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An identifiable model of lung mechanics to diagnose and monitor COPD

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ABSTRACT

Background: Current methods to diagnose and monitor COPD employ spirometry as the gold standard to identify lung function reduction with reduced forced expiratory volume (FEV_1)/vital capacity (VC) ratio. Current methods utilise linear assumptions regarding airway resistance, where nonlinear resistance modelling may provide rapid insight into patient specific condition and disease progression. This study examines model-based expiratory resistance in healthy lungs and those with progressively more severe COPD.

Methods: Healthy and COPD pressure $(P)[cmH_2O]$ and flow $(Q)[L/s]$ data is obtained from the literature, and 5 intermediate levels of COPD and responses are created to simulate COPD progression and assess model-based metric resolution. Linear and nonlinear single compartment models are used to identify changes in inspiratory ($R_{1,insp}$) and linear ($R_{1,exp}$)/nonlinear ($R_2\Phi$) expiratory resistance with disease severity and over the course of expiration.

Results: $R_{1,insp}$ increases from 2.1 to 7.3 $cmH_2O/L/s$, $R_{1,exp}$ increases from 2.4 to 10.0 $cmH_2O/L/s$ with COPD severity. Nonlinear $R_2\Phi$ increases (mean $R_2\Phi$: 2.5 $cmH_2O/L/s$ (healthy) to 24.4 $cmH_2O/L/s$ (COPD)), with increasing end-expiratory nonlinearity as COPD severity increases.

Conclusion: Expiratory resistance is increasingly highly nonlinear with COPD severity. These results show a simple, nonlinear model can capture fundamental COPD dynamics and progression from regular breathing data, and such an approach may be useful for patient-specific diagnosis and monitoring.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common, treatable disease marked by persistent respiratory illness symptoms indicative of airflow limitation caused by airway and/or alveolar anomalies [1]. COPD is sometimes mischaracterised as a self-inflicted disease caused by tobacco smoking, accelerated by age [2], but its causes are more widespread. Risk factors include occupational exposure to organic and inorganic dusts, indoor pollution from biomass cooking and heating in poorly ventilated dwellings, chemical agents and fumes, and a history of respiratory infection, including HIV or tuberculosis [1,3–5].

COPD is a leading cause of morbidity globally and is projected to increase the global burden on health sectors and society [6]. The most recent evidence shows 3.2 million deaths due to COPD, placing it as the 7th leading cause of years of life lost, accounting for 81.6 million disability-adjusted life years. These negative outcomes are forecast to rise due to population growth and ageing populations [7].

Respiratory illness is classified by obstructive and restrictive pulmonary function, where restrictive disease requires costly full body plethysmography for diagnosis [8]. Differences in methods of diagnosing and assessing COPD make guidelines, and thus treatment, inconsistent and clinician specific. A review of the varying diagnostic standards showed guidelines fundamentally focus on the ratio of forced expiratory volume (FEV_1)/vital capacity (VC) obtained through spirometry [9]. While low peak flow pulmonary function, detectable by spirometry, is associated with an increased incidence of respiratory, cardiovascular and metabolic abnormality, and premature death [10], spirometry is limited in the ability to classify two main phenotypes of COPD [8,11,12].

In addition, relying on peak flow measurements for diagnosing COPD often leads to misdiagnosis, as the breathing maneuvers are often performed inadequately [13,14]. This limitation leads to groups of people being excluded from these types of tests, such as the elderly and children [15]. Overall, relying on peak flow measurement is a poor indicator of indices of disease activity and its application is therefore limited [16].

Simple clinic or at home based tests are needed for respiratory monitoring, without the limitations of peak flow. With global healthcare costs rising [17–19], and systemic inequities increasing [20–22], clinicians are feeling more overwhelmed and overworked [23]. Patients accessing pulmonary function tests in their own homes or community-based clinics reduces clinical burden and mitigates current location-based inequities. Increasing the frequency of tests carried out per

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patient, earlier than conventional tests could be conducted, would allow earlier intervention, improving outcomes and reducing social and economic burden on the health system. A promising solution to these issues are model-based methods.

Model-based methods identify patient specific pulmonary mechanics where other methods, such as spirometry, fail [24–33]. Such a model should capture all ranges of COPD dynamics observed in measured airway pressure and flow in normal breathing. It is also important these parameters are physiologically relevant, so their identification from data has physiological meaning. Physiologically relevant parameters with useful resolution across disease severity would enable a good diagnostic and monitoring clinical tool if easily obtained.

Airway resistance, and sometimes compliance, are lung mechanics properties used to diagnose respiratory disease. Clinically motivated prior studies treat resistance in COPD or other lung dysfunction as purely linear, even when graphical PQ loop analyses show expiration is strongly non-linear [34–37]. This study is a first quantification of the non-linear resistance in COPD, and an analyses of its potential as a model-based marker of disease severity.

2. Methods

2.1. Linear single-compartment model

The ubiquitous [13,38–43] linear, single-compartment model (Eq. (1)) in non-spontaneous breathing is defined:

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

where $P_{aw}(t)$ [cmH_2O] is pressure at the airway opening, $Q(t)$ [L/s] is airflow defined positive for inspiration, R [$cmH_2O/L/s$] is airflow resistance, $V(t)$ [L] is tidal volume, E [cmH_2O/L] is lung elastance, P_0 is the end-expiratory pressure and t [s] is time. This single compartment model assumes no change in pleural pressure relative to alveolar pressure, causing inspiratory drive, and thus is used in instances of non-spontaneous breathing only.

A modified single compartment model is presented in Fig. 1, as a lumped alveolar volume with tissue elastance (stiffness) E [cmH_2O/L] and an airway resistance R [$cmH_2O/L/s$]. A surrogate term incorporating breathing effort is included via the transpulmonary pressure, which is the difference between alveolar pressure, P_{alv}, and pleural pressure, P_{pl}. The transpulmonary pressure difference across the lung wall is assumed to follow Hook's law [38]:

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

where P_{pl} is modelled as a pressure deviating from a starting value of atmospheric pressure and is represented as a signal generator in the electrical circuit analogy in Fig. 1. The pressure drop across the airways is defined as a function of flow rate:

$$P_{aw}(t) - P_{alv}(t) = RQ(t) \tag{3}$$

In plethysmography, there is no externally applied end expiratory pressure (P_0), and P_{alv} is calculated relative to the atmospheric pressure [34,36], which also represents the pressure at the airway opening.

Thus, Eq. (3) reduces to:

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

For $-P_{alv}$ [cmH_2O] defined relative to $P_{atm} \cong 0$. Thus, plethysmographic measurements of alveolar pressure are commonly combined with a model based approach to evaluate airway resistance.

The linear, single compartment model in Eq. (1) treats resistance as a constant R. A linear least squares parameter identification approach thus yields [31,38,44–46]:

$$\underbrace{\begin{bmatrix} Q(t_0) \\ \vdots \\ Q(t_N) \end{bmatrix}}_{\mathbf{A}} \underbrace{[R]}_{\mathbf{x}} = \underbrace{\begin{bmatrix} -P_{alv}(t_0) \\ \vdots \\ -P_{alv}(t_N) \end{bmatrix}}_{\mathbf{b}} \tag{5}$$

where t_0 is the first time point of a single breath and t_N is the last time point of a single breath. Airway resistance is known to differ between inspiration and expiration [47,48]. Thus, airway resistance is identified separately for inspiration and expiration, yielding $R_{1,insp}$ and $R_{1,exp}$. This linear model formulation still holds resistance constant over the inspiratory and expiratory periods, and thus may not fully capture airway dynamics in COPD patients, where expiratory resistance can be volume dependent and nonlinear [34–37,49].

2.2. Non-linear single-compartment model

It is hypothesised a non-linear resistance is required to capture the non-linear airway behaviour during expiration in flow limited patients. The non-linear resistive model incorporates the constant linear term ($R_{1,insp}$) identified during inspiration (Q_{insp}) alongside an additional dynamic resistive term ($R_{exp} = \sum R_2 \Phi(t)$), during expiration. Thus, Eq. (3) becomes:

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

where R_{exp} is modelled using M 2nd order ($d = 2$) b-spline functions to fit the unknown shape function, capturing any non-linear, time-varying dynamics during expiration. The second order b-splines are defined over time [24,29,50], with T equally spaced time points:

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

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

where $R_{2,exp,i}$ are constant coefficients of these splines identified using the linear least squares method from measured data. The number of 2nd order ($d = 2$) splines with knot width (k_w) of 0.01 s and a maximal spline timespan for expiration are defined:

$$M(n) = ceil\left(\frac{T_{max}(n)}{k_w}\right) + d \tag{8}$$

Linear least squares is used to fit $R_{1,insp}$ and $R_{2,exp,i}$:

$$\underbrace{\begin{bmatrix} Q_{insp} & \emptyset & \dots & \emptyset \\ \emptyset & \Phi_1 Q_{exp} & \dots & \Phi_m Q_{exp} \end{bmatrix}}_{\mathbf{A}} \underbrace{\begin{bmatrix} R_{1,insp} \\ R_{2,exp,1} \\ \vdots \\ R_{2,exp,M} \end{bmatrix}}_{\mathbf{x}} = \underbrace{\begin{bmatrix} -P_{alv} \end{bmatrix}}_{\mathbf{b}} \tag{9}$$

Matlab command lsqlin (The Mathworks, Inc., Natick, Massachusetts, United States.) is used to constrain all identified parameters as positive, which is physiologically realistic and mitigates identifiability issues [51].

2.3. Patient data

Pressure-flow loops for a healthy adult and an adult with severe COPD who underwent constant volume full body plethysmography were obtained from Radovanovic et al. (2018) [34,37,52,53] using Engauge Digitizer (Open source) [54]. Further clinical details can be found in [34]. To represent a fuller range of possible patient conditions between the healthy (Patient 1) and COPD (Patient 7) patient states, five intermediate patients (Patients 2–6) were created by evenly spaced weighted averages of Patients 1 and 7. Thus, the data set for this proof of concept model based analysis comprised pressure-flow (P,Q) data for 7 'patients' ranging from fully healthy to severe COPD. This analysis tests model utility on this full range of possible disease states to assess the resolution of identified model parameters as model-based markers of disease state.

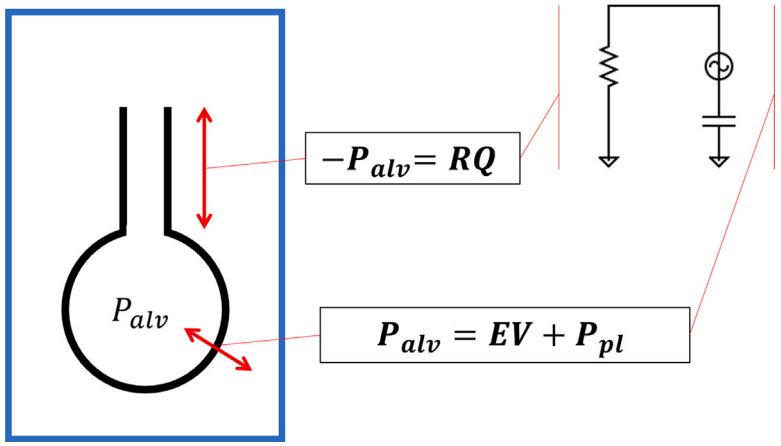

Fig. 1. Single compartment model of spontaneous breathing.

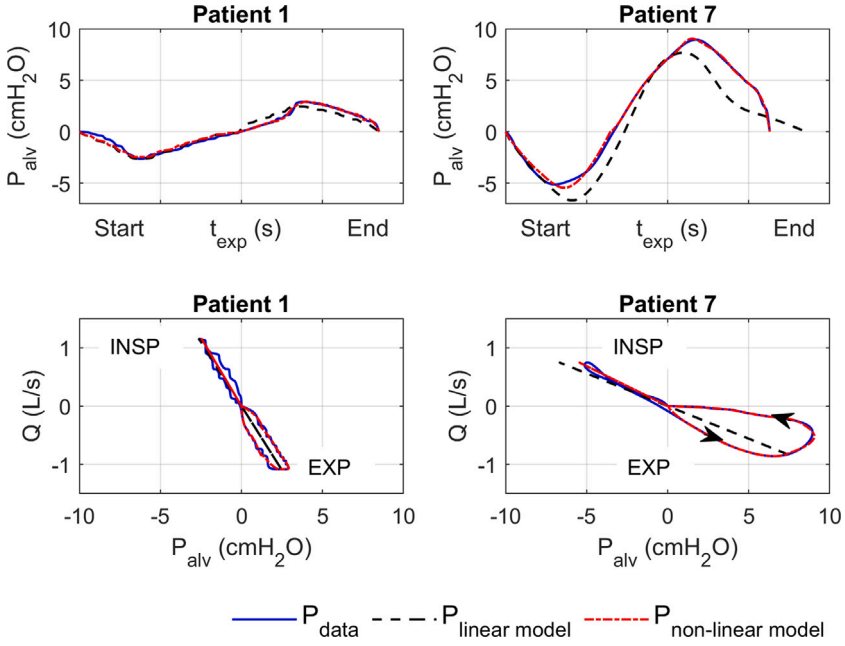

Fig. 2. Plethysmographic alveolar pressure (P_{alv}) data with linear and non-linear model fits for Patients 1 (Healthy) and 7 (COPD). A perfect linear model produces a straight line in a PQ plot. The PQ plot is arranged per [34,36,37] with expiration on the RHS of the plot. Expiratory flow is here defined negative as is consistent with the single compartment model sign convention.

Radovanovic et al. [34,52,53] present alveolar pressure (P_{alv}) and flow at the airway opening (Q), per standard plethysmographic analysis. P_{alv} is derived from changes in barometric pressure inside the plethysmography box using Boyle's law [35]. The use of Boyle's law implicitly treats the lungs as a single volume with a uniform pressure, P_{alv}, representing the average alveolar pressure across the entire lung, which matches the assumptions and formulation of the single compartment model in Eqs. (2)–(4).

2.4. Analyses

The linear and non-linear modelling approaches are fit to plethysmographic data (Patients 1–7) and compared. Both modelling approaches assume airway resistance is linear over inspiration ($R_{1,insp}$), but treat expiration differently with linear ($R_{1,exp}$) and non-linear ($R_2\Phi(t)$) resistance terms, respectively. Root mean squared error (RMSE) is compared for both models to assess model fit to different degrees of COPD. Inspiratory and expiratory resistance are compared, and expected to be strongly linearly related with $R_{1,exp} > R_{1,insp}$ [55]. PQ loops are presented, as they are used clinically to evaluate COPD. Where inspiratory and expiratory resistance is purely linear, the PQ loop reduces to a straight line. As non-linearity in R increases, one or both halves of the PQ loop balloons out. The shape of $R_{2,exp}$ with time and flow is assessed to examine the time and potential flow dependence of airway resistance during expiration, where previous clinical work suggests a flow or volume dependent resistance causing this change in PQ loop shape [37,49,55].

3. Results

3.1. Model identification of goodness of fit

Plethysmographic alveolar pressure is shown in Fig. 2 with linear and non-linear resistive model fits for Patients 1 (Healthy) and 7 (COPD). Identified parameters and RMS errors for the resistive models are given in Table 1. Inspiratory resistance ($R_{1,insp}$), expiratory resistance ($R_{1,exp}$) and the mean non-linear $\sum R_2\Phi$ all increase with the progression from healthy toward COPD as expected. The linear model

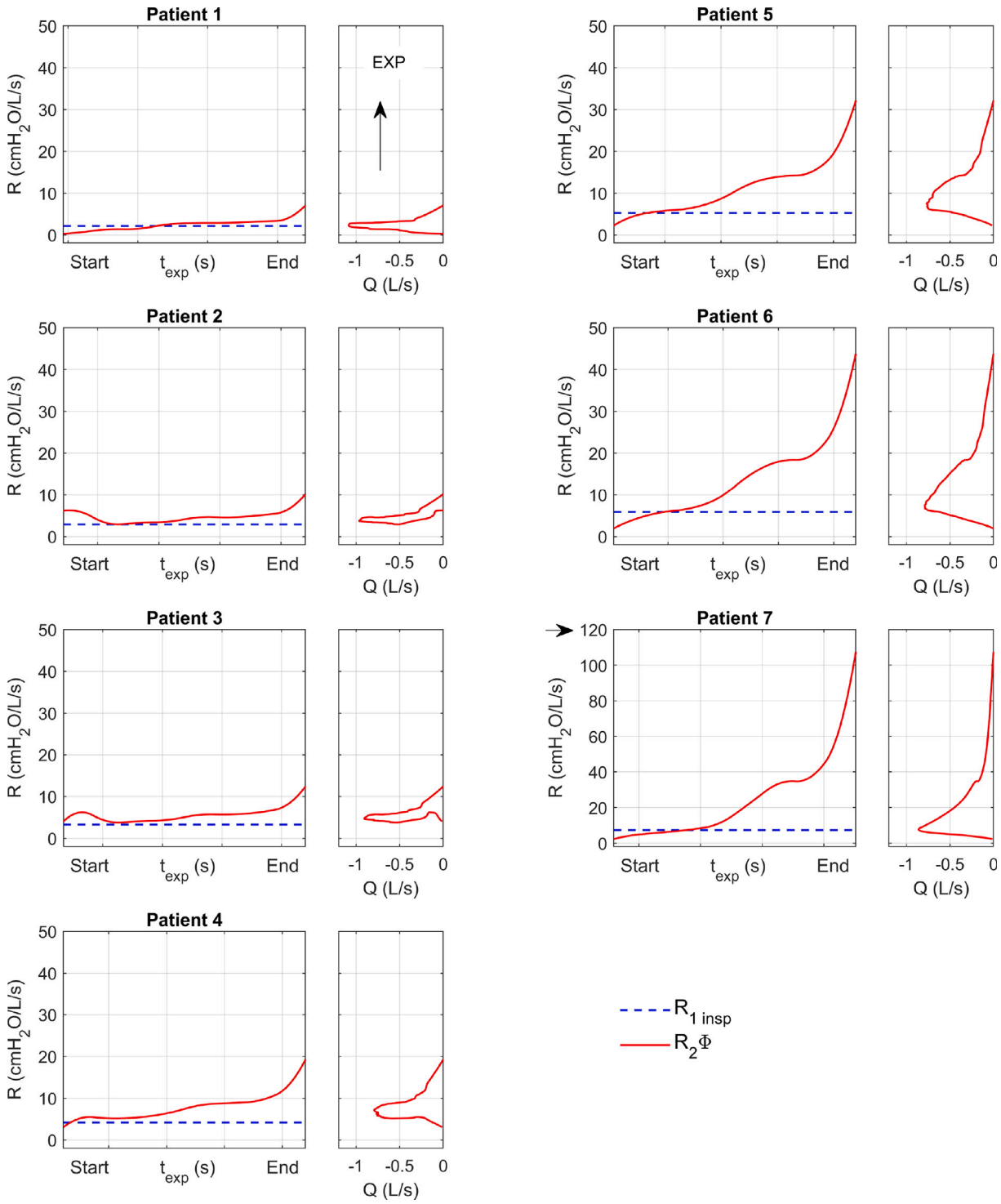

Fig. 3. Expiratory resistance ($R_2\Phi$) with time and flow for each patient. Linear inspiratory resistance ($R_{1,insp}$) is shown for comparison. Note: the scale for the resistance of Patient 7 is much larger than the other patients.

fits the data for the inspiratory part of the breath well, as shown in Fig. 2, indicating inspiratory resistance is largely linear. A linear expiratory resistance term has relatively low RMS error for the healthy patient. However, the RMS error (Table 1) increases with increasing COPD when a linear expiratory model is used, reflecting the non-linear dynamics in expiration [34,36,52,56–59].

Healthy Patient 1 data fits the linear model with a low RMSE value of 0.4 cmH_2O, as shown in Table 1. The mean non-linear resistance $R_2\Phi$ is identified as 2.5 $cmH_2O/L/s$, close to the linear value. The non-linear resistance model terms produce a model fit with an RMS error 0.2 cmH_2O value for the severe COPD patient (Patient 7), with the mean $R_2\Phi$ = 24.4 $cmH_2O/L/s$ capturing the amplified dynamic behaviour of this severe COPD patient. Table 1 shows good resolution between patients and COPD severity for $R_{1,insp}$, $R_{1,exp}$ and mean $R_2\Phi$, with increasing $R_2\Phi$ as disease state worsens.

Fig. 3 depicts the differences between the constant resistance ($R_{1\ insp}$) and the non-linear $R_2\ \Phi$ for expiration only. As the tidal volume of the lungs depletes in the second half of expiration, the resistance

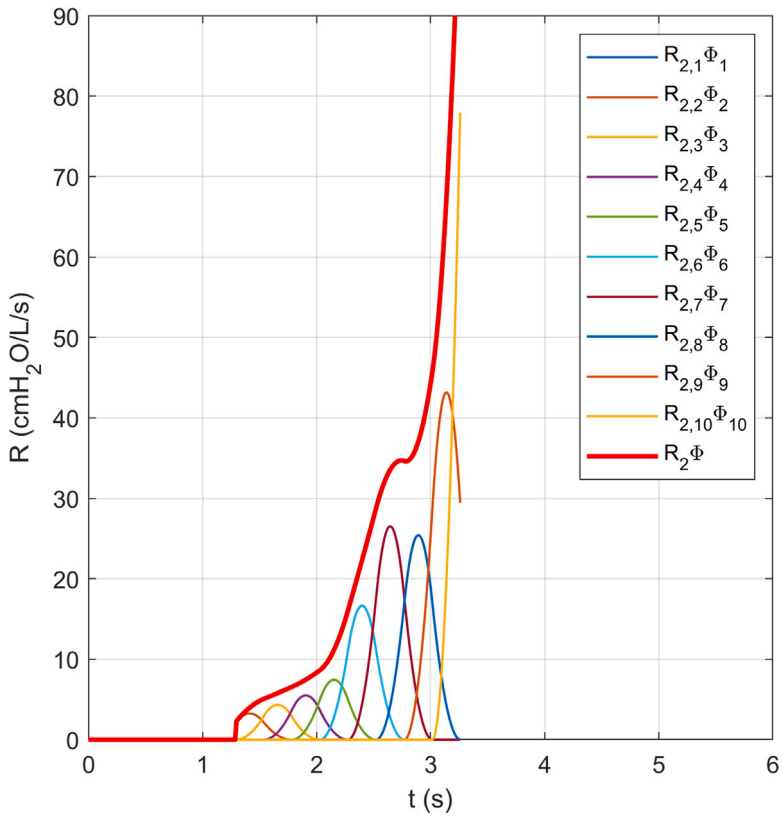

Fig. 4. An example (Patient 7) of individual splines multiplied by individual identified coefficients to illustrate how the splines create the overall shape of the total expiratory resistance.

Table 1
Identified values for model parameters of inspiratory resistance ($R_{1,insp}$), expiratory resistance ($R_{1,exp}$), mean $R_2\Phi$, root mean squared error for the linear model ($RMSE_{lin}$) and root mean square error for the non-linear model $RMSE_{nlin}$.

Patient	$R_{1,insp}$	Linear		Non-linear	
	[$cmH_2O/L/s$]	$R_{1,exp}$ [$cmH_2O/L/s$]	$RMSE_{lin}$ [cmH_2O]	Mean $R_2\Phi$ [$cmH_2O/L/s$]	$RMSE_{nlin}$ [cmH_2O]
1	2.1	2.4	0.4	2.5	0.2
2	2.8	4.1	0.5	4.7	0.2
3	3.2	5.1	0.7	5.6	0.2
4	4.2	7.1	1.1	7.9	0.2
5	5.2	8.8	1.6	11.2	0.2
6	5.8	9.4	1.9	13.7	0.2
7	7.3	10.0	2.7	24.4	0.2

in flow limited COPD patients increases almost exponentially. This non-linear increase in resistance increases in magnitude from Patient 1 through to Patient 7 as the severity of COPD increases, matching physiological expectations [35,60]. Fig. 3 also shows the change in non-linear resistance ($R_2\,\Phi$) with a change in flow for expiration.

An example of what the b-spline functions look like individually and collectively is shown in Fig. 4. Using an infinite number of b-spline functions, model fit to the data would be perfect. However, the number of spline functions used is intended to capture overall dynamics, without over fitting.

Pressure-Flow loops are shown in Fig. 5 for Patient 1 and 7 plotted on the same axes (a) for comparison, with the other Patients (b–f) illustrated to show the progression from a healthy patient toward a COPD patient. The "ballooning" of the expiratory PQ loop is clearly visible for increasing COPD and contrasts with the linearity of the inspiratory portion of the loop.

4. Discussion

This study presents alveolar pressure derived resistance for a range of patient disease states from healthy to advanced COPD. Figs. 2 and 5 show good model fit, with largely linear resistance in inspiration and a clear non-linearity in resistance over expiration as disease state progresses toward advanced COPD. Identified constant inspiratory resistance $R_{1,insp}$ ranges from 2.1 $cmH_2O/L/s$ (Healthy) to 10.0 $cmH_2O/L/s$ (COPD) and time and flow varying, mean non-linear resistance $R_{2,exp}$ ranges from 2.5 $cmH_2O/L/s$ (Healthy) to 24.4 $cmH_2O/L/s$ (COPD). Overall, non-linear model-based resistance improves expiratory model fit, and captures potentially clinically relevant features for COPD diagnosis and monitoring.

The change in non-linear expiratory resistance over time and flow are depicted in Fig. 3, showing small changes in resistance for healthier patients, compared to the larger changes in non-linear resistance in COPD patients, particularly toward the end of expiration. Thus, expiratory resistance is essentially constant in healthy subjects, and increasing non-linearity reflects physiological, or anatomical changes with increasing COPD disease severity. Increasing resistance with severity of COPD is consistent with literature [61–63], as is the result showing model-based expiratory resistance, $R_{1,exp}$, is greater than inspiratory resistance, $R_{1,insp}$ [35].

Resistance increases mostly during flow deceleration as shown in Fig. 3. Previous studies show expiratory resistance causes a temporary imbalance in inhaled and exhaled volume, triggering dynamic hyperinflation and is indicative of COPD [47]. Such patients, typically with severe COPD, will begin to breathe at a higher respiratory rate [64]. Expiratory flow limitation (EFL) is observed in COPD, and results in no increase in flow, despite a rise in pressure [65,66], which would be observed in a modelling approach as increasing nonlinear resistance. The mechanisms of EFL are not agreed upon in literature, but are

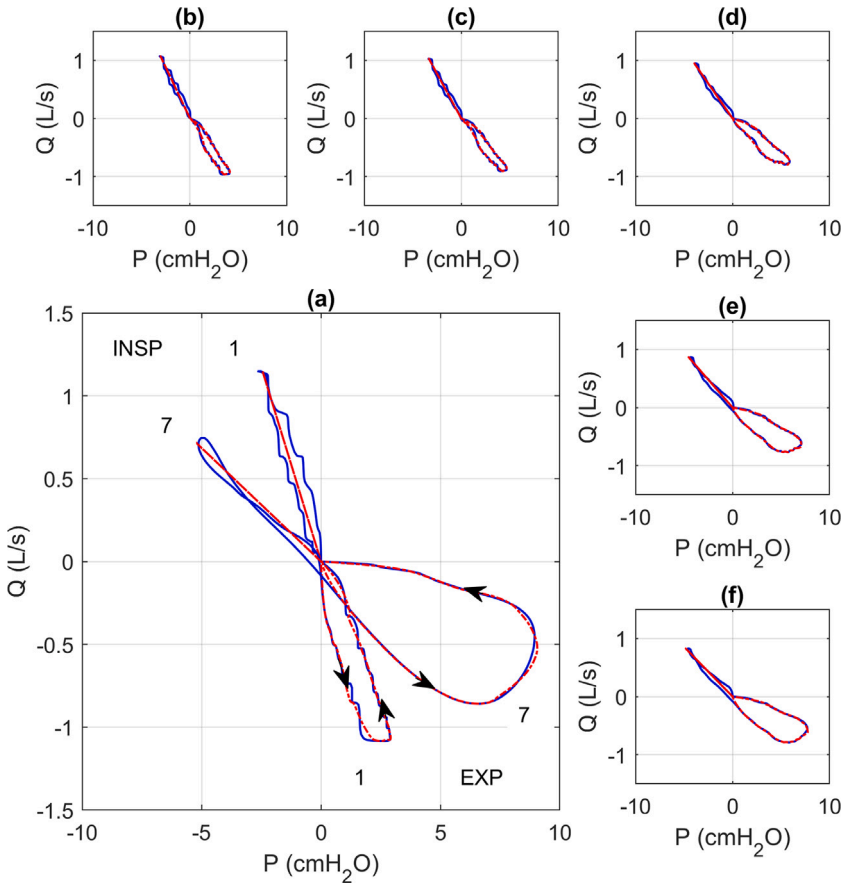

Fig. 5. Pressure-Flow (PQ) loops depicting data (solid) and non-linear model (dashed) Patients 1 and 7 (a), Patient 2 (b), Patient 3 (c), Patient 4 (d), Patient 5 (e), and Patient 6 (f). The PQ loops are arranged per [34,36,37] with expiratory flow, negative per the sign convention of the single compartment model.

believed to be related to airway obstruction [49] and/or small airway collapse [67]. Thus, EFL is more prominent in COPD patients in the supine position due to gravitational forces and increases with age and obesity [67]. EFL is associated with an increase in resistance and a concomitant decrease in tidal volume [34,68]. The nonlinear, increasing, expiratory resistance observed here follows trajectories that align with EFL and airway restriction/obstruction, and thus may be useful in non-invasive monitoring and diagnosis of COPD and its associated physiology.

Nonlinear expiratory resistance reflects an increased pressure gradient to achieve flow, indicative of airway narrowing and/or airway collapse during expiration. Typical linear models miss characteristics of the expiratory behaviour, as seen in Fig. 2. Using this nonlinear model, the mean nonlinear resistance captures significantly more of the dynamics of expiration, as can be seen in the significant difference in identified resistance in Table 1. Therefore, quantification of such a metric could be used with higher specificity to monitor disease state or progression and may have potential for enabling more targeted treatment by clinicians.

To the authors knowledge, no previous work directly models a non-linear COPD airway resistance from clinical data. Clinically, most derive an average resistance from $R = P/Q$, equivalent to the linear resistance $R_{1,exp}$ in this study. One previous study used geometric quantification of PQ loop "ballooning", but this analysis is empirical, rather than physiological, and cannot directly reflect anatomical effects or changes. Many other studies [69–72] have complex simulation models, with multiple resistance and elastance terms, which are unidentifiable from typical clinical data and non-invasive measurements, and thus not useful with plethysmography data without several population-based parametric assumptions or additional invasive pressure measurements.

This study uses only alveolar pressure and airflow plethysmography data, which restricts model complexity. Studies in the ICU with mechanically ventilated patients have examined the nonlinear resistive dynamics [73]. Approaches include viscoelastic [68,74,75] and flow and/or volume dependency of resistance [76–79]. No real consensus exists for flow or volume or flow and volume dependence [76], where reliance on model fit may collapse or alias different dynamics into model terms [73]. In particular it has been noted, volume and flow dependence may trade off [73]. Overall mechanically ventilated (MV) results in COPD patients match these presented here, with a negative dependence on flow and/or volume, capturing end-expiratory flow limitation [76]. Full comparison is complicated by the difference between positive pressure MV, and levels of sedation, compared to the full negative pressure spontaneous breathing here where spontaneous breathing in particular may change dynamics [59].

Plethysmography measures shift volume and corresponding decreases in pressure, applying Boyle's law to enable the derivation of alveolar pressure P_{alv} [34,35]. This derivation assumes no temperature dependence and some small pressure–volume effects are negated. Plethysmography derived alveolar pressure P_{alv} is essentially a lumped compartment pressure, which represents the average alveolar pressure, making this data perfect for single compartment model-based analyses. Assumptions made in the derivation of the plethysmographic, P_{alv}, are usually directly mitigated during data collection as part of standard plethysmographic methodology [35]. This plethysmographic data is useful for providing the alveolar pressure insights necessary for effective evaluation of airway resistance. This study adds to the clinical literature by considering the well known, observed non-linear characteristics of expiratory airway resistance.

In inspiration–expiration, and expiration–inspiration transitions there is a flow reversal. Expiratory flow experiences a different geometry and physical obstacles compared with inspiratory flow. For example, at airway bifurcations during inspiration, the flow splits around a wedge-shaped obstacle to create two separate flows into separate airways. During expiration the flow streams must merge from these two airways, and the resistance of splitting and merging flows is unequal. In addition, airways experience different forces during inspiration and expiration. During forced expiration, typical of COPD patients with flow limitation, airway collapse and airway narrowing may result from muscle contraction to compress the abdomen/chest, which may change the diameter and/or geometry of an airway. In contrast, during inspiration the muscle activity acts to expand the volume of the chest cavity, and thus is going to act differently on the airways and affect the diameter and geometry differently. Thus, there are good physiological reasons why resistance may experience a discontinuous step or jump between inspiration and expiration.

The original data used for this study is comprised of only measured data from two patients. However, these two patients are indicative of the extremes of respiratory health in terms of COPD. Intermediate derived patients show possible disease progression in terms of nonlinear changes in PQ loop shape. The model is able to reflect all theoretical intermediate states, and the use of B-splines means it will describe any resistance shape. Thus, this study is an effective proof of concept to demonstrate the physiological relevance and capability of the model and methods. The results presented justify a larger study utilising clinical data from a much larger range of respiratory disease states.

Future work will include analysis of comprehensive patient data, and identifying similar model parameters from airway pressure (P_{aw}), without alveolar pressure (P_{alv}). Identifying clinically relevant metrics 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 and disease management, particularly as healthcare demand and costs rise beyond our ability to meet or afford them [20].

5. Conclusions

A novel method for quantitative analysis of plethysmographic PQ loops is presented with an identifiable nonlinear model capturing changes in COPD disease state. The model captures static and dynamic changes in resistance as model-based markers for COPD diagnosis and monitoring. Finally, the nonlinear model presented delivers physiologically expected and relevant parameter values with possible future clinical use.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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