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Quantifying ventilator unloading in CPAP ventilation

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ABSTRACT

Background: The intrinsic (muscular) patient effort driving inspiration in non-invasive ventilation modes, such as continuous positive airway pressure (CPAP) therapy, has not been identified from non-invasive data. Current CPAP settings are based on clinical judgment and assessment of symptoms of respiratory distress. Non-optimal settings, including too much positive end expiratory pressure (PEEP) can cause unintended lung injury and ventilator unloading, where patient effort drops and the CPAP device enables too much work being imposed on the injured lung. Currently, there is no non-invasive means of quantifying or identifying these effects.

Methods: A novel model-based method of ascertaining intrinsic patient work of breathing (WOB) in CPAP is developed based on linear single compartment and 2nd order b-spline models previously used in invasive ventilation modes. Results are compared to current clinical indications, such as total Imposed WOB from the CPAP device and beak length, the latter of which is the clinical metric used to indicate alveolar overdistension. Intrinsic and Imposed WOB are compared.

The hypothesis is that ventilator unloading can be assessed as a decrease in Intrinsic WOB relative to Imposed WOB, as PEEP and associated ventilator unloading rise. This hypothesis is tested using 14 subjects from a CPAP trial of several breathing rates at two PEEP levels.

Results: The ratio of Intrinsic to Imposed WOB, normalised per unit tidal volume, decreased with increasing PEEP (4–7 cm H_2O), capturing the expected trend of ventilator unloading. Ventilator unloading was observed across all breathing rates. Beak length measurements showed no conclusive evidence of capturing overdistension at higher PEEP or ventilator unloading.

Conclusions: Patient Intrinsic WOB in CPAP was non-invasively quantified using model-based methods, based on pressure and flow measurements. The ratio of Intrinsic to Imposed WOB per unit tidal volume clearly and consistently showed ventilator unloading across all patients and breathing rates, with Intrinsic WOB decreasing with increasing PEEP. This trend was not observed in the current clinical metric of beak length. Non-invasively quantifying Intrinsic WOB and ventilator unloading is the critical first step to objectively optimising clinical CPAP settings, patient care, and outcomes.

1. Introduction

Spontaneous breathing is driven by contraction of the intercostal muscles, lifting of the thoracic cage, and distension of the diaphragm, to increase the volume of the pleural cavity [1]. This increase induces a pressure gradient, which drives inspiration. The work done to produce this inspiratory driving pressure is the intrinsic work done by the patient.

Expiration is a largely passive process generated from the relaxation of the diaphragm and intercostal muscles [1]. Thus, the rate of expiration is determined primarily by chest and lung elasticity, and airway resistance [1]. Expiration terminates at atmospheric pressure or a positive end-expiratory pressure (PEEP) sufficient to maintain open airways between breaths [1,2].

Respiratory system pathophysiology is categorised as either restrictive or obstructive abnormalities [3]. Restrictive conditions result from scarring of lung tissue, external pressure on the respiratory system, and/or insufficient muscular activation [1], which act to increase lung stiffness. Conversely, obstructive conditions increase airway resistance [4]. Airway collapse or restriction impedes the rate of expiration, which

CPAP, Continuous Positive Airway Pressure PEEP, Positive End Expiratory Pressure NIMV, Non-invasive Mechanical Ventilation WOB, Work Of Breathing.

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Table 1
Subject demographic data. Subject numbers per original numbering in [36].

Subject	Sex (M/F)	Age (Years)	Weight (kg)	Height (cm)	BMI	Asthmatic (Y/N)	Medication and frequency of use	Smoker (Y/N)	Years a smoker and frequency of use
1	M	33	70	180	21.6	N	–	Y	5/day for 10 years
2	M	22	75	185	21.9	N	–	N	–
3	F	21	65	169	22.8	N	–	N	–
4	M	21	65	185	19.0	N	–	N	–
5	M	21	75	185	21.9	Y	1 puff/month of Ventolin	N	–
6	F	21	70	175	22.9	N	–	N	–
7	F	22	80	165	29.4	N	–	N	–
12	F	19	65	164	24.2	N	–	N	–
14	M	22	96	189	26.9	N	1 puff/day of Ventolin	N	–
17	F	23	79	170	27.3	Y	–	N	–
22	F	23	72	170	24.9	Y	Infrequent use of Flixotide & Ventolin	N	–
24	F	30	66.5	167	23.8	Y	5 puffs/week of Ventolin	N	–
27	M	21	89	185	26.0	N	–	N	–
30	F	28	78	167	28.0	Y	–	N	15/day for 7 years

in turn causes air trapping [1,5,6].

Mechanical Ventilation (MV) is used to treat respiratory conditions and is either classed as invasive (IMV), or non-invasive, mechanical ventilation (NIMV) [7]. Both are used to maintain open airways, functional residual capacity (FRC), and sufficient oxygen exchange [8]. MV is either pressure-controlled or volume-controlled [9], where excess pressure or volume can result in lung injury [8]. Conversely, insufficient pressure or volume can lead to hypoxemia and atelectasis [8,10,11]. Direct measurement of respiratory lung mechanics to assess this risk cannot be obtained noninvasively. Hence, MV care is currently set based on limited measurements, guidelines, and clinical judgment [12–18].

In IMV, patients are anesthetised and intubated, with the most or all of the work of breathing (WOB) provided by the ventilator [7]. However, in NIMV, the patient breathes spontaneously and the ventilator provides support, reducing the intrinsic muscular WOB required from the patient [19]. A very common type of NIMV is continuous positive airway pressure (CPAP) therapy [20], which maintains a set PEEP at the mouth/nose orifices to retain open airways at end expiration [7,21], decreasing the required negative driving pressure to produce the same pressure gradient [8,19]. Thus, it reduces the required Intrinsic WOB.

However, the proportion of patient effort relative to ventilator effort is not easily or non-invasively quantified. Quantifying WOB components with relation to PEEP in CPAP would provide greater clinical insight into the impact of CPAP support. In particular, if too much support is provided, not only does barotrauma risk increase, but the patient's Intrinsic WOB may increase to oppose excess flow, leading to excessive muscle fatigue and respiratory distress [8]. Equally, too much support can lead to ventilator unloading, reducing patient effort too much, and preventing or delaying weaning [22–24]. It is not currently possible to identify or separate these effects without invasive tests or measurements.

Patient-specific pulmonary mechanics, specifically lung elastance and airway resistance, have been modelled, identified, and, in some cases, predicted and validated using models in IMV patients [15,25–31]. Recently, spontaneous breathing in IMV assisted breathing modes has been modelled and validated using scaled second order b-splines to identify patient-specific effort [32]. This research combines these models to quantify patient-specific Intrinsic WOB at several breathing rates. It compares these values to WOB imposed by a CPAP device to quantify ventilator unloading in CPAP as a function of identified patient-specific lung mechanics.

The single compartment model of the lungs is favoured for identifying patientspecific pulmonary mechanics, as it has been shown to accurately reflect pulmonary physiology using easily attainable data [15,25–31] and is identifiable compared to other models [25,33–35]. These advantages make it more appropriate for clinical applications and reduces the complexity and computational expense demanded from higher order models [25]. The advantage of identifying patient-specific driving pressure is that it can be used to quantify the portion of WOB done by the patient, which cannot otherwise be accurately and

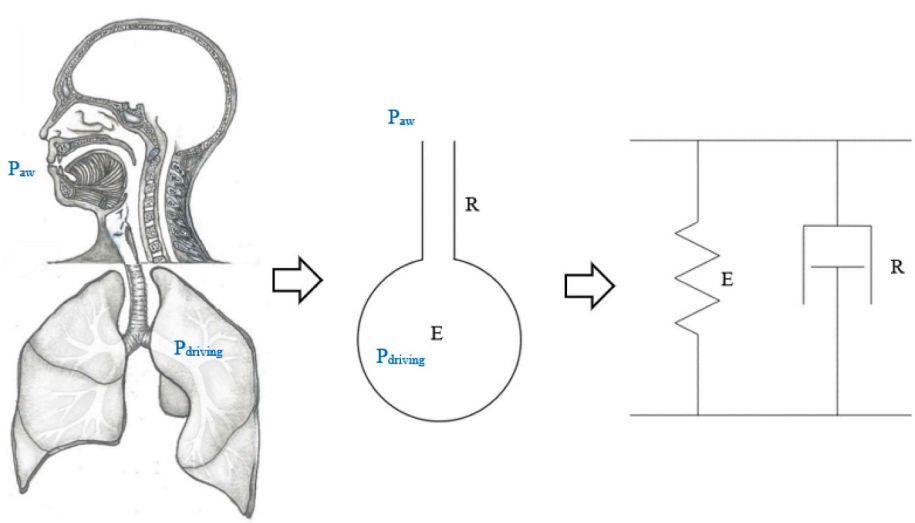

Fig. 1. Single compartment model representation, where the respiratory system is modelled as a tube (representing the respiratory tract/airways) connected to a balloon (representing lung tissue). In the single compartment model the tube is considered to have a constant resistance (R), and the balloon a constant elastance (E) [conceptual drawing by author Guy, E.F.S].

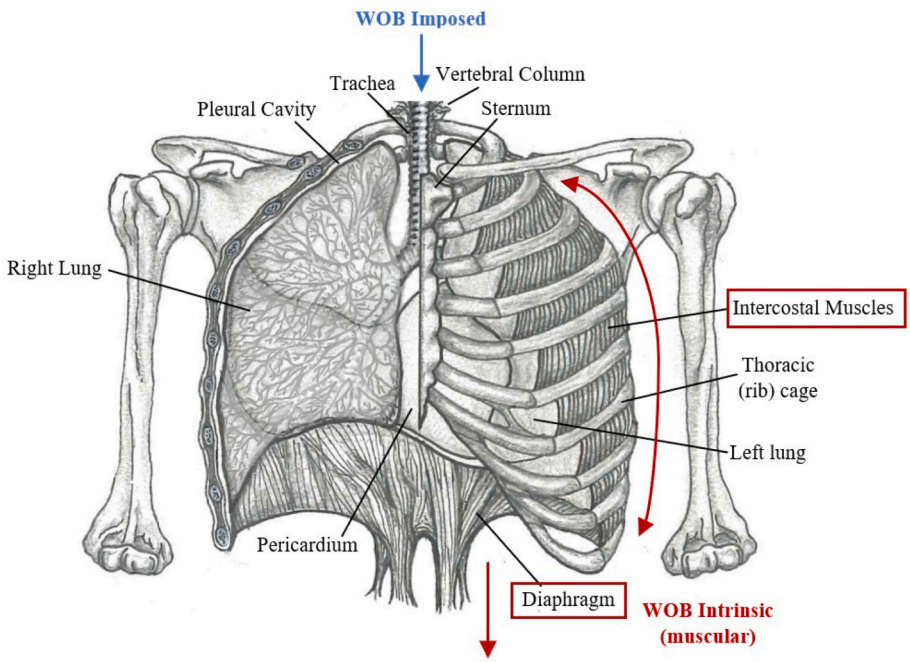

Fig. 2. Illustration of Intrinsic vs Imposed WOB [conceptual drawing by author Guy, E.F.S].

non-invasively ascertained.

Using this combined model to identify patient-specific pulmonary mechanics and spontaneous breathing effort has been shown to be difficult in data with small changes in airway pressure [32], which is characteristic of CPAP ventilation, and has been attributed to parameter trade-off [32]. Thus, using values and relationships from literature [26, 36], patient-specific pulmonary mechanics parameters were based on first applying a passive model, without patient driving pressure, to expiratory periods where there is no patient input.

2. Methods

2.1. Subjects and data

Subject data is from a trial of 30 healthy adults breathing with CPAP [36]. An audio-visual cueing system was used to record data at breath rates of 60 (short), 30 (medium short), 9 (medium long), and 6 (long) breaths per minute. Resting/normal breathing sections were uncued/-spontaneous (approximately 12 breaths per minute). These trials were repeated at PEEP levels of 4 and 7 cmH_2O. PEEP levels were chosen to provide a significant change in support, over which ventilator unloading could be expected to be seen, without causing substantial patient discomfort. Subject selection criteria for this analysis was 4–10 breaths, recorded with no acquisition error or large facemask leaks, at all 5 breathing rates for both PEEP levels (all 10 trials per subject), which yielded 14 subjects (Table 1) and excluded 16, of which 6 had large facemask leaks. Thus, these criteria required clean data from all breathing rates at both PEEP levels, which was difficult for some subjects, and, in addition, was subject to mask leakage and fit issues. All data and details for all 30 subjects is freely available [36].

2.2. Model

The model combines a well-validated single compartment model [15,25,26] (Fig. 1) with a recently published spontaneous breathing model, to model driving pressure by linear regression using non-invasive data [32]:

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

Thus, airway pressure (P_{aw} [cmH_2O]) is modelled based on identified lung elasticity (E [cmH_2O/L]) and airway resistance (R [$cmH_2O/L/s$]), using tidal volume (V [L]) and flow (Q [L/s]) data and a set PEEP [P_{PEEP} cmH_2O]:

Patient driving pressure ($P_{driving}$ [cmH_2O]) is modelled as a sum of scaled (P_s) second order b-splines (φ) [32]:

$$P_{driving}(t) = \sum_{i=1}^{M} P_{s,i}\varphi_{i,\ d=2} \tag{2}$$

Where the second order ($d = 2$) b-splines are defined:

$$\Phi_{i,0}(t) = f(x) = \begin{cases} 1, & T_i < t < T_i + 1 \\ 0, & otherwise \end{cases} \quad \Phi_{i,d}(t) = \frac{t - T_i}{T_{i+d} - T_i}\Phi_{i,d-1}(t) + \frac{T_{i+d+1} - t}{T_{i+d+1} - T_{i+1}}\Phi_{i+1,d-1}(t) \quad for\ d\ \geq 1 \tag{3}$$

Given a knot width (k_w) of 0.1 s defining the spline spacing, and T_i equal divisions in time. The length of inspiratory effort (T_{max}) is defined by the number of splines at k_w intervals in each inspiration (rounded up) and calculated as the number of b-spline basis functions (M) fitted to each (n) inspiration breath segment, yielding:

$$M\left(n\right) = ceil\left(\frac{T_{max}(n)}{k_w}\right) + d \tag{4}$$

First, patient-specific expiratory elastance (E_{exp}) was identified using only data from expiration using linear regression in MATLAB (Matlab 2020a, The Mathworks Inc, Natick, MA, USA):

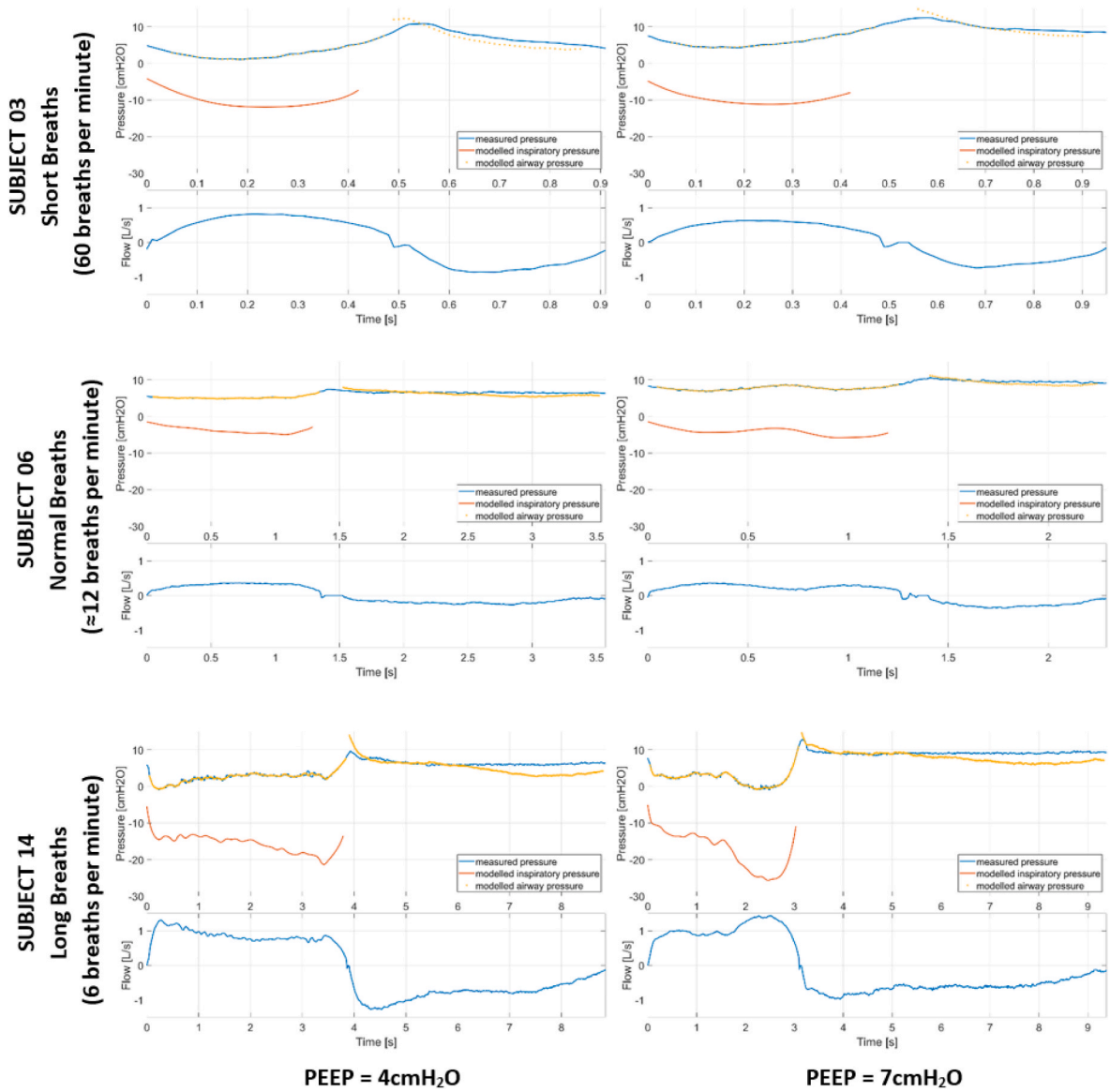

Fig. 3. Representative modelled breaths. Short breaths (Subject 03), Normal breaths (Subject 06) and Long breaths (Subject 14) at PEEP settings of 4 and 7 cmH_2O. Where measured flow and pressures are blue, identified inspiratory driving pressure is red, and the modelled airway pressure fit in yellow.

$$P_{airway,\ exp}(t) = E_{exp}V_{exp}(t) + RQ_{exp}(t) + P_{PEEP} \tag{5}$$

Resistance, R, is held constant $R = 5$ $cmH_2O/L/s$ [26] and PEEP is defined for each breath as the mean end expiratory pressure value from the last 0.2 s of each breath, yielding a regression problem and equations defined:

$$Ax = b\ A = \begin{bmatrix} V_{1,exp}(t) \\ \vdots \\ V_{n,exp}(t) \end{bmatrix} b = \begin{bmatrix} P_{aw,1,exp}(t) \\ \vdots \\ P_{aw,n,exp}(t) \end{bmatrix} - R \begin{bmatrix} Q_{1,exp}(t) \\ \vdots \\ Q_{n,exp}(t) \end{bmatrix} - PEEP\ x = E_{exp} \tag{6}$$

Patient-specific inspiratory elastance (E_{insp}) is then estimated based on its relationship to E_{exp} [37]:

$$E_{insp} = 1.04E_{exp} + 1.6 \tag{7}$$

These results allow the b-spline scaling coefficients (P_s), and thus $P_{driving}$ in Equation (2), to be identified using linear regression in a problem defined:

$$Ax = b\ A = \begin{bmatrix} (\varphi_{1,2}(t)1 \to M & [0]_{(n-1)\times M} \\ \ddots & \\ [0]_{(n-1)\times M} & \varphi_{n,2}(t)1 \to M \end{bmatrix} \quad b = \begin{bmatrix} P_{aw,1,}(t) \\ \vdots \\ P_{aw,n}(t) \end{bmatrix} - E_{insp} \begin{bmatrix} V_1(t) \\ \vdots \\ V_n(t) \end{bmatrix} - R_{insp} \begin{bmatrix} Q_1(t) \\ \vdots \\ Q_n(t) \end{bmatrix} - PEEP\ x = \left[P_{s,1,1} \ldots P_{s,1,M},\ \ldots,\ P_{s,n,1},\ \ldots,\ P_{s,n,M}\right]^T \tag{8}$$

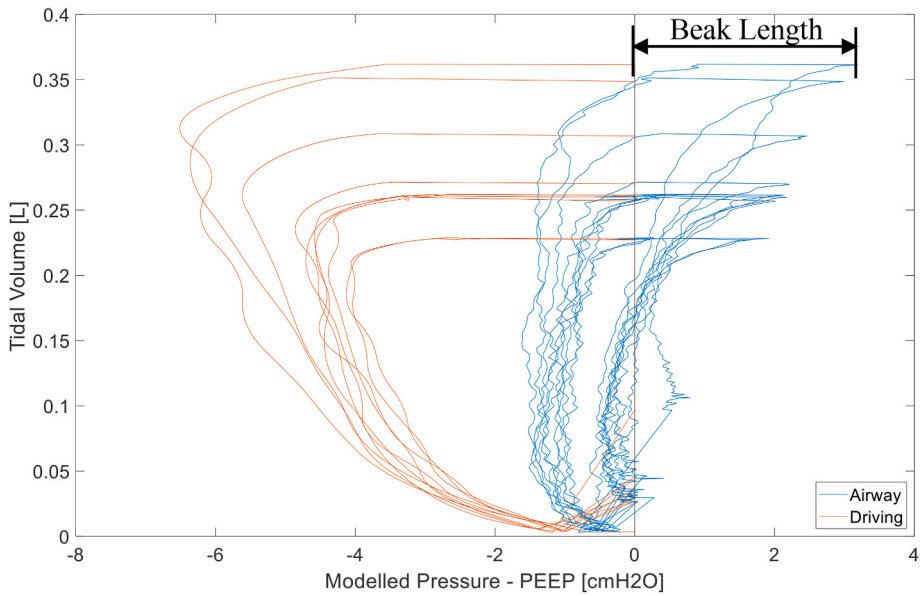

Fig. 4. PV loops for modelled airway pressure and driving pressures to give imposed and intrinsic work respectively (Subject 1: 10 breaths at PEEP = 4cmH_2O normal breathing). Beak length indicated for the largest breath loop.

2.3. Work of breathing (WOB)

WOB is defined as the integral of pressure with respect to volume:

$$WOB = \int P\, dV \tag{9}$$

The function of a CPAP device is to maintain a set PEEP. Thus, the WOB demanded from the ventilator is given by the pressure deviation from the set PEEP:

$$WOB_{Imposed\ on\ CPAP}(n) = \int_{t=start\ breath\ (n)}^{t=end\ breath\ (n)} P_{airway}(t) - P_{PEEP}(n)\, dV \tag{10}$$

The work done in CPAP ventilation has been considered in two reference frames. The first is the WOB imposed on the ventilator (Equations (9) and (10)). The CPAP device adjusts pressure to maintain the set PEEP against variation due to patient driving pressure, and elastic and resistive forces associated with the airway and lungs (Fig. 2). The second WOB considered is the intrinsic patient work associated with

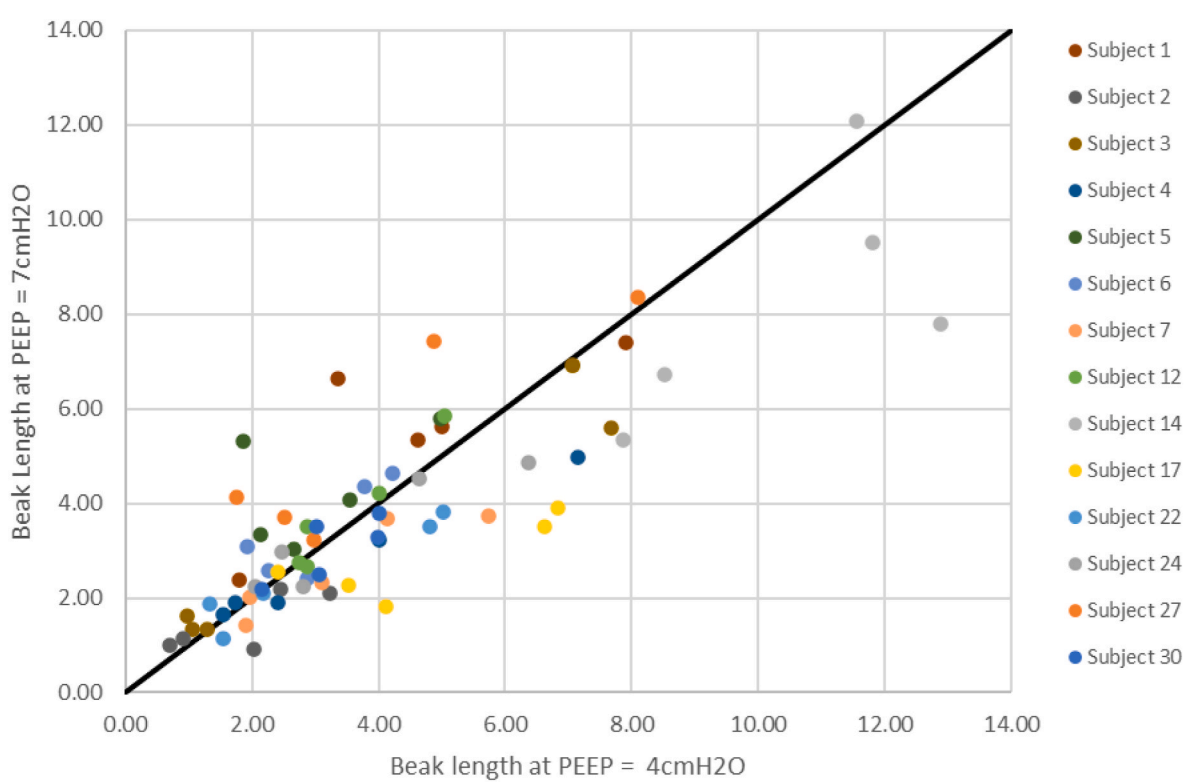

Fig. 5. Beak length comparison between PEEP levels by subject for each breath type, where the hypothesis would indicate all points above the y = x line shown.

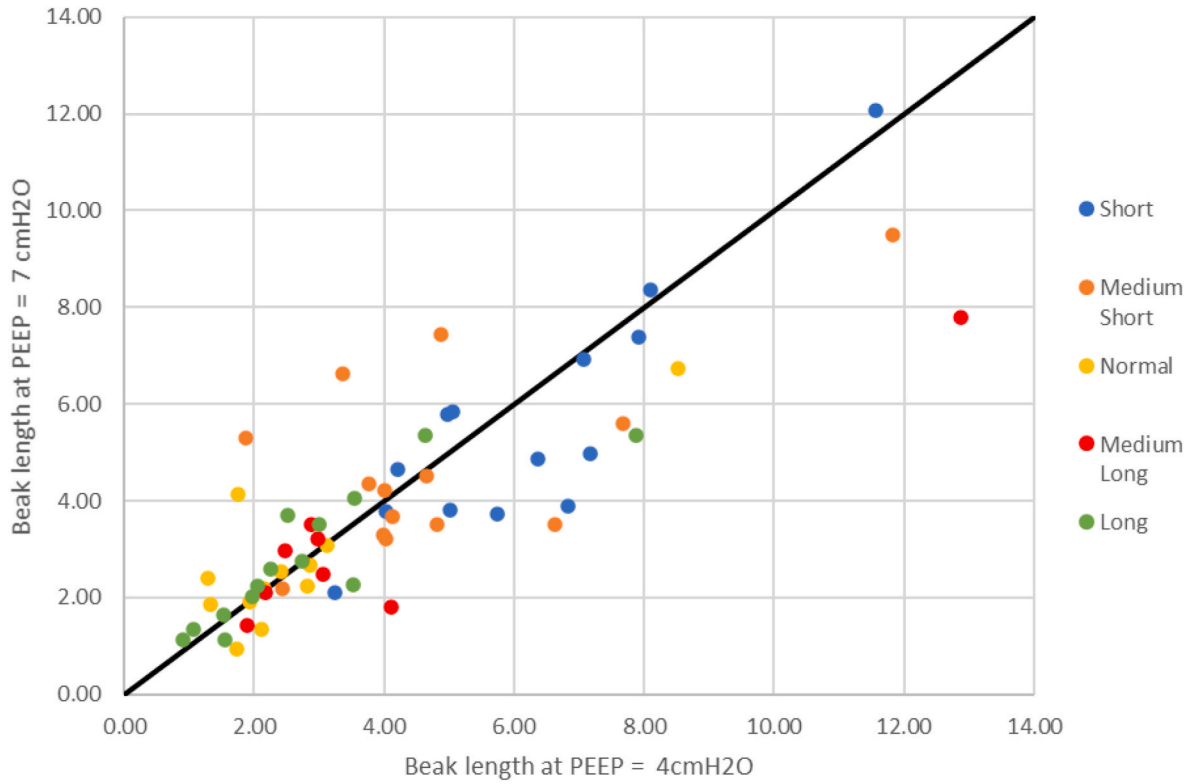

Fig. 6. Beak length comparison between PEEP levels by breath type for all subjects, so there are 14 dots of each colour in the legend.

muscular recruitment increasing the volume of the pleural cavity (Fig. 2). Comparing Intrinsic to Imposed WOB assesses the level of assistance provided by the CPAP device relative to patient effort, and potential ventilator unloading.

To enable this comparison, Intrinsic WOB is the integral of the patient driving pressure:

$$WOB_{Intrinsic\ Patient\ Work}(n) = \sum_{t=start\ breath(n)}^{t=end\ breath(n)} P_{driving}(t)V(t) \tag{11}$$

Where all the terms in Equation (11) are measured or identified from clinical data [32].

2.4. Hypothesis and analyses

This study hypothesises that the $WOB_{Intrinsic\ Patient\ Work}$ per unit of tidal volume will become smaller relative to $WOB_{Imposed\ on\ CPAP}$ per unit tidal volume, indicative of a patient unloading breathing work onto the CPAP device as the positive expired pressure increases.

To enable this comparison, the ratio of the $WOB_{Intrinsic\ Patient\ Work}$ (Equation (11)) per unit of tidal volume to $WOB_{Imposed\ on\ CPAP}$ (Equation (10)) per unit tidal volume is compared over the two PEEP levels (4 and 7 cmH_2O). WOB values are normalised to tidal volume so any changes in tidal volume at different PEEP levels or breathing rates are removed from the comparison, which also allows comparison across different subjects. This comparison is made over all breathing rates, as well as individually for each breathing rate, to ensure any trend is consistent across breathing rates tested, and to further assess if breathing rate impacts ventilator unloading.

Quantifying the ratio of intrinsic to imposed work also provides scope for clinical use to determine an optimal PEEP for CPAP in a clinical setting. Currently, visual waveform analysis [16] and other pathological clinical indicators of overdistension or underoxygenation are used to inform changes in PEEP levels [12,38,39]. However, it is too computationally complex for real-time use and would require a high level of clinical judgment, as it is not standardised. Moreover, the easily measured 'Beak' length is clinically used to assess overdistension of alveolar tissue [16–18]. Hence, this study also compares beak length, calculated for each breath for each subject as the maximum airway pressure minus PEEP, between the two PEEP levels. To confirm its consistency as the typical clinical metric, beak length is expected to be longer with higher set PEEP, which can increase distention of alveolar tissue.

3. Results

Representative modelled breaths are illustrated in Fig. 3 with the identified patient inspiratory driving curve included, in addition to the model results and data. Modelled airway pressure, using identified patient-specific parameters, shows a good fit to measured airway pressure, where the inspiratory driving pressure curve is negative, as expected, and shows the patient effort independent of this overall pressure. Full model outcomes are included in a supplementary file (Appendix A).

The combined Imposed WOB (blue loop) is compared to Intrinsic WOB (red inspiratory loop) in pressure-volume (PV) loops in Fig. 4, which also shows beak length for one PV loop as an example. The beak lengths for each subject, breath rate, and PEEP were recorded (Appendix C, Figures C1-C12) as the mean of recorded breath beak lengths (Fig. 4).

Beak length is plotted by subject (Fig. 5) and by breath type (Fig. 6) across PEEP levels. In both cases, a y = x line is included for comparison between 4 and 7 cmH_2O, where the expected result for increased alveolar distension at higher PEEP would be above this line. However, Figs. 5–6 show data distributed relatively evenly above and below this line, showing no expected trend, with most data above the y = x line still very close to it. Full results are included in Appendix D. Thus, these results are not nearly as consistent as those in Figs. 7–8, where the latter figures match expected ventilator unloading much more consistently, as hypothesised.

The Imposed WOB per unit tidal volume and corresponding Intrinsic WOB per unit of tidal volume for each subject, set PEEP, and breath-rate,

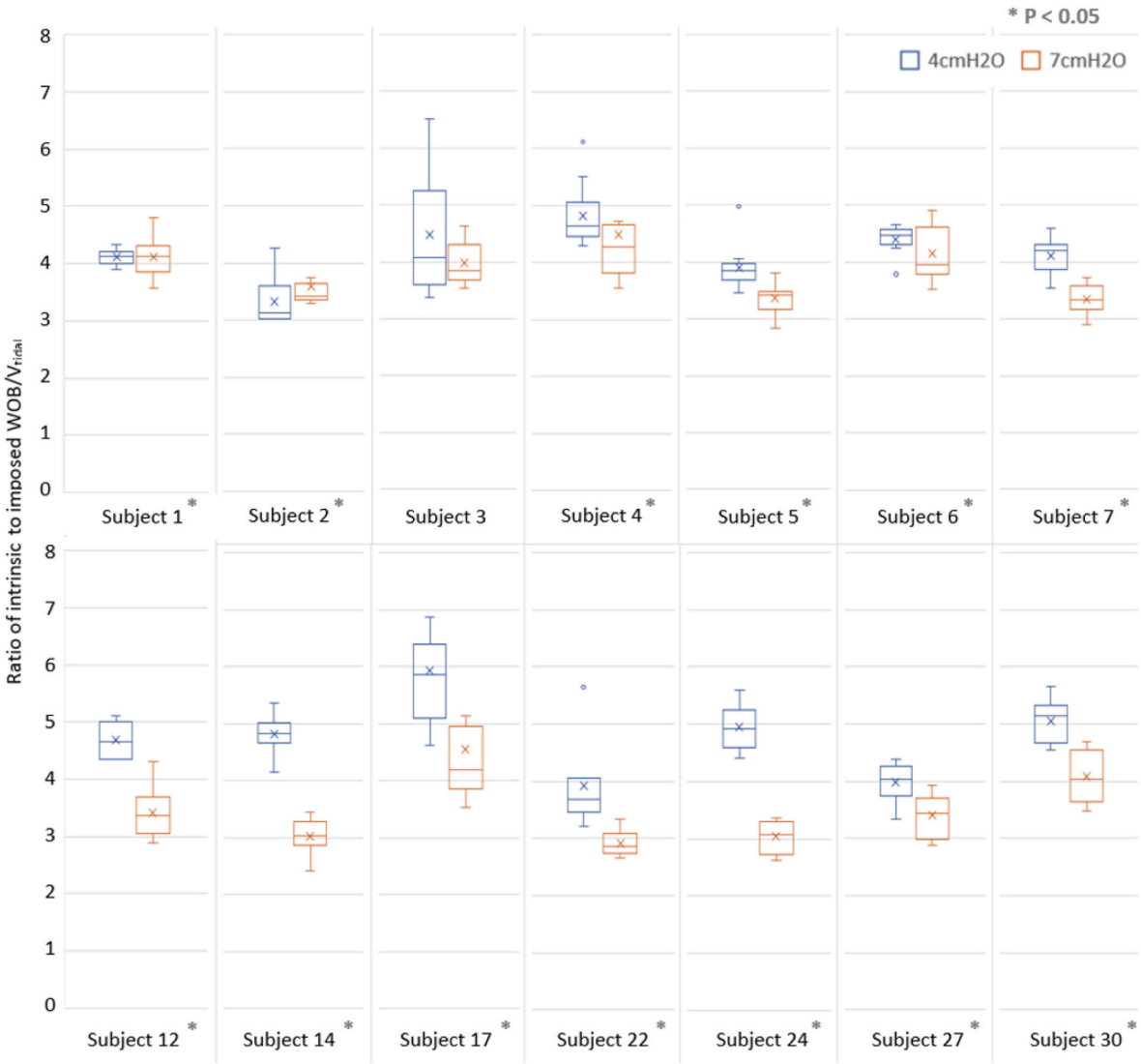

Fig. 7. Box plot comparison of the ratio of Intrinsic to Imposed WOB per tidal volume between 4 and 7 cmH_2O set PEEP levels for all 14 Subjects. Where 'x' marks the mean ratio and an astrix '*' denotes a p-value <0.05.

are outlined in Appendix B (Tables B1 and B2 respectively). Intrinsic and Imposed inspiratory WOB/V_{tidal} over all breath rates, is compared as a ratio (intrinsic/imposed) for each subject for both PEEP settings. The distribution of these results is compiled as a series of box plots in Fig. 7. This distribution shows that the mean and median of the ratios are lower at the higher PEEP (7cmH_2O) setting for 13 of the 14 subjects. The interquartile ranges overlap for 5 of the 14 subjects, but only completely in Subjects 1 and 3 (Fig. 7), where Subject 3 still has a lower mean and median value. Only Subject 2 has an ambiguous result. These results match the study hypothesis.

The ratio between intrinsic and imposed work of breathing is shown for one subject, separated by breath rate, in Fig. 8. These results show that the same ventilator unloading trend shown in the overall data holds at each breathing rate, demonstrating that the results are not skewed by a trend in a single breath rate. This outcome holds for all subjects, with the overall p-value being $p = 0.05$ (Subject 3), where full results for all subjects are found in a supplementary file (Appendix C).

4. Discussion

4.1. Outcomes

Patient intrinsic driving pressure was identified using model-based methods over a series of subjects, breathing rates, and PEEP levels (Fig. 3, Appendix A). The model fits the data well (Fig. 3) with the largest error (comparing modelled and measured airway pressure) obtained at the onset and the end of expiration (Fig. 3). At the onset of expiration the increase in airway pressure triggers a decrease in CPAP support, while the peak in pressure demonstrates the response time of the CPAP device. Initial active patient effort was not considered in the model and would explain an error in modelled pressure. At the end of expiration during low flow there may also be active patient driving pressure, as subjects were cued to breath out for a given length of time and may have actively expired to extend the length of their expiration to follow the cueing system.

A validated model-based means of identifying patient inspiratory driving pressure ($P_{driving}$) enables intrinsic patient work of breathing in CPAP to be calculated due to spontaneous effort for the first time without invasive procedures [32]. Significant work on ventilator unloading with invasive measurements (e.g. Refs. [22–24,40–42]) led to

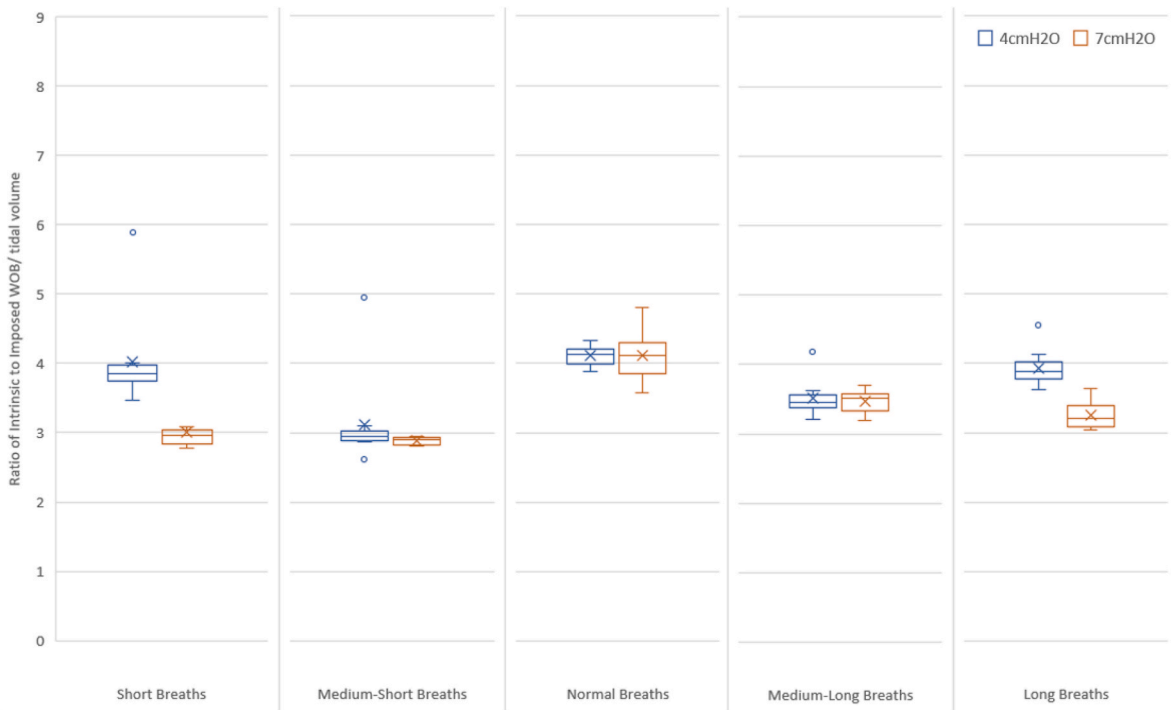

Fig. 8. Comparison of the ratio of Intrinsic to Imposed WOB per tidal volume at each breath rate between 4 and 7 cmH_2O set PEEP levels for Subject 01.

the hypothesis that the ratio of intrinsic patient work of breathing to ventilator work would decline as PEEP rose in CPAP. The results in Figs. 7–8 validated this hypothesis using the model-based method presented, and thus validated the model-based unloading metric presented.

In particular, comparing the values in Tables B1 and B2 for Intrinsic and Imposed WOB does not show the trend seen in their ratio. This difference arises from the fact that the total WOB in this reference frame is the WOB imposed by the CPAP device (Fig. 2), which varies with breathing rate and PEEP. Thus, the ratio defines the relative change between patient driven Intrinsic WOB and the Imposed WOB, where the change seen here captures ventilator unloading as PEEP increases. Hence, the ratio captures the relative change of patient contribution, which changes consistently with unloading as PEEP changes.

More specifically, the ratio of intrinsic to imposed work (Fig. 7) illustrated that the work done in inspiration tends to be less driven by muscular effort relative to work imposed on the CPAP machine with increasing PEEP. This result demonstrated the hypothesised ventilator unloading at higher PEEP support. As in Fig. 8 and Appendix C, ventilator unloading between 4 and 7 cmH_2O PEEP levels is shown to occur at all recorded breath rates in this trial. This outcome shows a clear consistency in ventilator unloading results across subjects using this model-based metric and approach, although the level of unloading is patient-specific.

The hypothesis that the ratio of Intrinsic to Imposed WOB decreases with increasing PEEP, as WOB is unloaded on the ventilator, is logically simplistic. However, quantification of this ratio allows this method to be applied to larger datasets to define optimal ranges of ventilator unloading for existing respiratory therapies. Thus, it provides consistent reliable clinical metrics of patient status, which is currently not available in the monitoring of CPAP ventilation.

Clinically, if an optimal Intrinsic to Imposed WOB ratio, or proportion of ventilator unloading, was found for specific patient types or demographics, it could yield a non-invasive, model-based means to identify the optimal CPAP PEEP level for a patient, to generate the most favourable amount of ventilator unloading. This information could further inform closed loop control systems, as these values can be monitored breath-to-breath with relatively low computational effort. However, this outcome would require clinical studies assessing this metric, which is only first developed in this work.

In addition, optimal ratios might be found in clinical studies, and used to wean patients from invasive ventilation towards assisted breathing MV modes by progressively reducing the proportion of ventilator unloading. Eventually, in hospitalised patients on CPAP, this ratio could replace PEEP setting protocols and identify optimal patient-specific PEEP, without causing barotrauma from excessive PEEP or hypoxia from insufficient support. Real-time data analysis and closed loop control of CPAP or PEEP in MV would enable more informed and rapid alterations to PEEP settings, reducing the clinical response time in respiratory therapy, which currently relies on symptomatic indicators of barotrauma or under-oxygenation [12,38,39]. Further analysis of clinical data from patients who require CPAP therapy in conjunction with outcome metrics is a logical next step in the determination of such optimal WOB ratios, should they exist.

The spike (beak) in pressure at the end of inspiration (maximum tidal volume) seen in Fig. 4 is a clinical indicator of alveolar overdistension [16–18]. However, the length of this beak shows no increase with higher PEEP level or amount of ventilator unloading (Figs. 5–6) across the subject pool and breath type, where the expected result would be all points above the $y = x$ line. Instead, Fig. 6 shows a modest correlation between breath rate and beak length along the $y = x$ line with shorter breaths having longer beak length.

In particular, normal (resting) breaths showed comparable beak length to long breaths (Fig. 6). Thus, the increase in beak length appears more indicative of ventilator response time and patient-specific lung elastance than alveolar overdistension from mechanical ventilation. Further testing of pressure-volume loops at a larger range of PEEPs, including a control trial with no ventilator support, would help profile the relationship between PEEP and beak length in healthy subjects, and its pathophysiological meaning. However, current findings indicate beak length does not provide consistent specific clinical information, which limits its value to clinicians.

4.2. Limitations

A limitation on the validation of these results is the lack of ability to directly measure lung driving pressure by non-invasive methods. Electrical activity of the diaphragm (EADI) has been used to validate the b-spline spontaneous breathing model of patient driving pressure [22,23,32,41,43,44]. Motion-captured change in circumferences of the upper chest cavity has been used in the analysis of respiration [45], and can be applied to CPAP therapy. Subsequent work correlating change in measured upper body volume (from circumferences) to patient driving pressure could provide a non-invasive and easily obtained validation measure for the model-based Intrinsic WOB presented.

Using a fixed value for resistance is also a limitation in the model identification. However, fitting patient-specific resistance in linear regression resulted in trade-offs between resistance and elastance in expiration, or driving pressure scaling coefficients in inspiration, due to limited practical identifiability [34,35,46]. Resistance may also change between inspiration and initial expiration due to head loss at (diverging) pulmonary junctions and is replaced with confluence in expiration (converging pulmonary junctions). However, during expiration the diameter of airways decreases, increasing respiratory resistance [1]. In addition, airway resistance is expected to change significantly in patients in a clinical setting with (obstructive) respiratory disorders [4]. Thus, a method of determining a patient-specific resistance value for both inspiration and expiration, augmenting this model-based approach, would improve the accuracy of the model-based methods presented.

Analysis of additional PEEP levels, including a baseline of zero PEEP (ZEEP) CPAP, would provide an increased understanding of the relationship between ventilator unloading and PEEP relative to normal unsupported breathing. Data from subjects who require mechanical ventilation (acute respiratory distress disorder (ARDS) or chronic obstructive pulmonary disorder (COPD)) would also provide additional useful indications of ventilator unloading in further clinical settings, by identifying any dependence on patient-specific demographic and pathophysiological data. These analyses have not yet been performed, but are justified by the proof of concept methods, results, and validation presented.

The extension of these analyses to population trends is limited by the reduced number of subjects available with complete datasets meeting the criteria defined. These 14 subjects were also taken from a limited demographic population, specifically young adults with no significant respiratory or health impairments. Even though they are healthy subjects, it is still possible to see ventilator unloading and prove the concept, without imposing undue burden on subjects with chronic disease. However, ensuring complete data sets for the 14 subjects included, also ensures there is no bias in the data and the results are as general as possible. Given this first validation of the model and methods, future efforts and validation will require a more diverse and substantial dataset.

5. Conclusions

A novel model-based method is presented and used to quantify patient Intrinsic WOB under CPAP ventilation using non-invasively attained pressure and flow data. Patient-specific Intrinsic WOB per unit tidal volume demonstrated the expected ventilator unloading trend, declining with increased PEEP relative to the imposed CPAP WOB. The consistency across subjects and breathing rates validates the efficacy and robustness of this model-based method of determining patient Intrinsic WOB. Ascertaining patient Intrinsic WOB has further clinical significance in optimising mechanical ventilation and, in particular, CPAP therapy, both for outpatients, as well as during the increasing in-hospital use of CPAP.

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Declaration of competing interest

None Declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.compbiomed.2022.105225.

References

[1] G.J. Tortora, B.H. Derrickson, Principles of Anatomy and Physiology, John Wiley & Sons, 2018.
[2] C.A. Mora, J. Mora, Positive End-Expiratory Pressure, StatPearls Publishing, Treasure Island (FL), 2020.
[3] R. Pellegrino, et al., Interpretative strategies for lung function tests, Eur. Respir. J. 26 (5) (2005) 948.
[4] J. Butler, C.G. Caro, R. Alcala, A.B. DuBois, Physiological factors affecting airway resistance in normal subjects and in patients with obstructive respiratory disease, J. Clin. Invest. 39 (4) (1960) 584–591.
[5] A. Baydur, J. Milic-Emili, Expiratory flow limitation during spontaneous breathing: comparison of patients with restrictive and obstructive respiratory disorders (in eng), Chest 112 (4) (1997) 1017–1023.
[6] M. Veezhinathan, S. Ramakrishnan, Detection of obstructive respiratory abnormality using flow–volume spirometry and radial basis function neural networks, J. Med. Syst. 31 (6) (2007) 461–465.
[7] B. Popat, A.T. Jones, Invasive and non-invasive mechanical ventilation (in eng), Medicine (Abingdon) 40 (6) (2012) 298–304.
[8] A.W. Duncan, T.E. Oh, D.R. Hillman, PEEP and CPAP, Anaesth. Intensive Care 14 (3) (1986) 236–250.
[9] M.B. Amato, C.S. Barbas, J. Bonassa, P.H. Saldiva, W.A. Zin, C.R. de Carvalho, Volume-assured pressure support ventilation (VAPSV). A new approach for reducing muscle workload during acute respiratory failure (in eng), Chest 102 (4) (1992) 1225–1234.
[10] K. Rajdev, P.S. Idiculla, S. Sharma, S.G. Von Essen, P.J. Murphy, S. Bista, Recurrent Pneumothorax with CPAP therapy for obstructive sleep apnea, Case Rep Pulmonol 2020 (2020), 8898621, 2020/12/01.
[11] V.J. Major, Y.S. Chiew, G.M. Shaw, J.G. Chase, Biomedical engineer's guide to the clinical aspects of intensive care mechanical ventilation, Biomed. Eng. Online 17 (1) (2018) 169. Nov 12.
[12] R.C. Heinzer, et al., Lung volume and continuous positive airway pressure requirements in obstructive sleep apnea (in eng), Am. J. Respir. Crit. Care Med. 172 (1) (2005) 114–117.
[13] A. Mercat, et al., Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial, JAMA 299 (6) (2008) 646–655.
[14] Y. Oba, D.M. Thameem, T. Zaza, High levels of PEEP may improve survival in acute respiratory distress syndrome: a meta-analysis, Respir. Med. 103 (8) (2009) 1174–1181.
[15] S.E. Morton, et al., Optimising mechanical ventilation through model-based methods and automation, Annu. Rev. Control 48 (2019) 369–382, 2019/01/01/.
[16] J.X. Lian, Understanding ventilator waveforms—and how to use them in patient care, Nurs. Crit. Care 4 (1) (2009) 43–55.
[17] J.O. Nilsestuen, K.D. Hargett, Using ventilator graphics to identify patient-ventilator asynchrony, Respiratr. care 50 (2) (2005) 202–234.
[18] J.B. Fisher, M.C. Mammel, J.M. Coleman, D.R. Bing, S.J. Boros, Identifying lung overdistention during mechanical ventilation by using volume-pressure loops, Pediatr. Pulmonol. 5 (1) (1988) 10–14.
[19] E. L'Her, et al., Physiologic effects of noninvasive ventilation during acute lung injury, Am. J. Respir. Crit. Care Med. 172 (9) (2005) 1112–1118.
[20] T. Theerakittikul, B. Ricaurte, L.S. Aboussouan, Noninvasive positive pressure ventilation for stable outpatients: CPAP and beyond, Cleve Clin. J. Med. 77 (10) (2010) 705–714.
[21] K.E.A. Burns, N.K.J. Adhikari, S.P. Keenan, M. Meade, Use of non-invasive ventilation to wean critically ill adults off invasive ventilation: meta-analysis and systematic review, BMJ 338 (2009) p. b1574.
[22] F. Lecomte, et al., Physiological response to increasing levels of neurally adjusted ventilatory assist (NAVA), Respir. Physiol. Neurobiol. 166 (2) (2009) 117–124.
[23] D. Ververidis, M. van Gils, C. Passath, J. Takala, L. Brander, Identification of adequate neurally adjusted ventilatory assist (NAVA) during systematic increases in the NAVA level, IEEE Trans. Biomed. Eng. 58 (9) (2011) 2598–2606.
[24] J. Beck, J. Spahija, C. Sinderby, Respiratory Muscle Unloading during Mechanical Ventilation, New York, NY, Springer, New York, 2003, pp. 280–287.
[25] J.H.T. Bates, Lung Mechanics: An Inverse Modeling Approach (No. Book, Whole), Cambridge University Press, Cambridge, UK;New York, 2009.

[26] Y.S. Chiew, J.G. Chase, G.M. Shaw, A. Sundaresan, T. Desaive, Model-based PEEP optimisation in mechanical ventilation, Biomed. Eng. Online 10 (1) (2011) 111, 2011/12/23.
[27] Y.S. Chiew, et al., Time-varying respiratory system elastance: a physiological model for patients who are spontaneously breathing (in eng), PLoS One 10 (1) (2015). e0114847-e0114847.
[28] J.G. Chase, et al., Next-generation, personalised, model-based critical care medicine: a state-of-the art review of in silico virtual patient models, methods, and cohorts, and how to validation them, Biomed. Eng. Online 17 (1) (2018) 24, 2018/02/20.
[29] S.E. Rees, The Intelligent Ventilator (INVENT) project: the role of mathematical models in translating physiological knowledge into clinical practice (in eng), Comput. Methods Progr. Biomed. 104 (Suppl 1) (2011) S1–S29.
[30] S.E. Rees, et al., Using physiological models and decision theory for selecting appropriate ventilator settings, J. Clin. Monit. Comput. 20 (6) (2006) 421–429.
[31] C. Zhou, et al., Virtual patients for mechanical ventilation in the intensive care unit, Comput. Methods Progr. Biomed. 199 (2021). Paper #105912, 24-pages, 2021/02/01.
[32] J.L. Knopp, J.G. Chase, K.T. Kim, G.M. Shaw, P. i. Biomedicine, Model-based estimation of negative inspiratory driving pressure in patients receiving invasive NAVA mechanical ventilation, Comput. Methods Progr. Biomed. (2021), 106300.
[33] J.H. Bates, G.B. Allen, The estimation of lung mechanics parameters in the presence of pathology: a theoretical analysis, Ann. Biomed. Eng. 34 (3) (2006) 384–392.
[34] C. Schranz, P.D. Docherty, Y.S. Chiew, J.G. Chase, K.J. Möller, Structural identifiability and practical applicability of an alveolar recruitment model for ARDS patients, IEEE Trans. Biomed. Eng. 59 (12) (2012) 3396–3404.
[35] P.D. Docherty, J.G. Chase, T.F. Lotz, T. Desaive, A graphical method for practical and informative identifiability analyses of physiological models: a case study of insulin kinetics and sensitivity, Biomed. Eng. Online 10 (1) (2011) 1–20.
[36] E. Guy, J. Knopp, and G. Chase. CPAP Pressure and Flow Data from a Local Trial of 30 Adults at the University of Canterbury (Version 1.0.0) [Online].
[37] S.L. Howe, et al., Inspiratory respiratory mechanics estimation by using expiratory data for reverse-triggered breathing cycles, Comput. Methods Progr. Biomed. 186 (2020), 105184, 2020/04/01/.
[38] Policy: CPAP Titration Protocol, U. O. T. M. B. C. F. S. Disorders, 2019.
[39] N.V. Koininklijke Philips (Ed.), Titration Protocol Reference Guide, Philips Respironics, 2017.
[40] A. Borghi-Silva, et al., Effects of respiratory muscle unloading on leg muscle oxygenation and blood volume during high-intensity exercise in chronic heart failure, Am. J. Physiol. Heart Circ. Physiol. 294 (6) (2008) H2465–H2472. June 1, 2008.
[41] C. Sinderby, et al., Inspiratory muscle unloading by neurally adjusted ventilatory assist during maximal inspiratory efforts in healthy subjects, Chest 131 (3) (2007) 711–717. March 1, 2007.
[42] J.P. Viale, et al., Time course evolution of ventilatory responses to inspiratory unloading in patients, Am. J. Respir. Crit. Care Med. 157 (2) (1998) 428–434. February 1, 1998.
[43] L. Brander, et al., Titration and implementation of neurally adjusted ventilatory assist in critically ill patients, Chest 135 (3) (2009) 695–703.
[44] J. Spahija, et al., Patient-ventilator interaction during pressure support ventilation and neurally adjusted ventilatory assist, Crit. Care Med. 38 (2) (2010) 518–526, https://doi.org/10.1097/CCM.0b013e3181cb0d7b.
[45] B. Laufer, S. Krueger-Ziolek, P.D. Docherty, F. Hoeflinger, L. Reindl, K. Moeller, Tidal volume via circumferences of the upper body: a pilot study, in: 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 2019, pp. 3559–3562.
[46] A. Raue, et al., Structural and practical identifiability analysis of partially observed dynamical models by exploiting the profile likelihood, Bioinformatics 25 (15) (2009) 1923–1929. August 1, 2009.