Model-based identification of flow-limited and non-flow-limited COPD patients in plethysmographic data.

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Abstract: Chronic Obstructive Pulmonary Disease (COPD) patients, unlike healthy subjects, develop an increase in resistance in expiration. Model-based methods have previously assumed resistance to change linearly with flow. This study explores nonlinear, dynamic expiratory resistance in COPD subjects with plethysmographic data of non-flow-limited (NFL) and flow-limited (FL) subjects.A nonlinear model that incorporates a time varying, dynamic resistance in expiration only is presented. Alveolar pressure and airflow measurements for subjects were separated into NFL ($n = 25$), and FL ($n = 35$). The median inspiratory resistance identified is 3 cmH_2O for NFL and 5.9 cmH_2O for FL, and the linear expiratory resistance is 4.2 (RMSE = 0.6) and 11.4 (RMSE = 1.7) cmH_2O. The nonlinear expiratory mean resistance is 4.9 (RMSE = 0.1) for NFL, and 13.5 (RMSE = 0.2). This study presents a method for examining nonlinear expiratory resistance in COPD subjects. The FL subjects showed significant nonlinearity in expiration. The model fit for the nonlinear expiratory resistance was good. A novel method for examining nonlinear, dynamic, expiratory resistance in COPD patients using plethysmographic P-Q loops is presented with an identifiable model, capturing disease state. The model captures static and dynamic changes in resistance as model-based markers for COPD diagnosis and monitoring, with possible future clinical use.

Keywords: Modelling, identification and signal processing, chronic obstructive pulmonary disease (COPD), plethysmographic loops, airway resistance, respiratory mechanics, respiratory modelling.

1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a leading, and increasing, cause of death and disability globally (Vogelmeier et al., 2017; Vincent et al., 2011) that has been neglected by the healthcare profession, governments and the pharmaceutical industry (Barnes, 2007). It is, however, treatable (Osthoff et al., 2013; van Buul et al., 2017). The direct healthcare cost of COPD in the United States was estimated to be $72 billion per annum (Khakban et al., 2017), and it is projected that hospitalization due to COPD will outstrip ischemic heart disease by 2025 (Khakban et al., 2017), regardless of any decrease in smoking prevalence.

While resistance to airflow in the lungs typically increases with age, COPD subjects, unlike otherwise healthy subjects, develop flow resistance in expiration (Dellaca et al., 2004; Diaz et al., 2000; Koulouris et al., 1997; Tantucci et al., 1991; Franssen et al., 2005). Expiratory airflow limitation (EFL) is a well-defined mechanical-pathophysiological condition that can occur at rest or during physical exercise (Tantucci, 2013; Van Helvoort et al., 2006; Franssen et al., 2005). Subjects with advanced COPD often present with EFL at rest, requiring full body plethysmography or negative pressure at the mouth during tidal expiration (NEP) for confirmatory diagnosis (Koulouris et al., 1995).

Patient specific model-based methods can identify specific pulmonary mechanics where other methods fail (Knopp et al., 2021; van Drunen et al., 2014; Schranz et al., 2013; Bhutani et al., 1988; Redmond et al., 2017; Langdon et al., 2016; Roth et al., 2017; Chiew et al., 2015; Lerios et al., 2019; Kim et al., 2020). Model-based methods have the potential to capture different disease states within COPD pathology from measured airway pressure and flow in tidal breathing. Alveolar mechanics and dynamics are very difficult to measure directly without invasive methods, increasing the value of model-based testing as a safer, non-invasive approach.

Model-based approaches in the past have assumed resistance to change linearly with flow in this cohort, when literature shows strong non-linearity of expiratory resistance change with flow (Radovanovic et al., 2018; Criée et al., 2011; Pecchiari et al., 2020; Zilianti et al., 2021;

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Pecchiari et al., 2016). This study explores nonlinearity of expiratory resistance in two COPD cohorts, namely: non-flow-limited (NFL) and flow-limited (FL) COPD subjects.

2. METHODS

2.1 Model

A simple, single-compartment model relating airway pressure (P_{aw}) $[cmH_2O]$ to lung elastance (E) $[cmH_2O \cdot L^{-1}]$ and airway resistance (R) $[cmH_2O \cdot s \cdot L^{-1}]$ is defined:

$$P_{aw}(t) = EV(t) + RQ(t) + P_0 \tag{1}$$

where P_0 $[cmH_2O]$ is the positive end expiratory pressure (PEEP), Q $[L/s]$ is flow, and V $[L]$ tidal volume, the time based integral of $Q(t)$. Alveolar pressure (P_{alv}) is related to pleural pressure (P_{pl}) via Hooke's law:

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

Pleural pressure is modelled relative to alveolar pressure and lung volume at end exhalation ($V = 0$), and is represented by a signal generator in the electrical circuit analogy of Figure 1. The pressure drop across the airways is defined as a function of flow rate:

$$P_{aw}(t) - P_{alv}(t) = RQ(t) \tag{4}$$

Alveolar pressure obtained through plethysmography is calculated relative to atmospheric pressure, reducing Equation 4 to:

$$-P_{alv}(t) = RQ(t) \tag{5}$$

The linear single compartment model in Equation 1 and Equation 5 present resistance as a constant R. It is hypothesized that a nonlinear resistance in expiration is required to capture airway behavior during expiration in flow limited COPD patients. The nonlinear model incorporates a constant linear term (R_{insp}) identified during inspiration (Q_{insp}), alongside an additional dynamic resistive term ($R_{2,exp} = \sum R_2\Phi(t)$) during expiration:

$$-P_{alv}(t) = \begin{cases} R_{1,insp}Q_{insp}(t) \\ \left[\sum_{i=1}^{M=10} R_{2,exp,i}\Phi_{i,d=2}(t)\right]Q_{exp}(t) \end{cases} \tag{6}$$

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), 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:

$$\Phi_{i,0}(t) = \begin{cases} 1 & T_i \le t \le T_{i+1} \\ 0 & otherwise \end{cases}$$
$$\Phi_{i,d}(t) = \frac{t - T_i}{T_{i+d} - T_i}\Phi_{i,d-1}(t) + \frac{T_{i+d+1} - t}{T_{i+d+1} - T_{i+1}}\Phi_{i+1,d-1}(t) \quad for\ d \ge 1 \tag{7}$$

Where T_i are $M + 1$ "knots" which define basis function spacing. The parameters $R_{1,insp}$ and $R_{2,exp}$ are identified using linear least squares as follows, with detailed matrix layouts in Equation 3, using Matlab (The Mathworks, Inc., Natick, Massachusetts, United States.) lsqlin command to constrain identified parameters positive, which is physiologically realistic.

2.2 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 60 subjects with COPD that were separated into two cohorts: non-flow-limited (NFL $n = 25$), and flow-limited (FL, $n = 35$). The linear model in Equation 5 and the nonlinear model of Equation 6 were fit to clinical data using linear least squares. Model error was assessed by root mean squared error (RMSE), comparing the measured alveolar pressure to each respective model. Nonlinearity in $R_2\Phi$ was assessed via $\int Q\,dR$, the area under the curve (AUC) of the $R - Q$ plot, and mean $R_2\Phi$, the average of the splines multiplied by their respective identified coefficients.

3. RESULTS

Table 1 shows the average linear and nonlinear resistance values, and associated RMSE. The inspiratory resistance ($R_{1,insp}$) increases in FL vs NFL subjects, and the nonlinear dynamic resistance in expiration ($R_2\Phi$) also increases for the FL subjects, compared to NFL subjects. A comparison of typical alveolar pressure, airflow, resistance over time and resistance as a function of flow are shown in Figure 2 for a NFL and a FL subject. Figure 2 also shows data from a young healthy individual (Radovanovic et al., 2018) for comparison. The work of breathing required to overcome expiratory resistance is highest in FL COPD subjects.

$$\underbrace{\begin{bmatrix} Q_{insp(t(insp),1)} & 0 & \dots & 0 & \\ \vdots & \vdots & \vdots & \vdots & \\ Q_{insp(t(insp),end)} & 0 & \dots & 0 & \\ 0 & \dots & Q_{exp(t(exp),1)}\Phi_{t(exp),1} & \dots & Q_{exp(t(exp),1)}\Phi_{t(exp),M} \\ \vdots & \dots & \vdots & \dots & \vdots \\ 0 & \dots & Q_{exp(t(exp),end)}\Phi_{t(exp),1} & \dots & Q_{exp(t(exp),end)}\Phi_{t(exp),M} \end{bmatrix}}_{\mathbf{Ax}} \begin{bmatrix} R_{1,insp,1} \\ \vdots \\ R_{1,insp,1} \\ R_{2,exp,1} \\ \vdots \\ R_{2,exp,end} \end{bmatrix} = \underbrace{\begin{bmatrix} -P_{alv,insp,1} \\ \vdots \\ -P_{alv,insp,end} \\ -P_{alv,exp,1} \\ \vdots \\ -P_{alv,exp,end} \end{bmatrix}}_{\mathbf{b}} \tag{3}$$

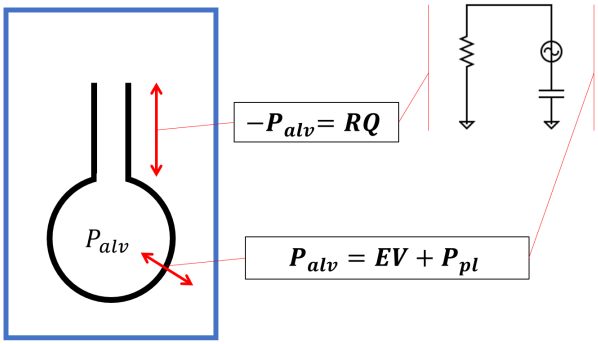

Fig. 1. Single compartment model of spontaneous breathing.

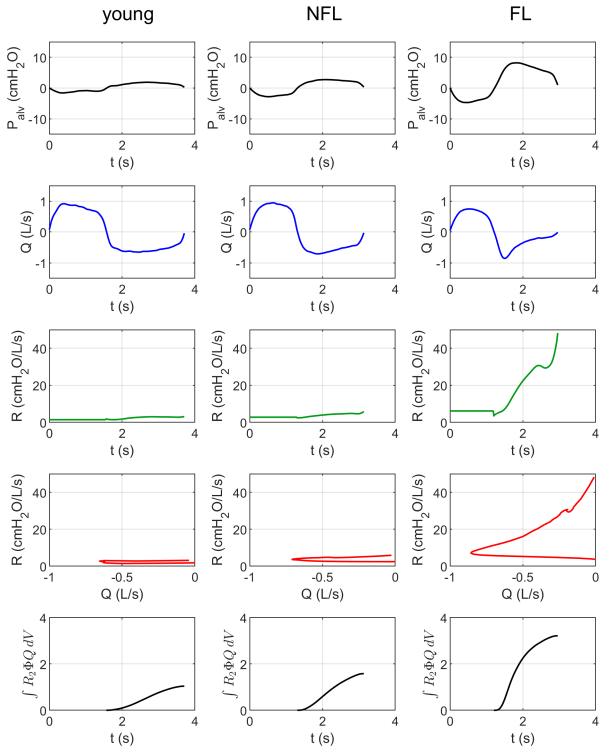

Fig. 2. Typical alveolar pressure (P_{alv}) $[cmH_2O]$, flow (Q) $[L/s]$, mean $R_2\Phi$ (R) $[cmH_2O/L/s]$ and work of resistance ($\int R_2\Phi Q\, dV$) $[cmH_2O]$ for the 2 patient cohorts of non-flow-limited (NFL), and flow-limited (FL) subjects, with a typical young patient for comparison.

Figure 2 shows a typical FL subject has significant nonlinear, dynamic resistance in expiration that increases with time. In contrast, NFL have relatively flat nonlinear resistance, similar to the healthy subject. Increasing nonlinear resistance is most apparent with decreasing flow. The work of resistance is also shown as increased for the flow-limited subject compared with the non-flow-limited subject.

Table 1. Median [IQR] of model parameters and model-fit to data for both cohorts.

		Linear exp		Nonlinear exp	
	$R_{1,insp}$ MED [IQR]	$R_{1,exp}$ MED [IQR]	RMSE MED [IQR]	Mean $R_2\Phi$ MED [IQR]	RMSE MED [IQR]
NFL	3 [0.9]	4.2 [2.9]	0.6 [0.5]	4.9 [2.7]	0.1 [0.1]
FL	5.9 [3.3]	11.4 [6.8]	1.7 [1.5]	13.5 [11.5]	0.3 [0.2]

Figure 3 shows a continuous distribution function (CDF) of the mean $R_2\Phi$ for all NFL and FL subjects. Subjects with mean $R_2\Phi$ values greater than approximately 15 $cmH_2O/L/s$ are clearly distinguishable as belonging to the FL cohort. However, there is an area of overlap of FL and NFL subjects when using $R_2\Phi$ as a measure of disease state.

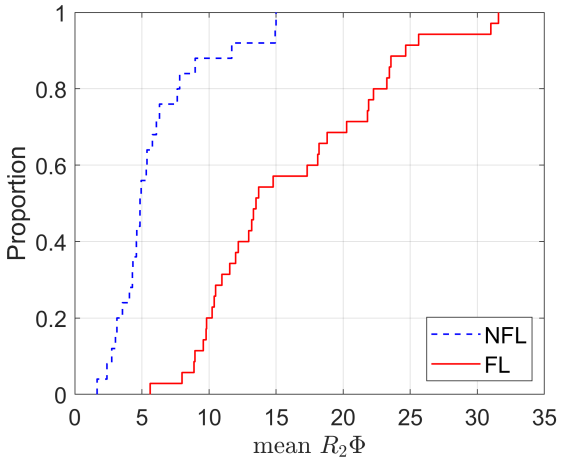

Fig. 3. A CDF of the mean $R_2\Phi$ (top) and the mean dynamic, expiratory resistance ($R_2\Phi$) of each subject relative to their inspiratory resistance ($R_{1,insp}$) for the non-flow-limited (NFL) and flow-limited (FL) cohorts respectively.

The mean $R_2\Phi$ values are shown as a function of the inspiratory resistance in Figure 4. Higher average resistance in expiration matches literature (Dellaca et al., 2004; Koulouris et al., 1995; Criée et al., 2011). The linear least squares fit of the NFL data points illustrate the deviation from linear behavior in the FL data. All NFL subjects are closely grouped around the line of best fit, and all subjects with significant deviation are FL. Figure 5 shows $R-Q$ plots for each of the subjects tabulated A-D in Figure 4, showing FL and NFL subjects that fall on and off the line of best fit. Nonlinear behaviour is increasingly prevalent with increasing R, even in NFL patients. The nonlinear expiratory rise gets more exponential with distance from the best fit line in Figure 4.

In Figure 6, the AUC of the $Q-R$ plot is shown as a function of the inspiratory resistance. The NFL cohort is closely grouped together and largely linear, while the FL subjects display an increase in nonlinear behavior. Figure 7 shows that the AUC of the $Q-R$ plot is significantly increased in the FL cohort, with very little overlap.

4. DISCUSSION

This study presents a method for examining nonlinear expiratory resistance in COPD patients. Model fit for linear resistance was good for FL and NFL subjects during

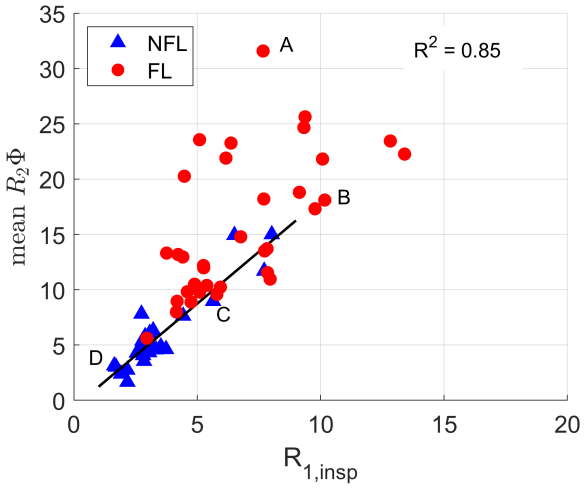

Fig. 4. Mean $R_2\Phi$ values as a function of inspiratory resistance ($R_{1,insp}$) with a linear least squares fit line for the NFL subjects.

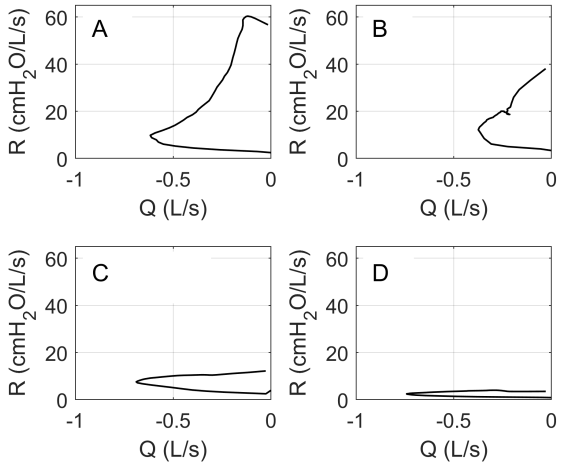

Fig. 5. Modelled vs Q for four subjects labelled A-D in Figure 4.

inspiration, but FL subjects showed significant nonlinearity in expiration. This nonlinearity likely reflects underlying physiological conditions and disease characteristics in these subjects.

Alveolar pressure and airway flow from the typical NFL patient is similar to the healthy subject shown in Figure 2, but the FL patient has significant differences. The median RMSE of 0.6 cmH_2O for the NFL subjects indicates a relatively good model fit for the linear model, suggesting that the expiratory resistance is mostly linear. Conversely, the larger median RMSE of 1.7 vs 0.3 cmH_2O for the linear vs nonlinear model in the FL cohort shows expiratory resistance dynamics are nonlinear. This suggests that expiratory resistance is a dynamic for COPD patients with FL, reflective of underlying flow limitation physiology.

This nonlinear resistance behaviour is a function of measured P and Q. The typical subject from the FL cohort achieves similar peak inspiratory and expiratory flows compared to the NFL cohort but the pressure is higher.

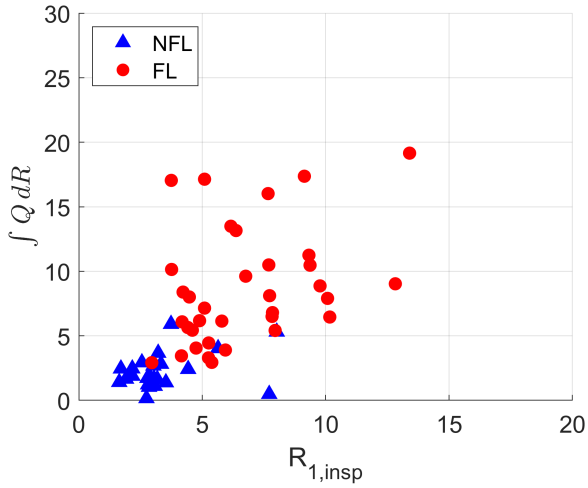

Fig. 6. A continuos distribution function (CDF) of the area of the flow relative to resistance compared with the flow-resistance area as a function of the inspiratory resistance ($R_{1,insp}$).

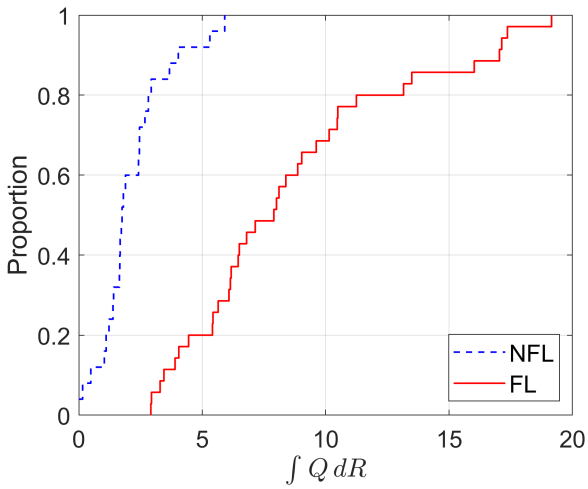

Fig. 7. A CDF of the area of the flow relative to resistance compared with the flow-resistance area as a function of the inspiratory resistance ($R_{1,insp}$).

This indicates that a FL patient requires more pressure to achieve similar flow of air compared to healthier patients, which reflects the definition of flow limitation and the NEP method for its detection. While small increases in flow limitation can be due to aging, larger increased flow limitation could be due to small airway collapse, increased airway resistance, bronchial tone, decreased lung elastance, airway-parenchyma uncoupling, an increase in dyspnea and airway collapse (Tantucci, 2013; Dellaca et al., 2004; Koulouris et al., 1995, 1997; Topalovic et al., 2013). However, Figure 5 shows nonlinear dynamics at higher resistance, even in NFL patients.

Figure 4 shows a linear relationship between inspiratory and expiratory resistance in NFL subjects. Interestingly, some of the NEP confirmed FL patients also fell along the linear line defined by the NFL subjects. This suggests that these subjects may not have experienced significant

flow limitation under the plethysmographic breathing conditions, even if it was apparent under the different NEP pressure-flow conditions. It is known that FL can present differently between rest and exercise conditions (Koulouris et al., 1997; Tantucci, 2013; Diaz et al., 2000; Franssen et al., 2005), reflecting different breathing rate, flow demand, and resultant pressures. These patients may also be the cause of overlap in CDF curves in Figures 3 and 7.

When observing the AUC of the $Q-R$ plot for all NFL and FL subjects in this study in Figure 6, the NFL subjects are more closely grouped together in comparison to the mean $R_2\Phi$ plot. The nonlinearity of the FL subjects is significant, and the NFL subjects non tightly clustered in Figure 6 may have some mild flow limited nonlinear resistance. The AUC CDF plot in Figure 7 shows that there is much less overlap in cohorts using the AUC compared to mean $R_2\Phi$, and thus may prove useful in identifying flow limited subjects undergoing plethysmography. The slight overlap at the lower end of the FL could reflect subjects with NEP confirmed FL who does not experience FL under the plethysmographic flow conditions measured.

This study uses alveolar pressure and airflow data obtained during plethysmography, restricting model complexity. The model used in this study is able to reflect different states, and the use of B-splines (Knopp et al., 2021; Guy et al., 2022; Sun et al., 2022) means it will describe any resistance shape. Results presented justify a larger study ustilising clinical data from a much larger range of respiratory states. Future work will identify similar model parameters from airway pressure (Howe, 2020), without alveolar pressure. Identifying clinically relevant parameters from measured airway pressures and flows could enable home or general practice clinic-based monitoring and thus could decrease time to diagnosis, making respiratory health monitoring more accessible to patients and clinicians . More accessible respiratory monitoring is desirable to decrease patient and clinical burden, and for improvement in health literacy, health inequities (Holder-Pearson and Chase, 2022), and disease management. Crucial healthcare management with model-based solutions, assessing pulmonary function have the potential to provide a cost effective approach to an ever growing global healthcare problem (Chase et al., 2021; Morton et al., 2020; Chase et al., 2018; Zhou et al., 2022)

5. CONCLUSIONS

A novel method for examining nonlinear, dynamic, expiratory resistance in COPD patients using plethysmographic P-Q loops is presented with an identifiable model, capturing disease state. The model captures static and dynamic changes in resistance as model-based markers for COPD diagnosis and monitoring, with possible future clinical use.

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