.4 [1.9-4.1]	-2.8 [-4.7- -2.4]	85.4 [45.6-148.6]	1.5 [0.8-2.3]	1.5 [0.5-1.2]
FL	6.9 [5.1-9.1]	2.8 [1.8-3.3]	6.1 [5.6-10.4]	-9.1 [-10.4- -8.2]	167.2 [132.4-227.0]	3.2 [2.2-5.1]	3.2 [1.4-1.9]

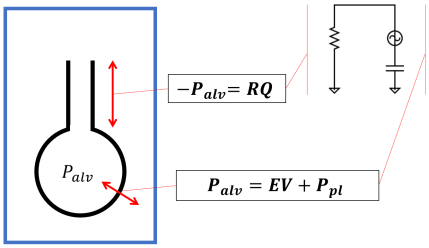

Fig. 1. Single-compartment model (spontaneous).

3. RESULTS

Linear inspiratory resistance, $R_{1,insp}$ (Equation 8) had a very good model fit over inspiration (RSME median [IQR] over all patients). RSME and resistance values for all patient cohorts can be found in Table 2, and $R_{1,insp}$ increased with age and COPD severity, as expected. Figure 3 shows this model fit for a typical FL patient, and indicates all key inspiratory resistance dynamics are captured by the linear term, even in FL patients.

Patient effort from the elastic model fit (Equation 4) is shown in Figure 2 for a single patient from each cohort. Negative P_{eff} shape and magnitude ranges match typical pleural/esophageal pressure measurements during spontaneous breathing in literature [refs]. Overall, E and the depth of the P_{eff} incursion increased with COPD, resulting in higher WOB, as seen in Figures 4 and 6. Figure 6 shows that as resistance increases, elastance also tends to increase concomitantly, resulting in higher WOB to overcome each of these dynamics (Figure 5). Interestingly, the elastic and resistive components of WOB were strongly correlated ($R^2 = 0.49$), suggesting that both dynamics contribute to increased WOB in COPD.

4. DISCUSSION

This study presents a simple model for estimating WOB from plethysmography data. Results showed increased WOB with age and COPD severity. Model-based effort shapes and magnitudes match existing literature (Arora et al., 2015; Sowho et al., 2022; Glos et al., 2018). Overall, this model appears to capture WOB.

Pleural pressure is modelled here as inspiratory effort. During inspiration, the diaphragm drops, creating a relative negative pressure in the pleural space compared to the lung alveoli. This in turn causes alveolar expansion. The relationship between pleural pressure dynamics and tidal volume inspired is a function of the lung elastance. In this study, the modelled inspiratory effort comprises pressure deviations relative to end expiratory volume just

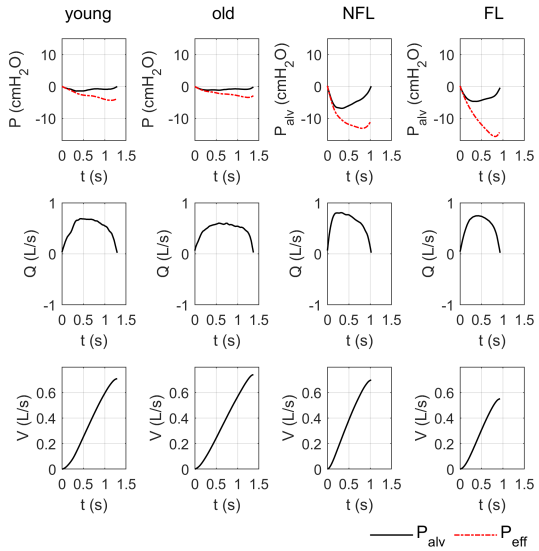

Fig. 2. Patient effort (P_{eff}) is shown increasing for a typical subject from each respective cohort, with flow and tidal volume data for comparison.

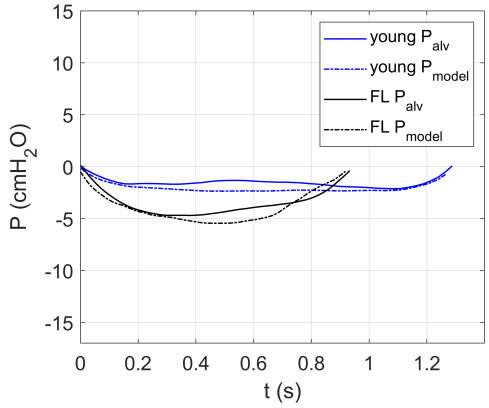

Fig. 3. The inspiratory resistance model shows a good fit for a typical young and FL patient.

prior to inspiration onset (V=0). These pressure swings are similar in magnitude (-2 to -10 cmH_2O typically) and shape to measured esophageal pressure changes in CPAP sleep literature (Bonta et al., 1977; Suzuki et al., 2005; Luo et al., 2009; Berg et al., 2004), where esophageal pressure is a common surrogate for pleural pressure. These literature outcomes suggest that the results presented here capture key inspiratory effort dynamics.

WOB increased with inspiratory resistance in Figure 4, as would be expected. The scatter about the linen of best fit in Figure 4 is likely a combination of the differing elastic

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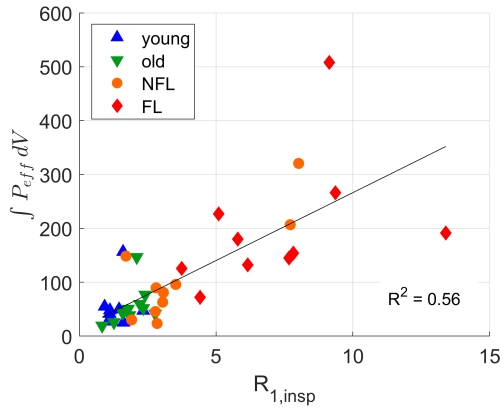

Fig. 4. Work of breathing for patient effort is shown to increase with inspiratory resistance.

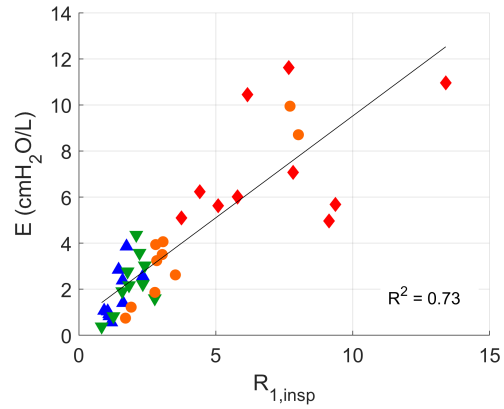

Fig. 5. Elastance (E) increases with an increase in inspiratory resistance and shows some linearity with $R^2 = 0.73$.

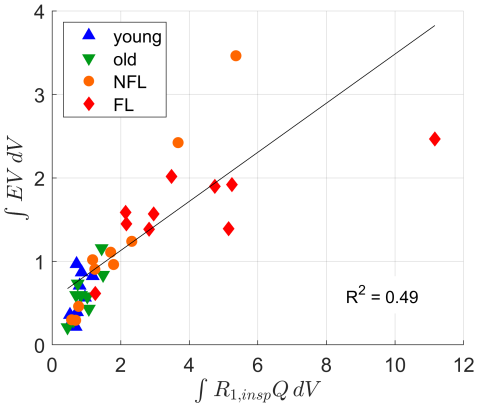

Fig. 6. Elastic work of breathing shown to increase with resistive work of breathing and depicts some linearity with $R^2 = 0.49$.

work of breathing per patient, and different inspiratory volume demand resulting in different inspiratory effort. By and large, COPD patients had higher WOB per mL of tidal volume.

WOB increased slightly with age, though young and old cohorts overlapped significantly. Figure 5 shows that an increase in resistance is generally associated with an increase in elastance in the young and old cohorts. This was also true in the COPD cohorts, though with the same linear slope. In the COPD cohorts, the resistance was higher per unit increase in elastance (lower slope in Figure 5), which was associated with increased resistive WOB compared to elastic WOB in Figure 6. These results match expectations, where a primary indicator of COPD is increased airway resistance (Santus et al., 2014; Nakagawa et al., 2015; Radovanovic et al., 2018).

All elastance values fell within the expected range (Loring et al., 2009). Elastance in healthy young and old subjects was $< 5\ cmH_2O$ (1.2[0.9–2.6] and 2.2 [1.6 – 3.0] cmH_2O of young and old respectively), matching literature (Loring et al., 2009). COPD can sometimes elevate elastance to 5 – 10 cmH_2O (Loring et al., 2009), a result seen broadly in Figure 5 and Table 2. Emphysema related tissue damage can reduce elastic recoil (Fessler et al., 2008; Finucane and Colebatch, 1969), while inflammation may increase lung elastance (Szabari et al., 2019). In addition, higher measured elastance can be associated with increased rate of breathing, where shorter breaths tend to engage and (over)extend lung units with lower time constants. Thus, elastance can vary significantly between COPD patients, as seen in Figure 4, and the identified elastances in this study are physiologically plausible.

Airway resistance is often increased in COPD patients (Dellaca et al., 2004; Tantucci, 2013; Koulouris et al., 1997; Topalovic et al., 2013). This was seen in Figure 4 and Table 2, where FL COPD subjects, and some NFL COPD subjects, had resistances in the elevated 5 – 15 $cmH_2O.s/L$ range expected from literature (Loring et al., 2009). Both inspiratory and expiratory resistance can be affected, where the causes of inspiratory resistance are generally related to airway narrowing and secretions/exudates related to inflammation (Loring et al., 2009). Expiratory resistance can present additional dynamics, such as FL and airway collapse, where a expiratory resistance focused model-based analysis observed increasingly nonlinear expiratory resistance in COPD patients. This analysis has focused on inspiratory resistance, as part of an overall picture of inspiratory WOB. Calculation of WOB is complicated in expiration by FL (Loring et al., 2009), and future work will attempt to combine the results presented here with nonlinear expiratory models.

The single compartment model used here assumed linear homogenous airway resistance and pulmonary elastance. A separate analysis has shown that expiratory resistance is increasingly nonlinear in COPD patients, particularly those with FL (Lerios et al., 2022). The linear airway resistance assumption is generally true even in COPD patients, where Figure 2 shows a typical case. In this case, as alveolar pressure is measured in this plethesmographic data, the elastic and resistive components of the single compartment model can be decoupled mathematically, allowing independent identification of both of these parameters, per Equations 1 and 2.

Identification of elastance and pleural pressure (inspiratory effort) requires a portion of the breath to be passive, with assumed pleural pressure at approximately zero. This is generally true during normal expiration in healthy subjects. However, with increasing COPD severity resistance

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to flow and flow limitation can result in active expiration, particularly towards the end of the breath. Thus, using end-expiration to fit elastance under an assumption of passive expiration can cause high elastance values as it incorporates some positive pleural pressure generated by active expiration. At start-inspiration visco-elsatic effects and the natural decay in pleural pressure as inspiratory muscle and tissue relaxation occurs going into expiration can also affect identification of an elastance value reflective of inspiratory dynamics. For this reason elastance was identified using data from the middle of expiration, as defined by peak flow. Future work should explore the effect of different expiratory dynamics on elastance identification.

This paper explores model-based quantification of WOB in adults with and without COPD. WOB follows expected trends with disease state and associated resistance, but can also offer additional insight as it also includes the WOB to overcome the elastic components, as well as to meet volume demand. Normalisation of WOB by tidal volume, in combination with other model-absed parameters, may offer insight into patient-specific condition and their unique medical and technical needs.

The data in this paper includes plethesmography-derived alveolar pressure. Alveolar pressure is derived as part of plethesmography (Radovanovic et al., 2018; Criée et al., 2011), but not directly measured. The plethesmogrphic method has been optimised to address potential inaccuracies. The alveolar pressure here represents average alveolar pressure across both lung units, matching well with the single compartment lung formulation. As a result, the pleural pressures modelled here, representing inspiratory effort, are average pressures across the pleural spaces, and representative of overall breathing effort. The results of this paper should thus be considered within the framework of the single compartment model.

This data set does not include measured pleural pressure as a final validation. Measurement of pleural pressure is extremely uncommon, as it is very invasive. Esophageal pressure is often used as a surrogate for pleural pressure, but measurements depend heavily on sensor placement, especially as typically pleural pressure differs across the pleural space. Measurement of esophageal pressures is not common, as it adds additional patient burden and clinical expense (Soroksky and Esquinas, 2012).

This study utilises plethysmography data as a first step towards a less involved clinical diagnosis and monitoring tool. The aim is to apply a similar model to airway pressure and flow data to provide model-based estimations of lung condition. Future work will explore the generalisation of this model to such data, and the strengths and limitations of such an approach from a clinical perspective.

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REFERENCES

Arora, N., Meskill, G., and Guilleminault, C. (2015). The role of flow limitation as an important diagnostic tool and clinical finding in mild sleep-disordered breathing. *Sleep science*, 8(3), 134–142.

Bates, J.H. (2009). *Lung mechanics: an inverse modeling approach*. Cambridge University Press.

Berg, S., Hoffstein, V., and Gislason, T. (2004). Acidification of distal esophagus and sleep-related breathing disturbances. *Chest*, 125(6), 2101–2106.

Bonta, B.W., Uauy, R., Warshaw, J.B., and Motoyama, E.K. (1977). Determination of optimal continuous positive airway pressure for the treatment of irds by measurement of esophageal pressure. *The Journal of pediatrics*, 91(3), 449–454.

Chase, J.G., Zhou, C., Knopp, J.L., Shaw, G.M., Näswall, K., Wong, J.H., Malinen, S., Moeller, K., Benyo, B., Chiew, Y.S., et al. (2021). Digital twins in critical care: what, when, how, where, why? *IFAC-PapersOnLine*, 54(15), 310–315.

Chiew, Y.S. (2013). Model-based mechanical ventilation for the critically ill.

Criée, C., Sorichter, S., Smith, H., Kardos, P., Merget, R., Heise, D., Berdel, D., Köhler, D., Magnussen, H., Marek, W., et al. (2011). Body plethysmography–its principles and clinical use. *Respiratory medicine*, 105(7), 959–971.

Dellaca, R., Santus, P., Aliverti, A., Stevenson, N., Centanni, S., Macklem, P., Pedotti, A., and Calverley, P. (2004). Detection of expiratory flow limitation in copd using the forced oscillation technique. *European Respiratory Journal*, 23(2), 232–240.

Diaz, O., Villafranca, C., Ghezzo, H., Borzone, G., Leiva, A., Milic-Emil, J., and Lisboa, C. (2000). Role of inspiratory capacity on exercise tolerance in copd patients with and without tidal expiratory flow limitation at rest. *European Respiratory Journal*, 16(2), 269–275.

Docherty, P., Lerios, T., Laufer, B., Moeller, K., and Chase, G. (2020). A method for observing ongoing patient respiratory behaviour with the narx model.

Fessler, H.E., Scharf, S.M., Ingenito, E.P., McKenna Jr, R.J., and Sharafkhaneh, A. (2008). Physiologic basis for improved pulmonary function after lung volume reduction. *Proceedings of the American Thoracic Society*, 5(4), 416–420.

Finucane, K. and Colebatch, H. (1969). Elastic behavior of the lung in patients with airway obstruction. *Journal of applied physiology*, 26(3), 330–338.

Glos, M., Sabil, A., Jelavic, K.S., Schöbel, C., Fietze, I., and Penzel, T. (2018). Characterization of respiratory events in obstructive sleep apnea using suprasternal pressure monitoring. *Journal of Clinical Sleep Medicine*, 14(3), 359–369.

Guy, E.F.S., Chase, J.G., Knopp, J.L., and Shaw, G.M. (2022). Quantifying Ventilator Unloading in CPAP Ventilation. *Computers in Biology and Medicine*, 142, 105225.

Khakban, A., Sin, D.D., FitzGerald, J.M., McManus, B.M., Ng, R., Hollander, Z., and Sadatsafavi, M. (2017). The projected epidemic of chronic obstructive pulmonary disease hospitalizations over the next 15 years. a population-based perspective. *American journal of respiratory and critical care medicine*, 195(3), 287–291.

Kim, K.T., Knopp, J., Dixon, B., and Chase, G. (2019). Quantifying neonatal pulmonary mechanics in mechanical ventilation. *Biomedical Signal Processing and Control*, 52, 206–217.

Knopp, J.L., Guy, E., Kim, K.T., Shaw, G.M., and Chase, J.G. (2021). B-spline modelling of inspiratory drive in nava-ventilated patients. *IFAC-PapersOnLine*, 54(15), 103–108.

Koulouris, N., Valta, P., Lavoie, A., Corbeil, C., Chassé, M., Braidy, J., and Milic-Emili, J. (1995). A simple method to detect expiratory flow limitation during spontaneous breathing. *European Respiratory Journal*, 8(2), 306–313.

Koulouris, N.G., Dimopoulou, I., Valta, P., Finkelstein, R., Cosio, M.G., and Milic-Emili, J. (1997). Detection of expiratory flow limitation during exercise in copd patients. *Journal of Applied Physiology*, 82(3), 723–731.

Langdon, R., Docherty, P.D., Chiew, Y.S., Moeller, K., and Chase, J.G. (2016). Use of basis functions within a nonlinear autoregressive model of pulmonary mechanics. *Biomedical Signal Processing and Control*, 27, 44–50.

Lerios, T., Knopp, J.L., Guy, E.F.S., Holder-Pearson, L., and Chase, J.G. (2022). An identifiable model of lung mechanics to diagnose and monitor COPD.

Loring, S.H., Garcia-Jacques, M., and Malhotra, A. (2009). Pulmonary characteristics in copd and mechanisms of increased work of breathing. *Journal of applied physiology*, 107(1), 309–314.

Luo, Y.M., Tang, J., Jolley, C., Steier, J., Zhong, N.S., Moxham, J., and Polkey, M.I. (2009). Distinguishing obstructive from central sleep apnea events: diaphragm electromyogram and esophageal pressure compared. *Chest*, 135(5), 1133–1141.

Nakagawa, M., Hattori, N., Haruta, Y., Sugiyama, A., Iwamoto, H., Ishikawa, N., Fujitaka, K., Murai, H., Tanaka, J., and Kohno, N. (2015). Effect of increasing respiratory rate on airway resistance and reactance in copd patients. *Respirology*, 20(1), 87–94.

Osthoff, M., Jenkins, C., and Leuppi, J.D. (2013). Chronic obstructive pulmonary disease–a treatable disease. *Swiss medical weekly*, (15).

Pecchiari, M., Radovanovic, D., Zilianti, C., Saderi, L., Sotgiu, G., D'Angelo, E., and Santus, P. (2020). Tidal expiratory flow limitation induces expiratory looping of the alveolar pressure-flow relation in copd patients. *Journal of Applied Physiology*, 129(1), 75–83.

Radovanovic, D., Pecchiari, M., Pirracchio, F., Zilianti, C., D'Angelo, E., and Santus, P. (2018). Plethysmographic Loops: A Window on the Lung Pathophysiology of COPD Patients. *Frontiers in physiology*, 9, 484.

Santus, P., Radovanovic, D., Henchi, S., Di Marco, F., Centanni, S., D'Angelo, E., and Pecchiari, M. (2014). Assessment of acute bronchodilator effects from specific airway resistance changes in stable copd patients. *Respiratory Physiology & Neurobiology*, 197, 36–45.

Soroksky, A. and Esquinas, A. (2012). Goal-directed mechanical ventilation: are we aiming at the right goals? a proposal for an alternative approach aiming at optimal lung compliance, guided by esophageal pressure in acute respiratory failure. *Critical Care Research and Practice*, 2012.

Sowho, M., Jun, J., Sgambati, F., Potocki, M., Schneider, H., Smith, P., Schwartz, A., Dietz, H., MacCarrick, G., and Neptune, E. (2022). Assessment of pleural pressure during sleep in marfan syndrome. *Journal of Clinical Sleep Medicine*, 18(6), 1583–1592.

Sun, Q., Chase, J.G., Zhou, C., Tawhai, M.H., Knopp, J.L., Möller, K., and Shaw, G.M. (2022). Overdistension prediction via hysteresis loop analysis and patient-specific basis functions in a virtual patient model. *Computers in Biology and Medicine*, 141, 105022.

Suzuki, M., Ogawa, H., Okabe, S., Horiuchi, A., Okubo, M., Ikeda, K., Hida, W., and Kobayashi, T. (2005). Digital recording and analysis of esophageal pressure for patients with obstructive sleep apnea–hypopnea syndrome. *Sleep and Breathing*, 9(2), 64–72.

Szabari, M.V., Takahashi, K., Feng, Y., Locascio, J.J., Chao, W., Carter, E.A., Vidal Melo, M.F., and Musch, G. (2019). Relation between respiratory mechanics, inflammation, and survival in experimental mechanical ventilation. *American journal of respiratory cell and molecular biology*, 60(2), 179–188.

Tantucci, C. (2013). Expiratory flow limitation definition, mechanisms, methods, and significance. *Pulmonary medicine*, 2013.

Topalovic, M., Exadaktylos, V., Peeters, A., Coolen, J., Dewever, W., Hemeryck, M., Slagmolen, P., Janssens, K., Berckmans, D., Decramer, M., et al. (2013). Computer quantification of airway collapse on forced expiration to predict the presence of emphysema. *Respiratory research*, 14(1), 1–9.

Vogelmeier, C.F., Criner, G.J., Martinez, F.J., Anzueto, A., Barnes, P.J., Bourbeau, J., Celli, B.R., Chen, R., Decramer, M., Fabbri, L.M., et al. (2017). Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. gold executive summary. *American journal of respiratory and critical care medicine*, 195(5), 557–582.

Zilianti, C., Santus, P., Pecchiari, M., D'Angelo, E., and Radovanovic, D. (2021). Diagnostic insights from plethysmographic alveolar pressure assessed during spontaneous breathing in copd patients. *Diagnostics*, 11(6), 918.

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