Pilot study of model-based estimation of inspiratory driving pressure in CPAP ventilation

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Abstract: Models of lung elastance, airway resistance, and patient work of breathing have been successfully applied to invasive mechanical ventilation data. Non-invasive mechanical ventilation data, including continuous positive airway pressure (CPAP), has presented challenges in predicting inspiratory driving pressure due to the combination of patient and device work. The model applied in this paper utilizes second order b-splines to describe inspiratory driving pressure. The model provided an accurate fit to the data, with an average root-mean-squared (RMS) error in model fit of 0.6 [0.425 – 0.675] cmH2O (median [lower quartile (LQ), upper quartile (UQ)]). Subject fit expiratory elastances were between 3.1 and 10.2 cmH2O/L and showed no correlation to set positive end-expiratory pressure (PEEP). Inspiratory driving pressure profiles approximated literature and work of breathing was shown to remain consistent between PEEP levels. Outlying data is hypothesized to be caused by subjects' expiratory effort which was assumed negligible in the model. Further application of this model alongside validation data would provide more information on this and provide more evidence of model accuracy.

Keywords: *Spontaneous breathing, inspiratory effort, physiological modelling, lung mechanics, CPAP.*

1. INTRODUCTION

During respiration, descension of the diaphragm and contraction of intercostal muscles increases the volume of the pleural cavity (Tortora and Derrickson, 2018), lowering the pleural pressure. The resulting pressure gradient drives inhalation (Tortora and Derrickson, 2018). The work done to produce this driving pressure ($P_{driving}$) describes the inspiratory part of patient-specific work of breathing (WOB).

In quiet breathing, expiration can be considered a passive process driven by the relaxation of the diaphragm and intercostal muscles (Tortora and Derrickson, 2018). Hence, lung elasticity (E) and airway resistance (R) predominantly dictate the rate of expiration to the positive-end expiratory pressure (PEEP) (Tortora and Derrickson, 2018). A minimum PEEP is required to maintain open airways in between breaths (Mora and Mora, 2020).

Respiratory dysfunction affects pulmonary mechanics and is classified as either restrictive or obstructive (Pellegrino et al., 2005). Restrictive dysfunction results from increased lung stiffness (increased E) which can occur from fibrotic scaring, pressure on the lungs and lack of muscle actuation (Tortora and Derrickson, 2018). Obstructive conditions, such as chronic obstructive pulmonary disorder (COPD) and asthma, involve abnormal restriction to or collapse of airways, slowing the rate of exhalation (increased R) and can cause air trapping if airways collapse (Baydur and Milic-Emili, 1997, Tortora and Derrickson, 2018, Veezhinathan and Ramakrishnan, 2007).

Treatment of respiratory conditions often involves mechanical ventilation (MV). MV can be either invasive or non-invasive, for either method, excessive tidal volumes can cause hyperinflation, while insufficient volumes can cause under-oxygenation and atelectasis (Duncan et al., 1986, Major et al., 2018, Rajdev et al., 2020). Ventilator settings are predominantly set based on clinical judgement of these risks, due to difficulty in directly measuring relevant information (Heinzer et al., 2005, Mercat et al., 2008, Morton et al., 2019a, Oba et al., 2009). A more comprehensive view of patient-specific pulmonary mechanics, through model-based methods, would inform patient-specific care (Howe et al., 2020a).

Continuous positive airway pressure (CPAP) is a form of non-invasive, pressure controlled, mechanical ventilation. CPAP is used in both hospital and home settings. It provides added PEEP at the nose/mouth to maintain lung volume at end expiration (Burns et al., 2009, Popat and Jones, 2012). This action also decreases the negative pressure ($P_{driving}$) required for breathing, and thus the overall WOB.

Linear single-compartment models have been extensively used to predict lung elastance (E) and airway resistance (R) in invasive MV (Bates, 2009, Chase et al., 2018, Chiew et al., 2011, Chiew et al., 2015a, Morton et al., 2019b, Rees et al., 2006, Rees, 2011). These models are effective for fully sedated invasive MV patients, where the WOB is done entirely by the ventilator (Chiew et al., 2011, Morton et al., 2019b). Recently a single compartment model with scaled b-splines describing inspiratory patient effort has been successfully fit to spontaneous breathing in invasive MV patients (Kim et al., 2021). This study extends this method to identify and describe spontaneous breathing (SB) in CPAP ventilation.

2. METHODS

2.1 Subjects and Data

Data was taken from a 2020 trial of adults at the University of Canterbury (Guy et al., 2021). Passive Breathing data was analysed at the two prescribed PEEP levels (4 and 7 cmH2O). Subjects were included who had 10 consecutive breaths of continuous passive breathing data (at both PEEP levels). This criterion resulted in the analysis of 9 subjects. Demographic data for these subjects is outlined in Table 1, with relevant subject-specific data in
Table **2**
Table 3 (Guy et al., 2021).

Table 1: Subject demographic data

Subject	Sex (M/F)	Age (Years)	Weight (kg)	Height (cm)	BMI	Asthmatic (Y/N)	Smoker (Y/N)
1	M	33	70	180	21.6	N	Y
2	M	22	75	185	21.9	N	N
3	M	21	65	185	19.0	N	N
4	M	21	75	185	21.9	Y	N
5	F	21	70	175	22.9	N	N
6	F	22	80	165	29.4	N	N
7	F	21	60	167	21.5	N	N
8	M	22	96	189	26.9	N	N
9	F	23	79	170	27.3	Y	N

Table 2: Asthmatic specific subject demographic data

Subject	Medication Used	Frequency of Use
3	Ventolin	1 puff per month
9	Ventolin	1 puff per day

Table 3: Smoker/Vaper specific subject demographic data

Subject	Smoking/Vaping Frequency	Duration of Smoking
1	5 per day	10 years

2.2 Model

A linear single-compartment model (Bates, 2009, Chiew et al., 2011, Kim et al., 2021) is the basis of the model used:

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

where airway pressure (Paw [cmH2O]) is a function of lung elastance (E [cmH2O/L]), tidal volume (V [L]), airway resistance (R [cmH2O/L/s]), flow (Q [L/s]), positive end-expiratory pressure (P_{PEEP} [cmH2O]), and driving pressure ($P_{driving}$ [cmH2O]) generated by inspiratory muscles.

Scaled (P_s) second order (d=2) b-splines (ϕ) have described driving inspiratory pressure in invasive MV data (Kim et al., 2021). These splines are similarly applied to the CPAP non-invasive MV data in this study. The driving pressure is thus defined:

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

Where the b-splines are defined:

$$\phi_{i,0}(t) = f(x) = \begin{cases} 1, & T_i < t < T_i + 1 \\ 0, & otherwise \end{cases} \quad (3)$$

$$\phi_{i,d}(t) = \frac{t - T_i}{T_{i+d} - T_i}\phi_{i,d-1}(t) + \frac{T_{i+d+1} - t}{T_{i+d+1} - T_{i+1}}\phi_{i+1,d-1}(t) \quad (4)$$

$$for\ d \geq 1$$

They employ a knot width (k_w = 0.1 s) defining the spacing between splines (T_i equal divisions in time). T_{max} is the inspiration length of each given breath and the number of splines at k_w intervals in this period (rounded up) defined the number of b-spline basis functions (M) fitted to each (n) inspiration breath segments:

$$\mathrm{M(n)} = ceil\left(\frac{T_{max}(n)}{k_w}\right) + d \quad (5)$$

Expiratory elastance (E_{exp}) was identified first using only passive expiration data where there is no active driving pressure, as it is a good initial representation of inspiratory elastance (Howe et al., 2020b). This choice ensures elastance is unbiased by parameter trade off in identifying driving pressure during inspiration (Docherty et al., 2011, Schranz et al., 2011). Inspiratory elastance (E_{insp} [cmH2O/L]) can be estimated as linearly related to the expiratory value (Howe et al., 2020c):

$$E_{insp} = 1.04E_{exp} + 1.66 \quad (6)$$

2.3 Fitting expiratory elastance

Expiration was assumed to be passive. Expiratory elastance (E_{exp} [cmH2O/L]) can thus be identified as a function of the recorded flow (Q [L/s]) and airway pressure (P_{aw} [cmH2O]) data and Equation (1) with $P_{driving}(t) = 0$, yielding:

$$P_{aw,exp}(t) = E_{exp}V_{exp}(t) + RQ_{exp}(t) + P_{PEEP} \quad (7)$$

Where volume (V [L]) was integrated breath-wise from flow and time data. Airway resistance (R [cmH2O/L/s]) was taken as a constant 5 cmH2O (Chiew et al., 2011, Chiew et al., 2015b), and $PEEP$ [cmH2O] was computed for each breath as the mean pressure value from the last 0.2 seconds of the breath.

Equation (8) was used to identify E_{exp} using linear regression in MATLAB (Matlab 2020a, The Mathworks Inc, Natick, MA, USA) using a system of equations for n = 10 expirations, defined:

$$Ax = b$$

$$A = \begin{bmatrix} V_{1,exp}(t) \\ \vdots \\ V_{n,exp}(t) \end{bmatrix}$$

$$b = \begin{bmatrix} P_{aw,1,exp}(t) \\ \vdots \\ P_{aw,n,exp}(t) \end{bmatrix} - R\begin{bmatrix} Q_{1,exp}(t) \\ \vdots \\ Q_{n,exp}(t) \end{bmatrix} - PEEP \quad (8)$$

$$x = E_{exp}$$

Expiration was defined by the first transition from positive (or zero) to (0.1 seconds of) negative flow and ended 0.05 seconds before the flow first became positive or zero (for a minimum of 0.03 seconds) after the peak negative flow.

2.4 Identifying inspiratory driving pressure

Inspiratory driving pressure b-spline scaling coefficients (P_s [cmH2O]) were then identified. Splines were defined over inspiration, where inspiration was defined to start 0.05 seconds after flow becomes positive and remains positive for at least 0.28 seconds (minimum tidal volume of ~0.125 L). Inspiration was defined to end at the first point the flow became zero or negative for a minimum of 0.03 seconds. Linear regression was used with Equation (1) for each subject to identify the spline coefficients in Equation (2), in a problem defined:

$$Ax = b \tag{9}$$

$$A = \begin{bmatrix} (\phi_{1,2}(t))_{1\to M} & & [0]_{(n-1)\times M} \\ & \ddots & \\ [0]_{(n-1)\times M} & & \phi_{n,2}(t))_{1\to M} \end{bmatrix}$$

$$b = \begin{bmatrix} P_{aw,1,}(t) \\ \vdots \\ P_{aw,n}(t) \end{bmatrix} - E_{insp} \begin{bmatrix} V_1(t) \\ \vdots \\ V_n(t) \end{bmatrix} - R \begin{bmatrix} Q_1(t) \\ \vdots \\ Q_n(t) \end{bmatrix} - PEEP$$

$$x = \left[P_{s,1,1} \dots P_{s,1,M}, \dots, P_{s,n,1}, \dots, P_{s,n,M}\right]^T$$

Modelled airway pressure ($P_{aw(modelled)}$ [cmH2O]) was then re-simulated using Equation (1).

2.5 Analysis

The RMS of residual errors ($P_{aw(measured)} - P_{aw(modelled)}$) assesses model fit. The distribution of peak E_{exp} for each subject was compared between PEEP levels. $P_{driving}$ profiles were compared between each subject's (n=10) breaths and to literature. WOB was calculated for each breath and the distribution for each subject at each PEEP level presented, where WOB is defined:

$$WOB = \int P_s \, dV \tag{10}$$

3. RESULTS

Identified expiratory elastance for each subject were compared between the two PEEP level settings (Figure 1). No discernible trends were observable with this sample size, as expected given the lung mechanics should not change much with small changes in PEEP. A representative model fit to a breath from Subject 1 at both PEEP levels are shown in Figures 2-3 with the model-identified inspiratory driving pressure also shown. The inspiratory driving pressure curves, defined by the scaled splines, for each n=10 breaths are compiled for Subject 1 at both PEEP levels in Figures 4-5, showing modest variability breath-to-breath, and similar shapes, as expected, at both PEEP levels. Patient-specific driving pressure peak values are slightly greater at PEEP = 7 cmH2O, as might be expected.

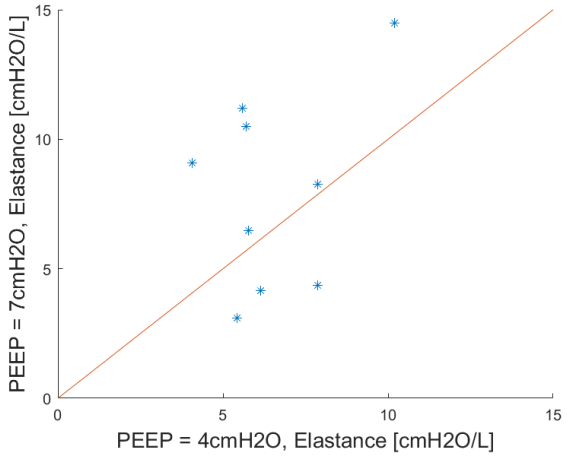

Figure 1: Scatter plot comparison of fit expiratory elastances comparing 4 and 7 cmH2O PEEP levels

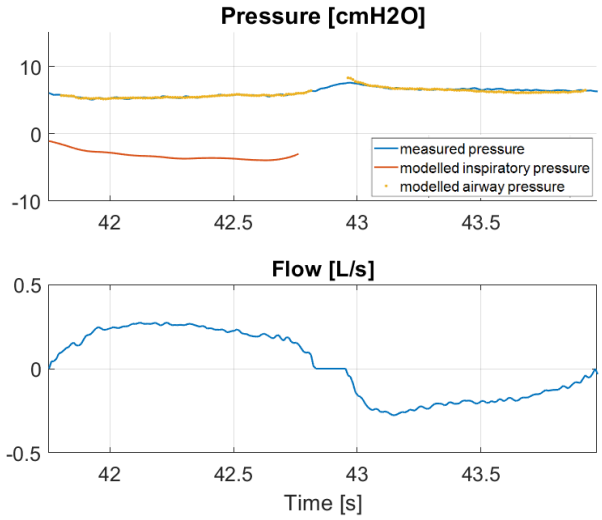

Figure 2: Model fit to 1 breath from Subject 1 at PEEP = 4cmH2O

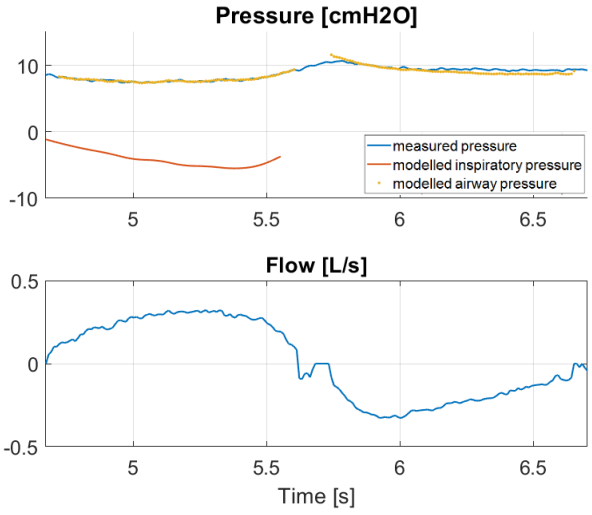

Figure 3: Model fit to 1 breath from Subject 1 at PEEP = 7cmH2O

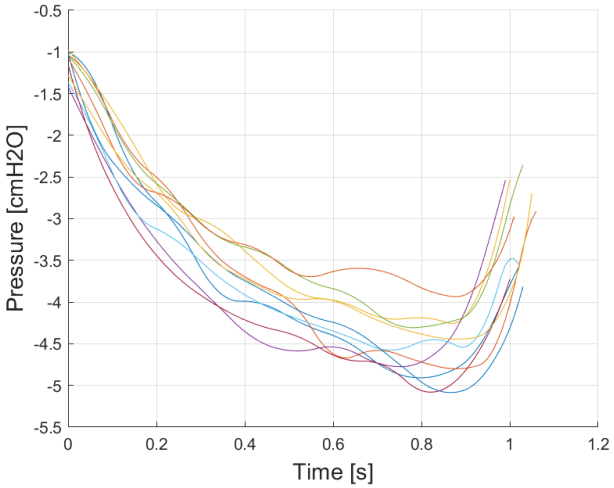

Figure 4: Inspiratory driving pressure for each (n=10) breath for Subject 1 at PEEP = 4cmH2O

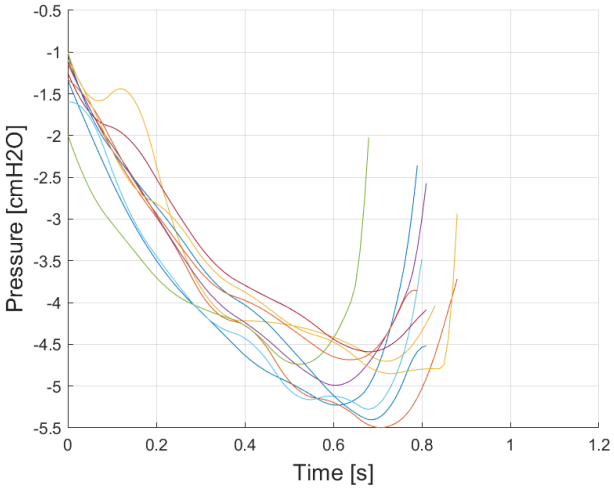

Figure 5: Inspiratory driving pressure for each (n=10) breath for Subject 1 at PEEP = 7cmH2O

Both inspiratory and expiratory modelled elastances are shown for each patient in Table 4 for PEEP = 4 and 7 cmH2O, respectively. Identified elastance values Median peak driving pressures (with interquartile range) assess peak inspiratory effort and its variability. The median RMS error of modelled versus measured airway pressure is shown for each subject as an indication of model accuracy. WOB was calculated using Equation (10) and shown in Table 4.

4. DISCUSSION

The model fit to this subject set was good, with an RMS error in model fit of 0.6 [0.425 – 0.675] cmH2O (median [LQ, UQ]). Subject 8 was the only subject with RMS values greater than 0.7 cmH2O. Active expiration could account for an initial peak in pressure and flow rate which could skew the model fit of elasticity in this case. A measurement of EADi could further validate the model and differentiate between passive and active breathing in test data.

Table 4: Model outcomes for n=10 normal (passive) breaths of CPAP ventilation at a PEEPs of 4 and 7 cmH2O

	4 cmH2O					7cmH2O				
Subject	**E_{exp}** [cmH2O/L]	**E_{insp}** [cmH2O/L]	**Median RMS** [cmH2O]	**$P_{driving}$ Median (IQR)** [cmH2O]	**WOB** [cmH2OL]	**E_{exp}** [cmH2O/L]	**E_{insp}** [cmH2O/L]	**Median RMS** [cmH2O]	**$P_{driving}$ Median (IQR)** [cmH2O]	**WOB** [cmH2OL]
1	10.2	12.3	0.3	4.7 (4.4 - 5.0)	1.0 (0.9 - 1.1)	14.5	16.8	0.4	4.9 (4.6 - 5.2)	0.7 (0.7 - 0.8)
2	5.4	7.3	0.5	5.7 (5.4 - 6.1)	2.0 (1.9 - 2.1)	3.1	4.9	0.6	3.7 (3.5 – 4.0)	1.2 (1.0 - 1.5)
3	5.8	7.7	0.5	3.9 (3.2 - 4.5)	0.9 (0.6 - 1.1)	6.5	8.4	0.4	4.2 (3.7 - 4.7)	1.1 (0.7 - 1.5)
4	4.1	5.9	0.3	4.7 (4.4 - 5.1)	1.9 (1.7 - 2.2)	9.1	11.1	0.7	7.2 (6.4 - 7.9)	2.3 (1.7 - 2.8)
5	5.6	7.5	0.6	5.1 (4.6 - 5.5)	1.6 (1.3 - 1.8)	11.2	13.3	0.6	5.3 (4.7 - 5.8)	1.2 (1.0 - 1.4)
6	6.1	8.1	0.4	6.5 (6.0 - 7.0)	2.8 (3.1 - 2.5)	4.2	6.0	0.6	6.2 (5.8 - 6.5)	3.5 (3.0 - 3.9)
7	7.9	9.8	0.7	5.1 (4.7 - 5.5)	1.4 (1.1 - 1.6)	8.3	10.2	0.5	5.7 (5.2 - 6.2)	1.6 (1.45 - 1.77)
8	7.9	9.8	1.7	14.7 (13.5 - 16.3)	12.6 (9.9 - 15.3)	4.4	6.2	2.2	15.7 (15.0 - 16.4)	20.9 (17.8 - 24.0)
9	5.7	7.6	0.6	5.2 (4.6 - 5.8)	1.8 (1.5 - 2.1)	10.5	12.6	0.7	6.1 (4.4 - 7.7)	1.3 (0.4 - 2.1)

Modelled expiratory elastances at 4cmH2O PEEP were predominantly within expected clinically reasonable range for healthy subjects (2 to 10 cmH2O/L)(Howe et al., 2020a). Subject 1 with elastances of 10.2 and 12.3 cmH2O/L for inspiration and expiration respectively, was the only deviation from this range in the 4cmH2O data. These values assume passive expiration and thus negligible $P_{driving}$ [cmH2O]. If expirations were partially active and this aspect was unaccounted, the model elastances identified would be artificially higher.

Similarly active expiration could be expected to increase at the higher PEEP level of 7cmH2O in healthy subjects working against the CPAP positive pressure. Therefore, this could explain the variation seen in the 7cmH2O elastances (Table 4). Over half the subjects (1, 4, 5, 7, and 9) modeled elastances were above the clinically reasonable range (Howe et al., 2020a) in the 7cmH2O PEEP data. Simultaneous tests of relevant muscular activity during expiration could provide evidence of this.

Lung elastance showed only a moderate correlation to PEEP level for the subject group (Figure 1). No correlation between elastance and PEEP was expected as elastance is a measure of resistance to change in volume given a change in pressure, and is thus partly independent of PEEP as modeled in Equation (1). Lung elastance could be expected to vary between subjects, particularly with restrictive respiratory anomalies. However, in this subject pool of healthy adults, was unlikely to be significant.

Inspiratory driving pressure profiles matched those reported in the literature (Kim et al., 2021)(Sinderby et al., 2007a). Peak driving pressures were consistently between 3 and 8 cmH2O for subjects, except Subject 8 who showed significantly higher inspiratory driving pressures (Table 4). This could have been caused by the impact of variables derived from active expiration effect on inspiratory modeling. Analysis of a longer period of breathing could also act to reduce trial-based effects, such as periods of forced active breathing or subject variability and fatigue. Subject 8 had the highest weight and was the tallest in the trial (Table 1) and thus external pressure associated with weight and/or increased driving lung volume changes due to size could also be a factor. A wider subject pool could be used to investigate potential correlations with demographic information or bedside assessable metrics.

The work of breathing remained consistent between PEEP levels for each patient (Table 4). Subjects were healthy and experiencing no respiratory distress. Thus, for passive breathing, inspiratory effort should typically be expected to remain consistent, particularly over a short period as in this study, providing further validation of the model, methods, and results obtained here. Future analysis could compare the composition of the work of breathing and the ratio of patient muscular contribution to provided CPAP work.

Patient driving pressure in CPAP is clinically useful information. Delineation of work of breathing into components is made possible by the extrapolation of patient driving pressure. It could be used to quantify work associated with muscular effort. This may additionally quantify ventilator unloading across PEEP levels. In a clinical setting optimal patient contribution to breathing effort can be used to ensure CPAP therapy is working and to optimise the process of weaning patients off MV.

Further analysis from subjects in a clinical setting with respiratory conditions would provide information on the reduction in required breathing effort over different PEEP levels. Subjects with respiratory conditions could be expected to have impacted lung elastance and airway resistance as well as less active contribution to breathing which could reduce active expiration effects in the model. Ventilator unloading onto the CPAP device is one possibility for lower effort at higher PEEP (Sinderby et al., 2007b). A baseline no-flow control would also provide a control measurement to assess the impact of CPAP on patient WOB.

5. CONCLUSIONS

A linear single-compartment model was successfully applied to CPAP data, with inspiratory driving pressure modelled by scaled b-splines basis functions. This pilot study subject group resulted in physiologically reasonable values for elastance, inspiratory driving pressures and work of breathing. A larger subject pool, in a clinical setting, would provide further information on the effects of CPAP therapy on subjects with respiratory conditions. Simultaneously collected validation data (such as diaphragm electrical activity) could also be acquired to support the model. The overall model and methods provide a means to obtain significant novel insight, both clinically and in research studies, and are a first effort at uniquely identifying patient-specific breathing effort in CPAP, an increasingly common modality.

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