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Comparison between single compartment model and recruitment basis function model on NICU patients

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Abstract: Respiratory distress syndrome (RDS) is commonly diagnosed in preterm infants in neonatal intensive care units (NICUs) due to prematurity at birth resulting in surfactant deficiency. Mechanical ventilation (MV) is used to support breathing of infants with RDS. In this study, respiratory mechanics of 10 invasively ventilated infants from Christchurch Women's Hospital under standard care are compared with two lung mechanics models validated in adult MV patients. A single compartment model is compared with a parabolic basis function model with dynamic elastance (Edrs) used to capture patient-specific effort. This latter model applies parabolic and linear shapes to identify lung recruitment and distension. The model was fit to 25,657 breaths. The median [interquartile range (IQR)] of elastance from single compartment model (E_{lung}) was 1.51[0.72 - 2.76] cmH_2O/ml, and elastance from recruitment basis function (E_1) was 3.42[1.88 - 5.97] cmH_2O/ml. Relative breath-to-breath variability ($\%\Delta E$) was also compared, with median IQR $\%\Delta E_{lung}$ of 0.22 [-9.73 - 12.06] and $\%\Delta E_1$ of -0.48[-9.28 - 10.34]. E_{lung} is less sensitive than E_1 to differences across infants where E_1 was also less variable breath-to-breath. The parabolic model thus captured patient condition and the use of Edrs captured patient effort.

Keywords: NICU, elastance, basis function, pulmonary mechanics, modeling, Mechanical Ventilation.

1. INTRODUCTION

Respiratory distress syndrome (RDS) is commonly diagnosed in premature infants in the neonatal intensive care unit (NICU) (Hendriks et al., 2018; Liggins and Howie, 1972; Sweet et al., 2013). It is due to prematurity and resulting under-developed lungs and immature surfactant production (Jobe, 2009; Liggins and Howie, 1972; Sweet et al., 2013; Torday and Nielsen, 1987). RDS is treated using mechanical ventilation (MV), which supports breathing and helps maintain adequate lung recruitment (Brown and DiBlasi, 2011; Liggins and Howie, 1972; Sweet et al., 2013).

Model-based methods allow identification of patient-specific respiratory mechanics, and can provide further insight into underlying conditions (Chiew et al., 2015, 2011; Kim et al., 2019; Morton et al., 2019, 2018). The most basic model is a single compartment model (Bates, 2009) treating the lungs and airways as a single homogeneous volume with associated elastance and airway resistance. It is readily identifiable using data available at the bedside real time (Chiew et al., 2011; Szlavecz et al., 2014). In particular, elastance, (1/compliance), describes lung stiffness, which varies with applied positive end-expiratory pressure (PEEP) and condition. Previous work examined iterations of this single-compartment model to identify patient respiratory elastance in both adults and infants (Chiew et al., 2011; Kim et al., 2019; Sundaresan et al., 2011).

This study compares two models validated in adults describing the contribution of elastance to pressure dynamics in different ways. The first treats elastance as constant across all pressures and volumes, and the second accounts for non-linear changes in apparent elastance with recruitment (Morton et al., 2019).

In a prior study (Kim et al., 2019), the single compartment model successfully identified elastance in NICU patients. While the model fit clinical data very well, NICU patients are not fully sedated, and thus elastance varied widely breath-to-breath as model-based elastance captures both lung tissue mechanics properties and patient inspiratory effort. This study is a first attempt at segregating lung mechanics and inspiratory effort, to better monitor the MV patient condition in the NICU.

2. METHODS

2.1 Patient data

Airway pressure and flow data from 10 invasively mechanically ventilated neonates in Christchurch Women's Hospital NICU was collected. Patients were recruited with informed parent consent to an observational, non-intervention study where MV pressure-flow data was recorded for up to 24 hours of standard care. Ethics was granted by the NZ Northern B Health and Disability Ethics Committee (ref: 16/NTB/16).

Patients were treated under standard care, and MV modes and settings were clinically set. Patients received conventional ventilation (CV) or high frequency oscillatory ventilation (HFOV) modes on a SLE 5000 Neonatal ventilator (SLE, UK). Most patients received patient triggered ventilation (PTV), but some were treated with multiple modes. Patient 1, who only received HFOV, was excluded from this analysis as HFOV exhibits very different dynamics with different time constants and unable to capture respiratory mechanic with same method. Table 1 gives the demographic data.

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Table 1: Demographic data

Patient	Gestational Age		Weight (g)		Sex	MV mode	Target Tidal volume [ml/kg]
	At birth (weeks)	Postnatal age (days)	Birth	Trial			
1	26.5	31	760	1120	F	HFOV	5
2	25	21	570	890	F	HFOV CV-PTV+TTV	5
3	41.5	3	3400	3400	M	CV-SIMV+TTV	3.8
4	37	2	2750	2750	F	CV-PTV+TTV	4
5	29.9	0	1580	1580	F	HFOV CV-PTV+TTV	5
6	27.4	2	1170	1170	M	CV-PTV+TTV	4.3
7	28.1	45	960	1990	F	CV-PTV+TTV	4
8	25.7	2	770	770	F	CV-PTV+TTV	3.9
9	25.3	4	820	-	M	CV-PTV+TTV	4.2
10	25.9	4	810	810	M	CV-PTV+TTV	5

MV was recorded at 125 Hz using software (MediCollector, USA) on a laptop computer connected to a Philips MP70 bedside monitor and Vuelink M1032A (Philips Healthcare, USA) connected to a SLE5000 ventilator (SLE, UK). The first 15 minutes of data for each of the first 4 hours is used.

A positive inflow with positive increase in pressure is identified as inspiration and negative flow with pressure decrease is expiration (Kim et al., 2019). Breaths were excluded if inspiration was shorter than 0.1 sec, as it typically indicates asynchrony in this mode.

2.2 Linear Single Compartment Model

The linear single compartment model with term to compensate for pressure loss across the endotracheal tube:

$$P_{aw} = E_{lung}V + R_{lung}Q + PEEP + \Delta P_{ETT} \qquad (1)$$

Where V and Q are clinical inputs of volume [ml] and flow [ml/s]. P_{aw} is the resulting airway pressure [cmH_2O]. The constants E_{lung} [cmH_2O/ml] and R_{lung} [cmH_2O.s/ml] describe elastance, airway resistance, and ΔP_{ETT} is the pressure loss across the ETT per Jarreau's equation (Jarreau et al., 1999).

2.3 Non-Linear Single Compartment Model

The second model is modified from Eq (1) using basis functions to describe recruitment (Φ_1) and distension (Φ_2). Recruitment and distension basis functions has been used previously adult critical care models (Morton et al., 2019). The basis function shapes are shown in Fig. 1 and defined over a volume range of 0-14 ml and pressure ranges 0-60 cmH2O, which covers all likely NICU MV ranges.

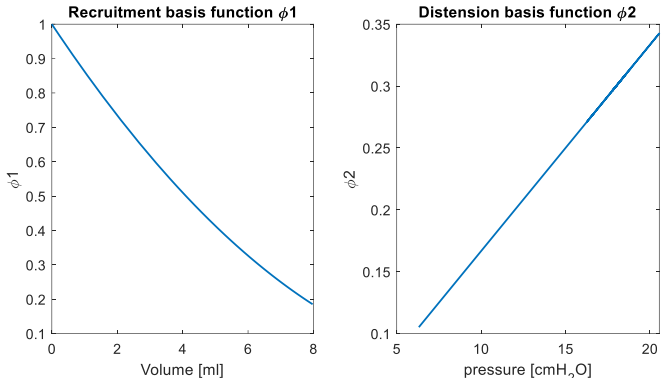

Fig. 1. Recruitment and distension basis function shapes. Both basis functions are dimensionless.

The recruitment basis function, Φ_1 captures the decreasing rate of recruitment alveoli based on positive volume delivered and is a piecewise function defined:

$$\Phi_1 = (\max(V\text{-}Vm,0))^2 \qquad (2)$$

Where Vm is the upper limit of 14ml. The distension basis function, Φ_2 captures the lung distension and is defined:

$$\Phi_2 = P_{aw}/60 \qquad (3)$$

The pressure loss across endotracheal tube (ETT), ΔP_{ETT} is defined from Jarreau's equation. This term in important in NICU context, as the small ETT tube diameter contributes the largest resistance to patient breathing. In many cases, most of the resistance gets absorbed into the ΔP_{ETT}, giving near zero value R_{lung}.

Combining the two basis functions with Equation (1) and lumping the resistance term with ΔP_{ETT} results in:

$$P_{basis} = E_1V\Phi_1 + E_2V\Phi_2 + PEEP + \Delta P_{ETT} \qquad (4)$$

However, the neonates are ventilated at low PEEP settings (< 6 cmH_2O), which is not typically changed. (Morton et al., 2019) showed distension elastance was only identified at higher PEEP levels. Therefore, it can be assumed these infants would have minimal or no distension ($E_2 = 0$), yielding:

$$P_{basis} = E_1V\Phi_1 + PEEP + \Delta P_{ETT} \qquad (5)$$

Ideally, Equations 2 and 3 capture all patient underlying tissue mechanics. Patient inspiratory effort is captured using a time-varying elastance or dynamic lung elastance term, Edrs(t). Edrs(t) is derived from a similar time-varying elastance model used adults (Chiew et al., 2015), and has been used to capture

patient effort in spontaneous breathing patients (Chiew et al., 2015; Kim et al., 2017). Edrs(t) is defined:

$$\text{Edrs}(t) = \frac{P_{aw}(t) - P_{basis}(t)}{V(t)} \quad (6)$$

Edrs(t) is applied after E_1 is identified from Equation (5), and is intended to capture remaining patient inspiratory effort, previously described as a negative elastance (Chiew et al., 2015; Kim et al., 2017). An estimate of patient effort is found taking the Edrs(t), separating it into positive and negative parts, and taking the area under the curve (AUC) for each.

For easier comparison between identified elastance values for the two models, the percentage difference *(%ΔE)* is used. This percentage breath-to-breath difference is the difference between current breath and the next breath, defined:

$$\%\Delta E = \frac{E_N - E_{N+1}}{E_{N+1}} \times 100 \quad (6)$$

3. RESULTS

A total of 25,647 breaths were used to fit E_{lung} using Model 1 and non-linear Model 2, compromising a total of 9 hours of CV. Median and interquartile range (IQR) E_{lung}, E_1, negative and positive *AUCEdrs* values are shown in Table 2.

Fig. 2 shows boxplot of E_{lung} from Model 1 and E_1 from Model 2, and a second boxplot of *%ΔE* for E_{lung} and E_1. The median [interquartile range (IQR)] for E_{lung} is 1.51 [0.72 – 2.76] cmH_2O/ml, E_1 is 3.42[1.88 - 5.97] cmH_2O/ml. The median IQR of *%ΔE* is 0.22 [-9.73 - 12.06] for E_{lung} and -0.48[-9.28 - 10.34] for E_1.

Figure 3 shows a plot of typical breath of pressure with elastance fits from both models, flow, and Edrs(t). It can be seen the fit to measured data for Model 1 and Model 2 (without Edrs) are similar. Model fit for Model 2 including Edrs is perfect, as expected. Figure 3 shows a typical case where Edrs describes patient effort as negative elastance at the start of inspiration before settling to 0.

Fig 4, shows boxplot of positive and negative AUCEdrs. The overall median IQR negative elastance was -0.33 [-0.41 - -0.25] cmH2O/ml and positive elastance was 0.02 [0.00 - 0.07] cmH2O/ml. As seen from Table 2, Patient 10 had largest patient effort with median IQR of negative AUCEdrs of 0.39 [-0.49 - -0.33] cmH_2O/ml and Patient 9 had the lowest patient effort with -0.21 [-0.29 - -0.13] cmH_2O/ml.

Patient 7 had highest breath-to-breath E_1 correlation of determination (R^2 = 0.73). Fig. 5 shows breath-to-breath elastasnce values for E_{lung}, and E_1 with examples of 10 consecutive 'good', 'typical' and 'variable' breath sequences. The good breaths have lower variability and stay relatively close to the one-to-one line. The typical breaths have slightly larger variability and variable breaths exhibit significantly larger variability. This trend can be seen in both *Elung* and *E1*.

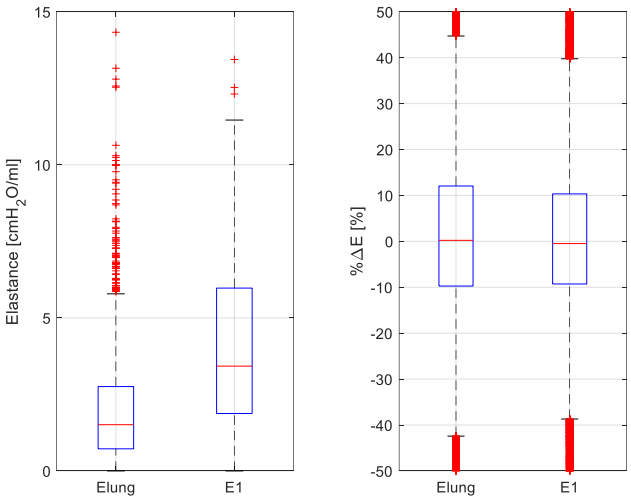

Fig. 2 Boxplot of model fit elastance values and %ΔE values (note unphysiological values are removed where E <=0)

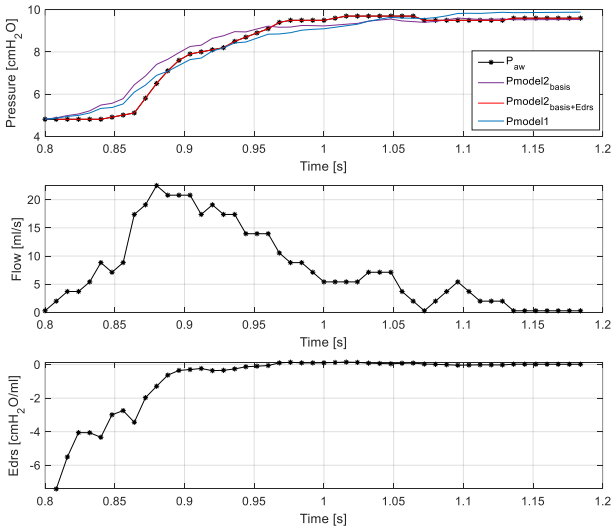

Fig. 3 Example of model fits and Edrs(t) for a typical breath.

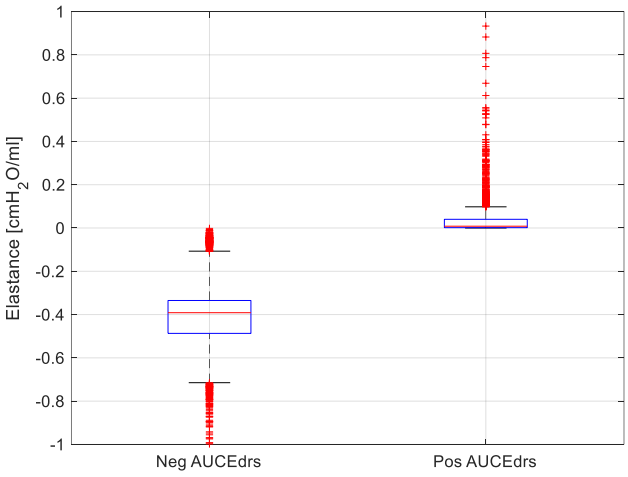

Fig. 4 Boxplot of AUCEdrs

Table 2. Model identified parameters – Elastance, %ΔE, AUCEdrs, and Number of un-physiological model fits

Patient	Median IQR [cmH2O/ml]				AUCEdrs [cmH2O/ml]			
	E_{lung}	$\%\Delta E_{lung}$	E_1	$\%\Delta E_1$	Neg	Pos	Number $E_{lung} = 0$	Number $E_1 = 0$
2	0.88 [0.68 - 1.80]	1.15 [-17.20 - 23.96]	1.71 [1.27 - 3.09]	0.31 [-13.42 - 19.03]	-0.36 [-0.41 - -0.30]	0.01 [0.00 - 0.02]	35	19
3	0.17 [0.09 - 0.27]	-7.46 [-67.59 - 32.15]	0.72 [0.24 - 1.30]	-1.20 [-45.85 - 89.66]	-0.28 [-0.37 - -0.18]	0.01 [0.00 - 0.06]	143	187
4	0.72 [0.51 - 1.01]	0.74 [-14.06 - 18.74]	3.63 [2.36 - 5.46]	-0.69 [-16.06 - 19.47]	-0.37 [-0.48 - -0.29]	0.01 [0.00 - 0.04]	15	20
5	0.46 [0.40 - 0.55]	0.40 [-12.93 - 14.14]	1.42 [1.27 - 1.83]	-0.87 [-14.98 - 14.68]	-0.30 [-0.36 - -0.26]	0.01 [0.00 - 0.04]	36	41
6	2.95 [2.73 - 3.19]	0.03 [-5.57 - 5.56]	6.35 [5.79 - 6.86]	-0.77 [-4.71 - 3.32]	-0.31 [-0.37 - -0.26]	0.00 [0.00 - 0.02]	2	1
7	1.35 [1.09 - 1.76]	-0.29 [-9.73 - 10.56]	4.79 [3.55 - 6.18]	-0.89 [-7.85 - 9.85]	-0.36 [-0.48 - -0.27]	0.04 [0.02 - 0.17]	11	5
8	1.46 [1.19 - 1.91]	-0.23 [-18.43 - 21.96]	2.42 [1.99 - 3.23]	0.32 [-12.85 - 16.63]	-0.31 [-0.37 - -0.25]	0.04 [0.01 - 0.29]	36	13
9	2.97 [2.52 - 3.22]	-0.49 [-8.69 - 9.38]	6.22 [5.09 - 6.73]	-0.54 [-6.16 - 4.11]	-0.21 [-0.29 - -0.13]	0.02 [0.00 - 0.06]	13	43
10	1.97 [1.48 - 2.75]	0.11 [-7.23 - 8.50]	3.12 [2.17 - 4.84]	0.09 [-7.58 - 8.58]	-0.39 [-0.49 - -0.33]	0.01 [0.00 - 0.02]	1	1
Total*	1.51[0.72 - 2.76]	0.22 [-9.73 - 12.06]	3.42[1.88 - 5.97]	-0.48[-9.28 - 10.34]	-0.33 [-0.41 - -0.25]	0.02 [0.00 - 0.07]	292	330

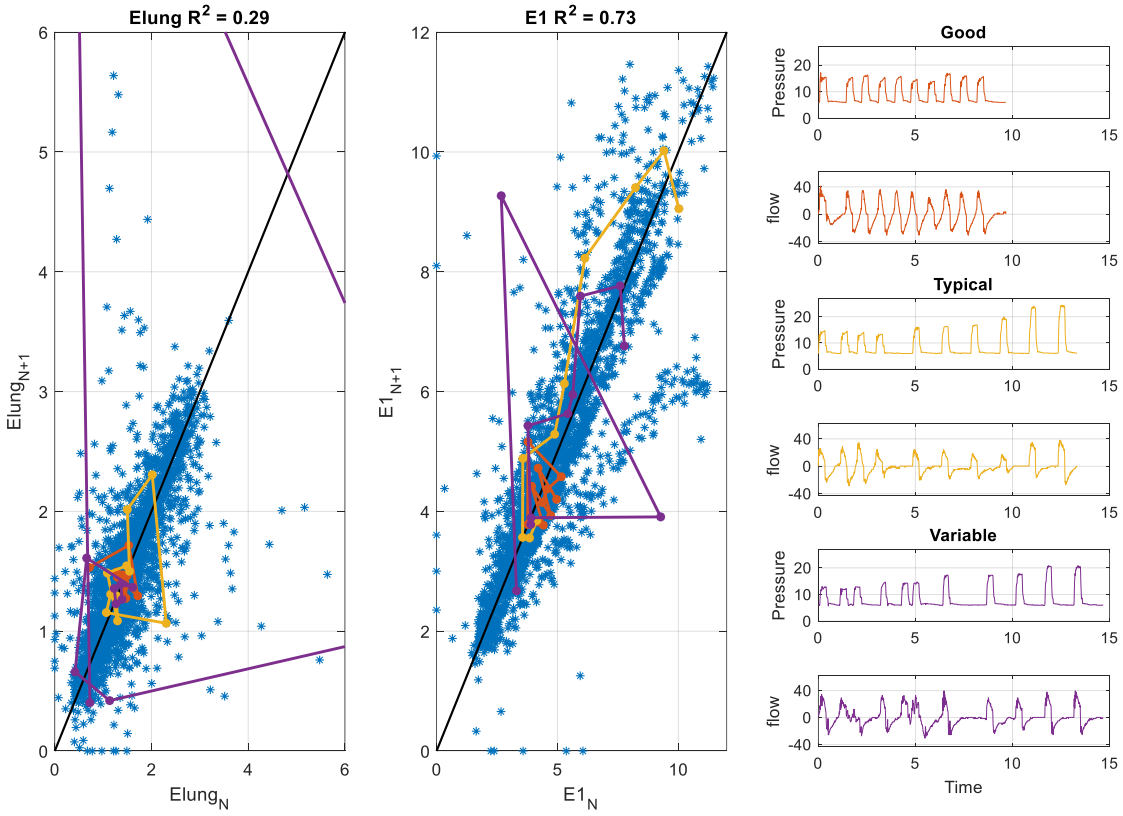

Fig. 5. Scatter plot of Patient 7's breath-to-breath elastance with example of good, typical and bad breaths and their relative position on scatter plot.

The breath-to-breath relationship of E_{lung} had correlation of determination $R^2 = 0.29$. This value is much lower than for E_1 of Model 2 which was R^2=0.73. The much lower correlation indicates the impact of outliers, and potential bias not visible with all the points.

4. DISCUSSION

4.1 Main results

The breath-to-breath elastance of E_{lung}, and E_1 showed overall good consistency in model. Fig 3 showed Models 1 and 2 (without *Edrs*) had near similar fits, a first step towards validation of the use of Model 2. As the *Edrs* term absorbed the remainder of pressure variation with volume after E_1 the Model 2 had a perfect fit.

The *Edrs* parameter typically was only in effect during the first 10% of a breath, where patient effort is greatest. The negative start and typical rise to zero is expected from diminishing patient effort as the lung fills. Thus, the shape and nature of *Edrs* as used here is capturing a surrogate of physiological, patient-specific and breath-specific inspiratory effort.

E_{lung} had much lower elastance IQR range (75^{th}-25^{th}) compared to E_1 with 2.04 and 4.09 cmH_2O/ml respectively, as seen in Fig 2 as E_{lung} is narrower. However, the percentage breath-to-

breath difference in elastance (*%ΔE*) for E_1 is smaller than E_{lung} with IQR range 19.62 and 21.79%, which is again shown in Fig 2 as *%ΔE*$_1$ is narrower than %ΔE_{lung}. More importantly, the larger range for E_1 does not indicate a poorer model. Narrower patient-specific box plots (not shown) indicate it provides better resolution between different patients.

Fig 5 showed breath-to-breath elastance scatter with 'good', 'typical', and 'variable' breaths. For good breaths, both E_{lung} and E_1 were less variable (shown by its distance from one-to-one line). The typical breath were more variable and 'variable' breaths showed significant variability. It should be noted a 'typical' breath for E_1 stayed closer to the one-to-one line whereas E_{lung} jumped significantly. The 'variable' breath with large asynchrony and variable breath exhibited significant breath-to-breath jump. The %ΔE_{lung} for this portion is significantly higher than %Δ E_1. These results shows that E_{lung} has higher breath-to-breath difference compared to E_1 and is validated by narrower IQR of %ΔE.

The time-varying elastance is the sum of chest, lung and demand elastances (Chiew et al., 2015). The basis functions of Model 2, Eq (4) incorporate recruitment (lung) and distension (chest) (Morton et al., 2019), and in sum, may include the chest wall's constant contribution. The residual is absorbed into time-varying Edrs, and assumed to be largely patient inspiratory effort (demand). In Fig. 3, the Edrs curve is only active during the early part of inspiration and settles to zero. This result validates the overall assumption Edrs is capturing patient demand elastance (patient effort) in the modelling framework used.

The negative and positive AUCEdrs across the patients were relatively similar with overall median IQR of -0.33 [-0.41 - -0.25] cmH_2O/ml for negative and 0.02[0.00-0.07] cmH_2O/ml for positive. Patient 9 had the lowest median IQR of negative AUCEdrs with -0.21 [-0.29 - -0.13] cmH_2O/ml and highest was Patient 10 with -0.39[-0.49 - -0.33] cmH_2O/ml.

The negative AUCEdrs were calculated based on negative Edrs portion at the start of inspiration. This negative portion equates to patient effort where pressure drops below set PEEP as the patient is breathing with the ventilator. The positive AUCEdrs calculated are large positive Edrs values occurring after the negative part (as seen in Fig 3).

The distension basis function in Eq (4) was set to zero and thus removed. The distension basis function is determined by capturing the increasing in elastance with pressure (Morton et al., 2019). However, unlike the adult data set, the infant data set does not increase in PEEP. Both E_{lung} and E_1 varies throughout the data but PEEP maintains its level. Therefore the distension elastance E2 was set to 0.

Table 2 shows number of bad model fits in E_{lung} and E_1. Elung had 292 breaths (1.14%) with model fit of 0 and E_1 had 330 breaths (1.29%) with model fit of 0. Patient 3 had the highest number of bad fits. Patient 3 was only patient to be on synchronized intermittent mechanical ventilation (SIMV) mode whereas other patients were on PTV. Fig 6 shows two examples of breaths that results in bad model fit.

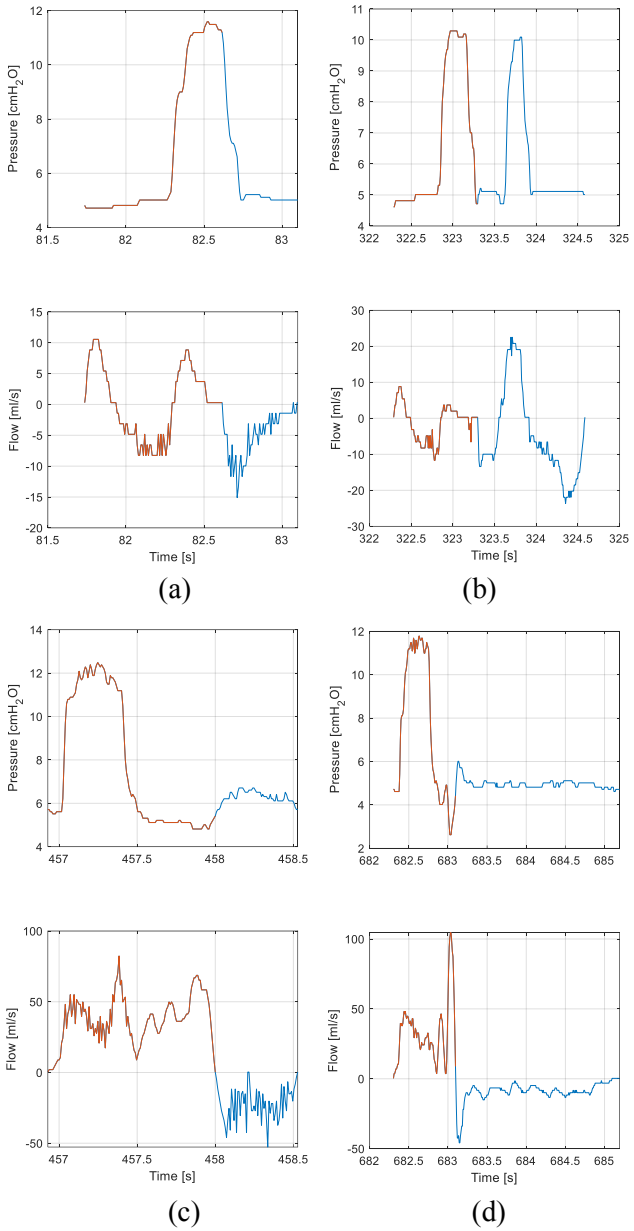

Fig. 6. Example of bad breaths that results in bad model fit (E = 0).

Fig 6 shows four examples of bad breaths which results in poor model fit (E = 0) where pressure profiles are on top and the corresponding flow on the bottom. The flow profile in 6a and 6b shows cases where there is flow but no pressure. Both 6a and 6b have clear increase in flow and decrease in flow but no pressure increase. 6c and 6d shows bad flow profiles resulting in poor model fit. Both 6c and 6d shows variable and inconsistent flow delivered. Breaths shown in Fig 6, are not ideal breaths for the assumed model dynamics and occurs throughout the dataset as seen in Table 2 by the number of breaths with poor model fit.

The infants in this study are not sedated and therefore their elastance is varied breath-to-breath. E1 was able to capture this breath-to-breath variability better than Elung as seen in

Table 2 and Fig 2. Given this and that Model 2 applies a Edrs to capture patient-specific and breath-specific effort, Model 2 is a reasonable model for NICU patients. Further work will be required to quantify patient-effort and asynchrony.

4.2. Limitations

This study is limited by the small number of patients (N = 9), but the number of breath used was large (25,647 breaths). Therefore the results are validated by the large number of breaths used.

5. Acknowledgement

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6. CONCLUSIONS

Two well-validated lung mechanics models were used to fit breath-to-breath elastances, E_{lung}, and E_I in a NICU infant cohort. Model 1 has been assessed in past, but Model 2, a nonlinear model, had very good fit and captured the respiratory mechanics well, particularly providing an estimate of patient-specific spontaneous breathing effort. The basis function used thus captured expected trends overall, with Edrs capturing time-varying and breath-varying patient-specific effort.

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