# Quantifying Neonatal Pulmonary Mechanics in Mechanical Ventilation


## Abstract

**Background:** Mechanical Ventilation (MV) is an important intensive care therapy. It is often used in neonatal intensive care units (NICUs) to treat respiratory distress syndrome. This paper uses model-based methods in a first in-depth attempt to quantify the underlying lung mechanics in NICU patients.

**Methods:** Up to 24 hours of airway flow and pressure data were recorded in 10 mechanically ventilated patients. A single compartment model with added term for the pressure drop across the endotracheal tube is used to identify breath-specific elastance and resistance.

**Result:** The model was fitted to 422,475 (79%) breaths of 535,428, with the remainder comprising a range of asynchronies. Elastance was median 1.62 [IQR: 0.85 – 2.25] $cmH_2O/ml$ and resistance 5.22 [0.00 – 33.85] $cmH_2O.s/ml$. Patients treated with surfactant therapy had significantly lower specific elastance (adjusting for weight) than those without ($p \leq 0.01$). A decrease in elastance with increasing weight was also noted.

**Conclusion:** The single compartment model was successfully fit with low error. The subgroup cohorts showed expected trends and further validates the identified model values. There was significant breath-to-breath variability in elastance within and between patients.

# 1.0. Introduction

Mechanical ventilation (MV) is an essential part of life support in recovering from respiratory failure [1–4]. It is used to support or fully control patient breathing, and is widely used in the neonatal intensive care unit (NICU) for infants suffering from respiratory distress syndrome (RDS). RDS commonly occurs in neonates due to a lack of surfactant [5,6] as a result of premature birth.

Currefnt clinical practice for treating respiratory failure is based on clinician intuition and/or a generalised, “one size fits all” approach [7]. Inter-patient variability and lung heterogeneity can make selection of optimum ventilator settings difficult. Subsequent poor MV can over distend the lung or provide inadequate support to maintain lung recruitment [1,8–10], resulting in reduced outcomes and/or ventilator induced lung injury (VILI) [11–14].

Model-based methods can be used to identify patient specific lung mechanics [15–22] and personalise care. They have been developed to guide and optimise MV therapy in the adult intensive care unit (ICU) [15,23,24]. However, there is a lack of studies exploring neonatal pulmonary mechanics.

A study by Bhutani et al. (1988) used neonatal data and a single compartment model similar to [15,25] to describe neonatal respiratory mechanics. However, this study was limited in both hardware used (external pneumotachometer and pressure transducer) and the size of the data (20-40 breaths per patient) [18].

This study is a first in-depth attempt to quantify the underlying lung mechanics for MV in the NICU. It will apply model-based methods, specifically a single compartment model to a clinical data cohort to assess and quantify the underlying elastance and resistance, with a secondary aim to identify the incidence of asynchrony and spontaneous breathing attempts, which can interfere with MV [26–29]. If the model translates and successfully captures respiratory mechanics in this cohort, it could be possible to apply a similar model-based MV approach [15] clinically in this cohort. This outcome would offer potential improved, patient-specific care to this cohort in a core area of NICU care.

# 2.0. Methods

## 2.1. Patient Data and Processing

Ventilator data from 10 invasively ventilated patients was collected from Christchurch Women's Hospital Neonatal Intensive Care Unit (NICU) as part of an observational study under informed consent given by parents. Ethics was approved by the New Zealand Northern B Health and Disability Ethics Committee (study ref: 16/NTB/16). Waveform data was nominally collected for 24 hours under standard care conditions. Eligibility criteria included the expectation MV would continue for 24 hours, clinical equipoise, and general clinically assessed patient medical stability. Informed consent from parents or legal guardians was obtained in all cases.

Patients received either conventional ventilation (CV) or high frequency oscillatory ventilation (HFOV) on a SLE5000 neonatal ventilator (SLE, UK) [30] as determined by standard clinical practice. None of the infants were sedated over the trial period, though some received morphine, which can have a sedative effect [31]. The clinical characteristics and demographics of patients are shown in Table 1.

In cases where an infant was re-intubated after being weaned from MV, or the infant was later switched to another ventilation mode, a subsequent 24 hours of data recording was carried out with further parental consent. This second stage allows comparison of lung mechanics over different modes, or changes over time. Infants thus had 1 or more recording periods.

Ventilator data was recorded using MediCollector [32] software on a laptop connected to Philips Healthcare MP70 bedside monitor [33]. The Philips bedside monitor was connected to the ventilator via a Vuelink respiratory module (Vuelink M1032A, Philips Healthcare) [34]. The equipment setup is shown in Fig. 1. Airway pressure (mbar) and flow (L/min) were recorded at a sampling rate of 125Hz. The airway pressure and flow are converted into $cmH_2O$ and mL/s in model fitting.

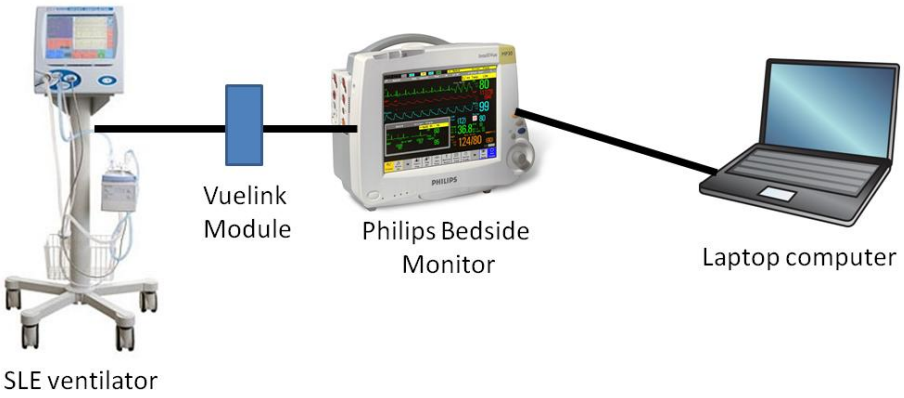


*Fig. 1. Clinical data recording set up*

Data was recorded from the ventilator, with no additional re-sampling, smoothing or filtering. Patient data was separated into individual breaths characterised by inspiration (positive flow) and expiration (negative flow). As tiny fluctuations in pressure and flow are observed prior to expiration and/or inspiration onset, additional criteria for inspiration/expiration onset are defined:

- Inspiration start: the first major positive airflow associated with an overall increase in flow (inspiratory flow rate > 16.67 ml/s) and pressure (Pressure increased to P > (PEEP + 2 $cmH_20$)).
- Expiration start: the first major negative airflow associated with an overall decrease in flow (expiration flow rate > 16.67 ml/s).

Both inspiration and expiration start is checked over 20 data points to ensure there is constant increase/decrease in flow and PEEP. Expiration is defined as first major negative airflow followed by an inspiration.

As the pressure-flow profiles can be interrupted, or modified by clinical care or patient asynchrony, additional criteria were applied to identify 'true' breaths from the raw signal:

- Total inspiratory volume was > 0.5 ml
- PIP was > (PEEP + 1 $cmH_20$)
- Expiration was identified within 1.1s of the calculated onset of inspiration defined above, where standard CV respiratory rates (RR) are 60/min or 1 sec for both inspiration and expiration.

**Table 1:** Clinical characteristics of recruited patients

| Patient | Ventilation mode | Gender | Gestational Age at birth (weeks) | Post-natal age (days) | Weight (g) | | Day of MV | Steroids | | | Surfactant therapy | Morphine | | Clinical notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Birth | Trial | | Prenatal | Postnatal | During recording | | Y/N | Dose [mcg/kg/h] | |
| 1 | HFOV | F | 26.5 | 31 | 760 | 1120 | 22 | y | N | Y | N | Y | 12 | RDS, severe lung disease |
| 2 | HFOV | F | 25 | 21 | 570 | | 21 | Y | Y | N | N | Y | ? | Severe lung disease, previous sepsis/pneumonia |
| | CV – PTV + TTV | | | 23 | | 770 | 23 | | | Y | | Y | PO | Severe RDS, CNS Sepsis. PPHN |
| | CV – PSV + TTV | | | 32 | | 890 | 27 | Y | N | N | N | Y | PO/ 5** | |
| 3 | CV – SIMV + TTV | M | 41.5 | 3 | 3400 | 3400 | 3 | N | Y | | N | Y | 10 | Severe Hypoxic Ischemic Encephalopathy, Seizures |
| 4 | CV – PTV + TTV | F | 37 | 2 | 2750 | 2750 | 2 | N | N | | N | Y | 6 | PPHN |
| 5 | HFOV CV – PTV + TTV | F | 29.9 | 0 | 1580 | 1580 | 1 | Y | N | | Y | N | - | MCDA twin, Maternal Pre-eclampsia Toxaemia |
| 6 | CV – PTV + TTV | M | 27.4 | 2 | 1170 | 1170 | 1 | Y* | N | | N | Y | ? | Oesophageal atresia, post op from surgery |
| 7 | CV – PTV + TTV | F | 28.1 | 45 | 960 | 1990 | 5 | Y | N | | N | Y | 20 | Abdominal surgery |
| 8 | CV – PTV + TTV | F | 25.7 | 2 | 770 | 770 | 2 | N | N | | Y | N | - | RDS |
| 9 | CV – PTV + TTV | M | 25.3 | 4 | 820 | - | 5 | Y* | N | | N | Y | ? | RDS |
| 10 | CV – PTV + TTV | M | 25.9 | 4 | 810 | 810 | 1 | Y* | N | | N | N | - | RDS |

* Partial course only. ** oral changed to infusion at stated rate. HFOV: High frequency oscillatory ventilation. CV: Conventional ventilation. PTV: patient triggered ventilation. PSV: pressure support ventilation. TTV: Targeted tidal volume. RDS: Respiratory Distress Syndrome. PPHN: Persistent pulmonary hypertension of the newborn. CNS: central nervous system. MCDA twins: monochrionic diamniotic twin gestation.

## 2.2. Model and identification

A linear single compartment model previously validated in the adult ICU is used [15]. Patient-specific, constant values of model-based lung elastance ($E_{rs}$) and airway resistance ($R_{rs}$) are identified from airway pressure ($P_{aw}$), flow ($Q$), volume ($V$), and pressure offset ($P_o$) inputs. Volume ($V$) is the integral of flow ($Q$), and $P_o$ is the Positive End Expiratory Pressure (PEEP). The single compartment model is fit over inspiration, and $E_{rs}$ and $R_{rs}$ are identified using least squares methods [25,35,36]. However, the pressure loss across the endotracheal tube (ETT) may be significant in the NICU context as small ETT diameters (3-5mm) can significantly increase resistance to flow compared to adult cases. As such, the single compartment model is modified to directly compensate for the ETT, yielding a modified model:

$$P_{aw} = E_{rs}V + R_{rs}Q + P_0 + \Delta P_{ETT} \quad (1)$$

Jarreau et al 1999, [37] describes the pressure loss across the ETT. Jarreau et al took measurements of clinical setup and used physiological and mathematical approach to come up with an equation to estimate the pressure loss across the ETT. The pressure drop ($\Delta P_{ETT}$) across the ETT is modelled [37]:

$$\Delta P_{ET} = L(0.0203D^{-4.25}Q^{1.5} + 0.319D^{-4}Q) \quad (2)$$

Where $L$ is the length of the ETT tube in cm, $D$ is the diameter in mm, and $Q$ is the flow rate in mL/s.

Equation 2 assumes laminar flow. Turbulence occurs if the Reynolds number is above the critical value. In this case, the flow is always laminar for small ETT diameters (under 3.5mm) [37], as turbulent, flow requires flow rates greater than 250 ml/s for an ETT diameter of 3.5mm and typical tidal volumes are 5-20mL. For all patients and breaths in this study, peak flow rates were less than this value.

The ETT diameter is typically a function of patient weight, as shown in Table 2. Clinically, ETTs are shortened to an appropriate patient-specific length by 1-2cm post-insertion, as clinically determined. The shortened length was unavailable for this study and thus, it was assumed that all ETTs are shortened by 2 cm, providing a minimum estimation of $\Delta P_{ETT}$, where $R_{rs}$ may capture additional resistance due to longer lengths.

**Table 2** – Clinical guidelines for ET tube selection

| ET tube diameter [mm] | Unshortened ET tube length [cm] | Indication for use |
|---|---|---|
| 2.0 | | Cannot insert a 2.5 mm ET tube |
| 2.5 | 18 | Weight < 1.5 kg |
| 3.0 | 19.5 | Weight 1.5 – 2.5 kg |
| 3.5 | 20 | Weight 2.5 – 4.0 kg |
| 4.0 | | Weight > 4 kg |

## 2.3. Analyses

This first study only examines model fit to conventional ventilation data. Data from Patient 1 was excluded because they were recorded in only HFOV mode, where preliminary analysis suggests pressure characteristics are more a function of the ventilator, rather than patient specific lung mechanics, due to the rapid Respiratory Rate (RR=300+/min). An analysis of HFOV was thus deemed out of scope in this study, leaving N = 9 patients (Patients 2-10 in Table 1).

Elastance ($E_{rs}$) is fit breath-to-breath, and resistance ($R_{rs}$) is fit using a moving window of 30 breaths to avoid mild parameter trade-off between $E_{rs}$ and $R_{rs}$ in identifying Equation (1) [15,25,38]. This moving window reduces variability, and improves both identifiability and breath-to-breath consistency in identified values.

In particular, the model used in this study is focused on non-spontaneous breathing [15]. Non-sedated infants cry, try to breath spontaneously, and have clinical interactions, causing asynchronous breaths, all of which can be detected by the model [15,27]. These asynchronous breaths do not yield the patient's true underlying pulmonary mechanics or condition as these events distort the pressure and flow waveforms, and spontaneous breathing provides a negative pressure which trades off with the positive pressure supplied by ventilator. This study aims to capture these underlying lung mechanics in neonates and thus, some breaths are eliminated for this analysis.

Further filtering criteria used to remove outlier breaths and/or poor model fits include:

- Model-fit error >15%
- Model-based $E_{rs} \leq 0$ (un-physiological, occurs with spontaneous effort [22])
- Model-based $E_{rs}$ outside $5^{th}$ and $95^{th}$ percentiles as the focus is on central behaviour and mechanics.

Model fit is assessed using the percent mean absolute relative difference (MARD). Data is presented as median and [IQR] (interquartile range), unless specified otherwise.

Model fitting error >15% are discarded for this analysis because fitting error >15% indicates that model does not accurately represent patient's physiological condition [15]. Considering this is a proof of concept paper, in attempt to quantify NICU pulmonary mechanics, including breaths with error >15% is not included.

Different subgroup comparisons were carried out to validate the identified model-based elastance against expected trends. Elastance and resistance are compared in infants who received surfactant treatment to untreated infants, where surfactant is expected to reduce elastance. However, it is difficult to directly compare patients treated with surfactant and not treated with surfactant due to the large range of weight, as larger infants would have more developed lungs [1]. Thus, specific compliance is used.

Specific compliance is often used metric in neonatal MV as it is a measure of intrinsic elasticity of the lung tissue while being independent of lung volume [39]. Compliance is an inverse of elastance, and specific compliance can be calculated by dividing compliance by the weight [40]. Thus, specific elastance can be calculated using: $C_{specific} = C/m = 1/E_{rs} * 1/m = 1/ E_{rs}*m$ and therefore $E_{specific} = E_{rs} *m$ is used in this comparison. Where, C is the compliance and m is the mass of the infant.

Because infant size is a factor affecting respiratory mechanics, increased birth weight is expected to result in decreased elastance due to more developed lung structures and larger volumes [40]. Therefore, different birth weight groups are compared based on the hypothesis larger infants would have lower elastance. As they are compared by weight, elastance, $E_{rs}$, is used directly.

## 2.4. Statistics

All statistical comparisons are made using non-parametric statistics due to non-Gaussian distributions. Statistically as noted, to get the main or broad central tendency of behaviour we analyse the 90% range of results for each infant. Due to very large data sets and smaller number of patients, bootstrapping was used to examine the difference in median values, in each comparison [41]. Data was bootstrapped 10,000 times with replacement. A 99% Confidence Interval (CI) for difference in median specific elastance values are created. If the CI does not cross zero, differences in medians are statistically significant with $p \leq 0.01$, which is more conservative than $p \leq 0.05$ because of multiple comparisons and very large data vectors [42].

This bootstrapping statistical comparison are chosen between surfactant and non-surfactant cohort. Patients are not individually compared but rather compared as whole group. 10,000 data are randomly

chosen from each surfactant and non-surfactant cohorts with replacement. Then the difference in medians and mean of medians are calculated. This is repeated another 10,000 times and 99% CI is calculated.

# 3.0. Results

## 3.1. Breaths and Asynchrony

Airway pressure and flow data were recorded for 10 patients, comprising 205.9 hours of conventional ventilation (CV; N= 9; Patients 2-9), and 53 hours of HFOV (N = 3; Patients 1,2,5). Measured ventilator outcomes are given in Table 3 for the conventionally ventilated patients analysed here. Patient 2 had three different recording sessions (2 CV, 1 HFOV). However, due to technical difficulties resulting in a loss of laptop power, the CV recordings were cut to 2 and 3 hours. Patient 5 has <24 hours of data in CV as they started with HFOV, but switched to CV. In many cases, total hours per patient was slightly <24 hours due to these issues, extubation, or other clinical factors. Patient 2 episode 2 (2-2 in Table 3) had the minimum number of breaths with 4110, and Patient 10 had the maximum of 93185. Table 3 also shows number of filtered breaths per patient. From this table it can be seen that the PSV and SIMV mode creates higher occurrence of fitting error and extremities in elastance as they have more filtered breaths in comparison to those on PTV.

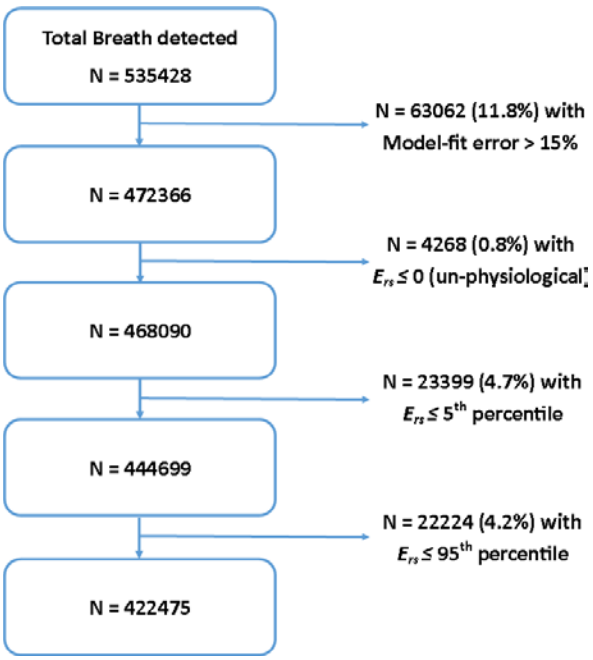


*Fig. 2. Cohort diagram showing tabulated post filtering process. Percentages reflect percentage of total breaths detected.*

Fig. 2 shows filtering criteria used to remove further outlier breaths and/or poor model fits with total number still left. Most breaths removed using this filtering criteria were unusual breaths with significant spontaneous breathing effort, or effects in the pressure-flow profiles caused by clinical interactions with the infant. Examples of filtered breaths due to significant spontaneous breathing and/or clinical interaction are shown in Fig. 3 where it is clear these breaths were not representative of the underlying lung mechanics in the infants typical breathing pattern, and thus were excluded. Between initial filtering and post-fitting filtering a total of 112,953 of 535,428 (21%) breaths were excluded as asynchronous or otherwise altered, leaving 422,475 breaths over the n=9 infants.

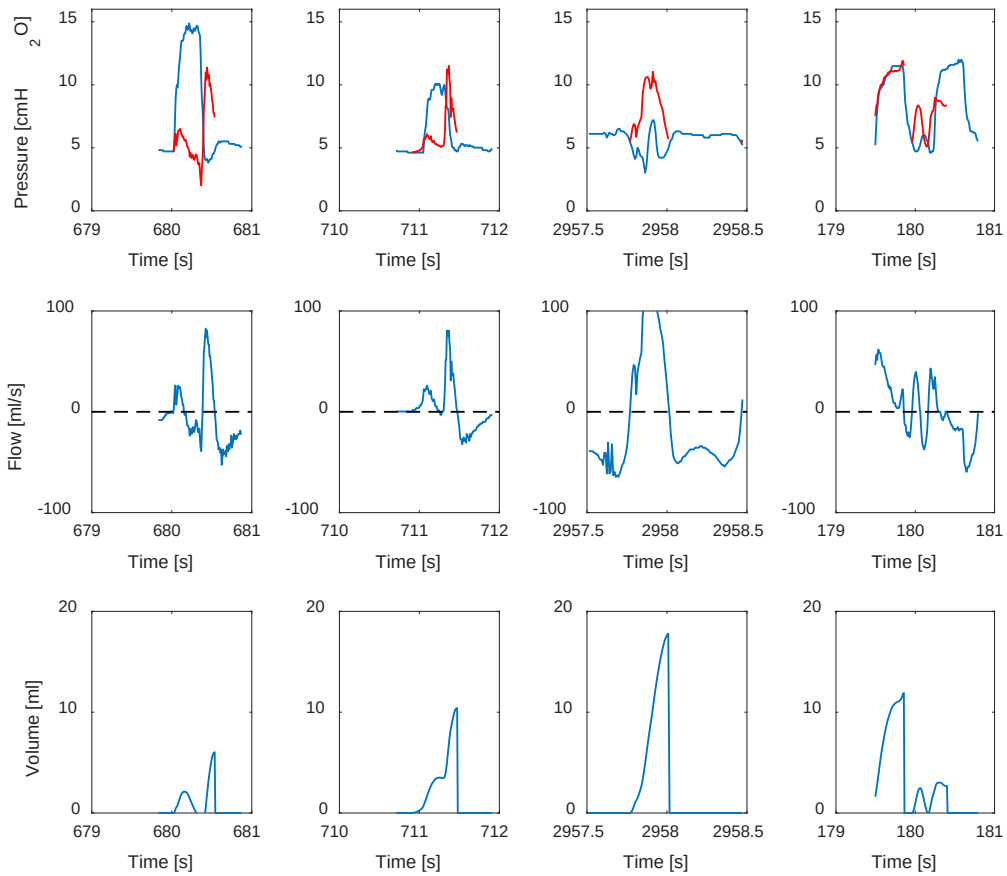


*Fig. 3. Four examples of excluded breaths showing poor model fit (red) along with the corresponding pressure-flow and volume profiles (blue).*

Table 4 shows mean and standard deviation of PEEP, driving pressure ($\Delta P$) and volume/target volume per patient of normal and filtered breath. It can be seen that the standard deviation for filtered breaths are higher. Filtered breath have higher standard deviation as they are mostly asynchronous and/or spontaneous breathing.

## 3.2. Cohort Elastance and Resistance

The single compartment model with ETT compensation in Equation 1 was fit to every breath. Overall, model fit was very good with median [IQR] percentage MARD of 5.7 [5.2-6.3] % across all conventionally ventilated patients. Elastance across all patients was median 1.622 [0.854 - 2.253] $cmH_2O/ml$ and resistance was median of 5.223 [0.000 - 33.851] $cmH_2O.s/ml$. The median [IQR] of elastance, resistance and MARD across 6 hourly time intervals (~21600 breaths per patient) are given in Table 5. Fig. 4 shows a range of fitting outcomes, demonstrating extremely good fit (MARD, 2.27%), good fit with spontaneous breathing effort causing a dip in pressure at inspiration onset (MARD, 6.93%), and relatively poor fit (MARD, 11.50%).

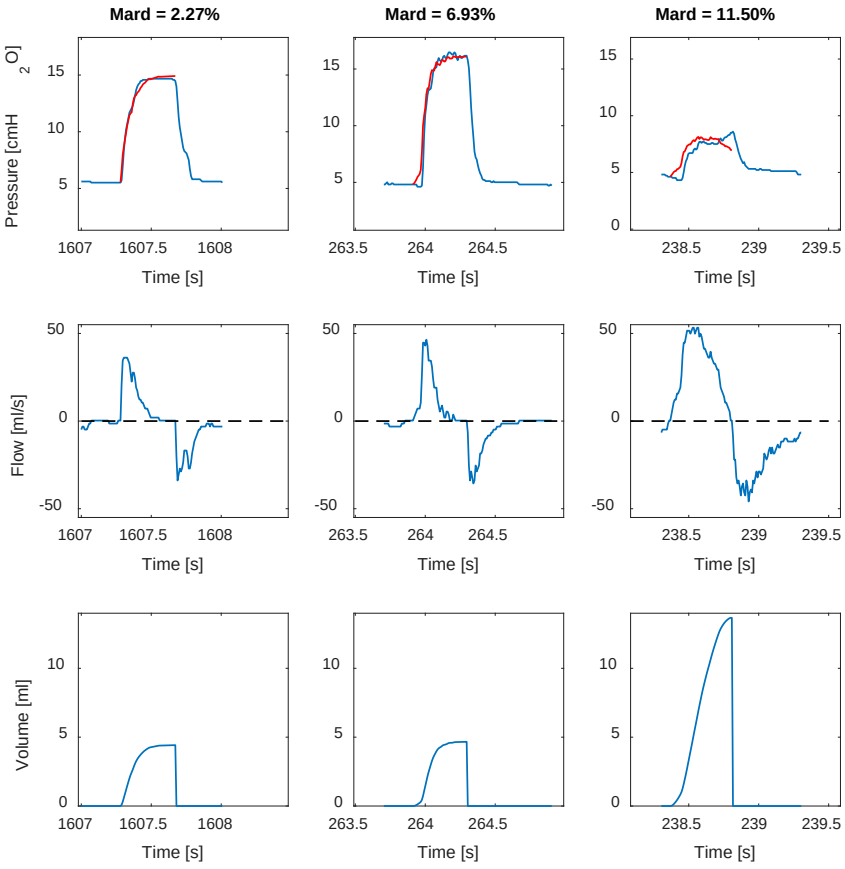


*Fig. 4. Three examples of model fit (red) showing low MARD (2.27%), medium MARD (6.93%) and high MARD (11.5%)*

**Table 3:** Mechanical Ventilation characteristics of recruited patients on conventional ventilation (CV)

| | | | Ventilator settings | | | | | | | Recorded outcomes | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | Ventilation mode | Day of MV | PEEP ($cmH_2O$) | Target Tidal Volume | | Surfactant therapy | Hours of Recording | Number of Breaths* | Filtered Breaths | Median [IQR] delivered inspired tidal Volume [ml] | Max PIP [$cmH_2O$] | Median [IQR] PIP [$cmH_2O$] | Median [IQR] PEEP [$cmH_2O$] | Median [IQR] Inspiration Time [s] |
| | | | | ml/kg | ml | | | | | | | | | |
| 2-2 | CV – PTV +TTV | 23 | 5 | 5 | 4 | N | 2 | 4110 | 676 | 4.4 [3.8 - 5.6] | 18.3 | 10.5 [9.5 – 13.2] | 5.1 [5.0 - 5.1] | 0.4 [0.4 - 0.5] |
| 2-3 | CV –PSV + TTV | 27 | 5 | 5 | 4 | N | 3 | 8695 | 2325 | 5.1 [4.3 – 5.9] | 22.9 | 10.0 [9.2 - 12.5] | 5.5 [5.5 - 5.6] | 0.4 [0.4 - 0.5] |
| 3 | CV – SIMV + TTV | 3 | 5 | 3.8 | 13 | Y | 21 | 60322 | 36642 | 21.6 [18.2 - 25.0] | 21.1 | 9.7 [9.4 - 10.4] | 5.1 [5.0 - 5.2] | 0.4 [0.4 - 0.5] |
| 4 | CV – PTV + TTV | 2 | 5 | 4 | 11 | Y | 19.3 | 52590 | 10063 | 12.1 [10.7 - 14.1] | 19.1 | 9.7 [8.5 - 12.6] | 4.3 [4.2 - 4.5] | 0.4 [0.4 - 0.5] |
| 5 | CV – PTV + TTV | 1 | 5 | 5 | 7.9 | N | 8.2 | 25346 | 4606 | 8.6 [7.7 - 9.5] | 32.8 | 9.5 [9.3 - 9.6] | 5.1 [5.1 - 5.2] | 0.4 [0.4 - 0.4] |
| 6 | CV – PTV + TTV | 1 | 5 | 4.3 | 5 | Y | 21 | 74081 | 8327 | 5.0 [4.8 - 5.3] | 25.6 | 16.5 [15.2 - 18.6] | 5.5 [5.4 - 5.5] | 0.4 [0.4 - 0.4] |
| 7 | CV – PTV + TTV | 5 | 5 | 4 | 6.6 | N | 23.6 | 60109 | 9364 | 6.2 [5.7 - 6.9] | 26.9 | 13.0 [11.2 - 14.6] | 6.0 [6.0 - 6.1] | 0.4 [0.4 - 0.4] |
| 8 | CV – PTV + TTV | 2 | 5 | 3.9 | 3 | N | 22 | 72905 | 12210 | 3.2 [2.9 - 3.6] | 21.8 | 10.3 [9.2 - 12.2] | 4.8 [4.7 - 5.0] | 0.4 [0.3 - 0.4] |
| 9 | CV – PTV + TTV | 5 | 5 | 4.2 | 4 | Y | 24.6 | 84085 | 14495 | 4.8 [4.3 - 5.2] | 27.8 | 17.8 [14.8 - 19.9] | 4.7 [4.7 - 4.8] | 0.3 [0.3 - 0.4] |
| 10 | CV – PTV + TTV | 1 | 5 | 5 | 4 | N | 42.8 | 93185 | 14245 | 3.7 [3.4 - 4.0] | 22.8 | 12.3 [11.1 - 13.8] | 4.7 [4.6 - 4.7] | 0.4 [0.3 - 0.4] |

* Filtered out breaths with poor fitting error and extremes in elastance. HFOV: High frequency oscillatory ventilation. CV: Conventional ventilation. PTV: patient triggered ventilation. PSV: pressure support ventilation. TTV: Targeted tidal volume.

Table 4. Mean and standard deviation of PEEP, driving pressure (ΔP) and volume/target volume for normal and filtered breaths.

| | | PEEP | | | | ΔP | | | | V/targetV | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Normal Breath | | filtered Breath | | Normal Breath | | filtered Breath | | Normal Breath | | filtered Breath | |
| | | mean | std | mean | std | mean | std | mean | std | mean | std | mean | std |
| Patient | 2* | 5.38 | 0.28 | 5.59 | 0.57 | 11.44 | 2.96 | 11.55 | 3.44 | 0.98 | 0.23 | 0.95 | 0.39 |
| | 3 | 5.59 | 0.17 | 5.63 | 0.46 | 10.23 | 1.66 | 7.84 | 2.39 | 5.43 | 1.62 | 6.68 | 6.53 |
| | 4 | 4.62 | 0.13 | 4.70 | 0.41 | 10.98 | 3.03 | 10.78 | 3.55 | 3.12 | 0.74 | 4.03 | 2.49 |
| | 5 | 5.36 | 0.19 | 5.31 | 0.70 | 9.78 | 0.93 | 9.93 | 2.65 | 1.71 | 0.29 | 1.73 | 0.87 |
| | 6 | 5.61 | 0.32 | 5.68 | 0.88 | 16.85 | 2.58 | 16.70 | 3.61 | 1.17 | 0.15 | 1.23 | 0.47 |
| | 7 | 6.18 | 0.22 | 6.23 | 0.45 | 13.45 | 2.71 | 13.94 | 3.76 | 1.60 | 0.32 | 1.95 | 0.87 |
| | 8 | 5.14 | 0.76 | 5.24 | 0.84 | 11.33 | 2.63 | 11.20 | 2.65 | 0.86 | 0.23 | 0.96 | 0.50 |
| | 9 | 4.97 | 0.45 | 5.04 | 0.79 | 17.34 | 3.69 | 15.52 | 5.22 | 1.14 | 0.26 | 1.35 | 0.71 |
| | 10 | 4.80 | 0.17 | 4.85 | 0.45 | 11.85 | 1.87 | 11.85 | 2.60 | 0.76 | 0.12 | 0.84 | 0.32 |
| | ALL | 5.24 | 0.61 | 5.37 | 0.74 | 13.36 | 3.81 | 11.30 | 4.45 | 1.55 | 1.26 | 3.26 | 4.57 |

* Patient 2 -2 and Patient 2-3 are merged under 2 due to smaller number of breaths.

**Table 5:** Mechanical Ventilation characteristics of recruited patients on conventional ventilation (CV). Elastance ($E_{rs}$) is in $cmH_2O/ml$, and Resistance ($R_{rs}$) is in $cmH_2O.s/mL$.

| | | Hours | | | | |
|---|---|---|---|---|---|---|
| | | Median [IQR] | | | | |
| **Patient #** | | 1-6 | 7-12 | 13-18 | 19-24 | **Overall** |
| **2-2 *** | $E_{rs}$ | 1.24 [0.76 - 2.08] | | | | **1.20 [0.76 – 2.08]** |
| | $R_{rs}$ | 0.00 [0.00 - 0.00] | | | | **0.00 [0.00 – 0.00]** |
| | %MARD | 5.39 [4.13 - 7.80] | | | | **5.39 [4.13 – 7.80]** |
| **2-3 *** | $E_{rs}$ | 0.78 [0.57 - 1.62] | | | | **0.78 [0.57 – 1.62]** |
| | $R_{rs}$ | 0.00 [0.00 - 0.00] | | | | **0.00 [0.00 – 0.00]** |
| | %MARD | 8.58 [7.09 - 0.29] | | | | **8.58 [7.09 – 0.29]** |
| **3** | $E_{rs}$ | 0.16 [0.11 - 0.23] | 0.14 [0.09 - 0.20] | 0.14 [0.10 - 0.19] | | **0.14 [0.10 - 0.21]** |
| | $R_{rs}$ | 0.00 [0.00 - 0.00] | 0.00 [0.00 - 0.00] | 0.00 [0.00 - 0.00] | | **0.00 [0.00 - 0.00]** |
| | %MARD | 8.05 [6.78 - 9.87] | 8.33 [6.78 - 0.28] | 8.23 [6.38 - 10.84] | | **8.20 [6.66 - 10.32]** |
| **4** | $E_{rs}$ | 0.49 [0.29 - 0.74] | 0.46 [0.24 - 0.75] | 0.27 [0.18 - 0.47] | | **0.39 [0.23 - 0.67]** |
| | $R_{rs}$ | 0.02 [0.01 - 0.03] | 0.03 [0.02 - 0.04] | 0.01 [0.00 - 0.02] | | **0.02 [0.01 - 0.03]** |
| | %MARD | 6.27 [5.20 - 8.09] | 6.33 [5.26 - 7.99] | 6.65 [5.52 - 8.26] | | **6.43 [5.32 - 8.11]** |
| **5** | $E_{rs}$ | | 1.67 [1.31 – 1.92] | | | **1.67 [1.31 – 1.92]** |
| | $R_{rs}$ | | 0.00 [0.00 – 0.00] | | | **0.00 [0.00 – 0.00]** |
| | % MARD | | 6.05 [4.80 – 7.73] | | | **6.05 [4.80 – 7.73]** |
| **6** | $E_{rs}$ | 2.79 [2.55 - 2.98] | 2.12 [1.90 - 2.29] | 1.87 [1.69 - 2.06] | | **2.18 [1.87 - 2.60]** |
| | $R_{rs}$ | 0.00 [0.00 - 0.00] | 0.00 [0.00 - 0.01] | 0.00 [0.00 - 0.00] | | **0.00 [0.00 - 0.00]** |
| | % MARD | 3.83 [3.22 - 4.58] | 3.12 [2.65 - 3.88] | 2.91 [2.33 - 3.83] | | **3.31 [2.68 - 4.22]** |
| **7** | $E_{rs}$ | 1.21 [0.92 - 1.49] | 1.12 [0.91 - 1.30] | 0.90 [0.65 - 1.21] | 0.65 [0.49 - 0.92] | **1.01 [0.68 - 1.28]** |
| | $R_{rs}$ | 0.08 [0.06 - 0.12] | 0.05 [0.04 - 0.06] | 0.06 [0.04 - 0.08] | 0.05 [0.04 - 0.07] | **0.06 [0.04 - 0.08]** |
| | %MARD | 6.29 [4.98 - 8.20] | 5.03 [4.21 - 6.33] | 5.64 [4.67 - 7.32] | 5.54 [4.54 - 7.18] | **5.58 [4.55 - 7.28]** |
| **8** | $E_{rs}$ | 1.39 [1.11 - 1.78] | 1.46 [1.16 - 1.84] | 2.13 [1.49 - 3.21] | | **1.58 [1.23 - 2.16]** |
| | $R_{rs}$ | 0.03 [0.01 - 0.06] | 0.00 [0.00 - 0.01] | 0.04 [0.01 - 0.07] | | **0.02 [0.00 - 0.05]** |
| | %MARD | 5.82 [4.11 - 8.26] | 4.45 [3.39 - 6.11] | 5.42 [3.99 - 7.33] | | **5.13 [3.73 - 7.23]** |
| **9** | $E_{rs}$ | 2.99 [2.73 - 3.21] | 2.73 [2.03 - 3.23] | 2.70 [2.02 - 3.09] | 2.36 [1.70 - 2.78] | **2.73 [2.11 - 3.11]** |
| | $R_{rs}$ | 0.03 [0.02 - 0.04] | 0.04 [0.02 - 0.07] | 0.03 [0.02 - 0.04] | 0.01 [0.00 - 0.02] | **0.03 [0.01 - 0.04]** |
| | %MARD | 4.59 [3.88 - 5.68] | 6.46 [4.69 - 8.85] | 5.72 [4.32 - 8.01] | 6.51 [5.14 - 8.34] | **5.70 [4.34 - 7.81]** |
| **10** | $E_{rs}$ | 1.64 [1.26 - 2.20] | 1.67 [1.31 - 1.92] | 1.73 [1.45 - 1.95] | 1.88 [1.59 - 2.11] | **1.74 [1.38 - 2.02]** |
| | $R_{rs}$ | 0.00 [0.00 - 0.02] | 0.00 [0.00 - 0.00] | 0.00 [0.00 - 0.00] | 0.00 [0.00 - 0.01] | **0.00 [0.00 - 0.00]** |
| | %MARD | 6.66 [5.51 - 8.19] | 6.02 [4.79 - 7.67] | 5.49 [4.43 - 7.19] | 5.48 [4.44 - 7.36] | **5.95 [4.71 - 7.66]** |

* Patients 2-2 and 2-3 did not have enough recording time for 6 hourly time frame therefore median IQR represents 3 hours.

## 3.3. Subgroup analyses

### 3.3.1. Surfactant

Patients treated with surfactant, shown in Table 6, had significantly lower specific elastance than those without the treatment, as seen in Fig. 5, showing the expected response to treatment [43,44]. The difference of the median of specific elastance with 99% CI is -0.48 [-0.49 -0.48] $cmH_2O.kg/ml$, showing $p \leq 0.01$ statistically significant different in specific elastance. Resistance is similar across both cohorts as the difference of the median of resistance with 99% CI is 0.21 [-0.12 0.53] $cmH_2O.s/ml$. As surfactant lowers surface tension, lowering the pressure required to keep alveoli and airways open, a lowering of respiratory elastance in patients treated with surfactant is expected. This result thus shows the model's ability to capture a known response to typical care [43,44].

**Table 6:** Patient characteristics of selected patients who were and were not treated with surfactant

| | Subject | Study Weight [g] | Day of MV | Morphine | Target Tidal Volume [ml] | ET tube Diameter [mm] |
|---|---|---|---|---|---|---|
| **Treated with Surfactant** | **5** | 1580 | 1 | Y | 7.9 | 3.0 |
| | **8** | 770 | 2 | N | 3 | 2.5 |
| **Not treated with Surfactant** | **2** | 890 | 27 | Y | 4 | 2.5 |
| | **3** | 3400 | 3 | Y | 13 | 3.5 |
| | **4** | 2750 | 2 | Y | 11 | 3.5 |
| | **6** | 1170 | 1 | Y | 5 | 2.5 |
| | **7** | 1990 | 5 | Y | 6.6 | 3.0 |
| | **9** | 820 | 5 | Y | 4 | 2.5 |
| | **10** | 810 | 1 | N | 4 | 2.5 |

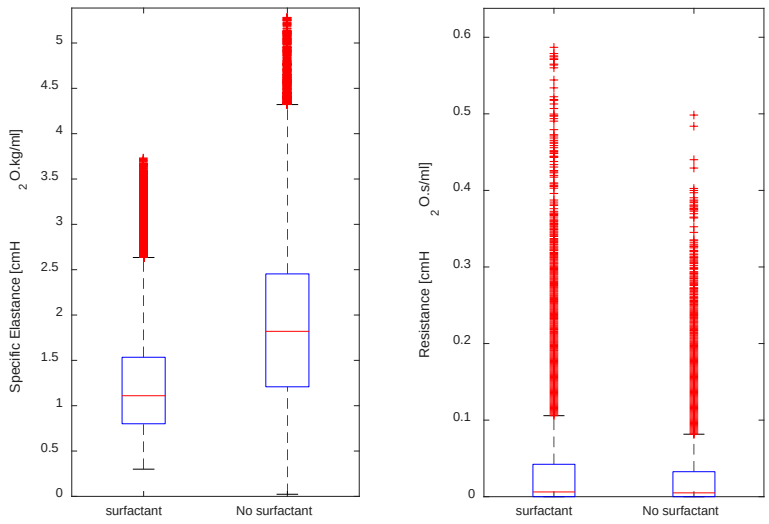


*Fig. 5. Specific elastance and resistance in subgroups of patients (5, 8; N = 81,435 breaths) with surfactant therapy, and patients (6, 7, 9, 10; N = 341,040 breaths) without surfactant therapy*

### 3.3.2. Weight based trends

Elastance decreased with increasing weight as seen in Fig. 6 and Table 7 ($p < 0.01$ in all comparisons). This result is expected, as PEEP and the plateau pressure remain largely the same over all these the patients, and thus effective elastance drops due to increasing in tidal volume. This result may also reflect greater lung maturity with increasing infant weight (and maturity) resulting in lower, less stiff lungs [45]. Resistance was similar, as expected.

**Table 7:** Patient characteristics of selected patients grouped by weight

| | Subject | Study Weight [g] | Day of MV | Surfactant | Morphine | Target Tidal Volume [ml] | ET tube Diameter [mm] |
|---|---|---|---|---|---|---|---|
| **<1000g** | **2** | 890 | 27 | N | Y | 4 | 2.5 |
| | **8** | 770 | 2 | Y | N | 3 | 2.5 |
| | **9** | 820 | 5 | N | Y | 4 | 2.5 |
| | **10** | 810 | 1 | N | N | 4 | 2.5 |
| **1000-2000g** | **5** | 1580 | 1 | Y | N | 7.9 | 3.0 |
| | **6** | 1170 | 1 | N | Y | 5 | 2.5 |
| | **7** | 1990 | 1 | Y | Y | 6.6 | 3.0 |
| **>2000g** | **3** | 3400 | 3 | N | Y | 13 | 3.5 |
| | **4** | 2750 | 2 | N | Y | 11 | 3.0 |

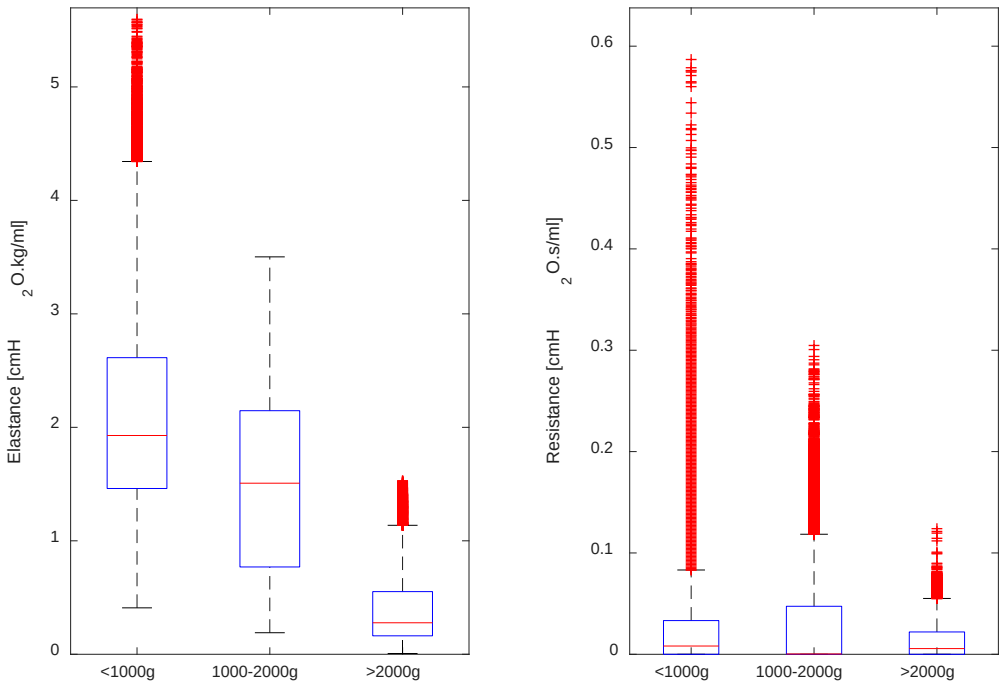


*Fig. 6: Model-based elastance and resistance in selected patients grouped by weight with <1000g (Patients 8, 9, 10; N = 219,029 breaths); 1000-2000g (Patients 5, 6, 7; N = 137,239 breaths); >2000g (Patients 3, 4; N = 66,207 breaths).*

# 4.0. Discussion

## 4.1. Breaths and Asynchrony

A total of 422,475 (79%) of identified breaths from raw data were used in the model-based analyses, and 112,953 (21%) breaths were removed. The filtered out breaths primarily represent significant spontaneous breathing and/or clinical interactions affecting the pressure-flow waveforms. These breaths are thus asynchronous for one or more of these reasons, and per Fig. 3, and do not represent typical MV supported breaths determined primarily or solely by the underlying fundamental pulmonary mechanics. The authors could find no prior studies of this scale to compare this incidence rate.

Table 4 shows mean and standard deviation of PEEP, driving pressure and volume/targeted volume for normal and filtered breaths. The filtered breaths shown to have higher standard deviation, these breaths are much more variable. High variability in standard deviation implies either asynchrony or spontaneous breathing effort.

Many of the breaths that were filtered are 'odd' breaths like shown in Fig 3, and the standard deviation is higher in filtered breaths in comparison to normal breaths shown in Table 4. For these reasons, the 21% filtered breaths are considered asynchronous or highly spontaneous breathing efforts. It should also be noted that Chiew et al 2011, states that fitting error >15% does not represent patient physiological condition [15].

Table 3 shows number of filtered breaths. It can be seen that PSV and SIMV modes have higher number of breaths removed. Patient 3 who was ventilated using SIMV mode has significantly high number of breaths removed compared to other patient and ventilation modes. However, Patient 3 was most developed infant with weight of 3400g, gestation age of 41.5 weeks and severe hypoxic ischemic encephalopathy and seizures. However, given the lack of patient numbers and data on other SIMV ventilation mode, it is hard to determine whether the ventilation mode is the cause for such large number of breaths removed. Patient 2 was on both PTV and PSV modes. When comparing PTV to PSV modes for this patient, it can be considered that PSV mode results in higher incidence of filtered breath.

## 4.2. Cohort Elastance and Resistance

A single compartment lung model is used with clinical data to capture respiratory mechanics in the NICU patients. Model fit error (MARD) was 5.7 [5.2 – 6.3]%. Overall results were consistent across weight and a known therapy directly affecting elastance for a smaller number of infants in these subgroups. Thus, based on this first analysis, the model can be used without further alteration to

Equation (1) to estimate clinical breath-to-breath lung mechanics, specifically, elastance and resistance.

Elastance and resistance values across all conventionally ventilated patients are given in Table 5. Elastance differed significantly within and between patients. Elastance was also found to differ significantly across periods as short as 30 seconds (~30 breaths) due to commonly occurring increases in PIP, as shown in Fig. 7 and Fig. 8. Elastance can be approximated by change in pressure over change in volume. Thus, a doubling in PIP, with no change in tidal volume, will result in a doubling of elastance for that breath. This outcome is clearly seen in Fig. 9, where elastance changes with increases in PIP, while inspired tidal volume remains roughly the same. These increases in elastance may reflect periods of patient relaxation/weakness with no spontaneous breathing, or clinical interactions compressing the thorax, muscle tension, or crying. Unfortunately, all these potential observations were not directly recorded at the bedside, and thus remain to be confirmed.

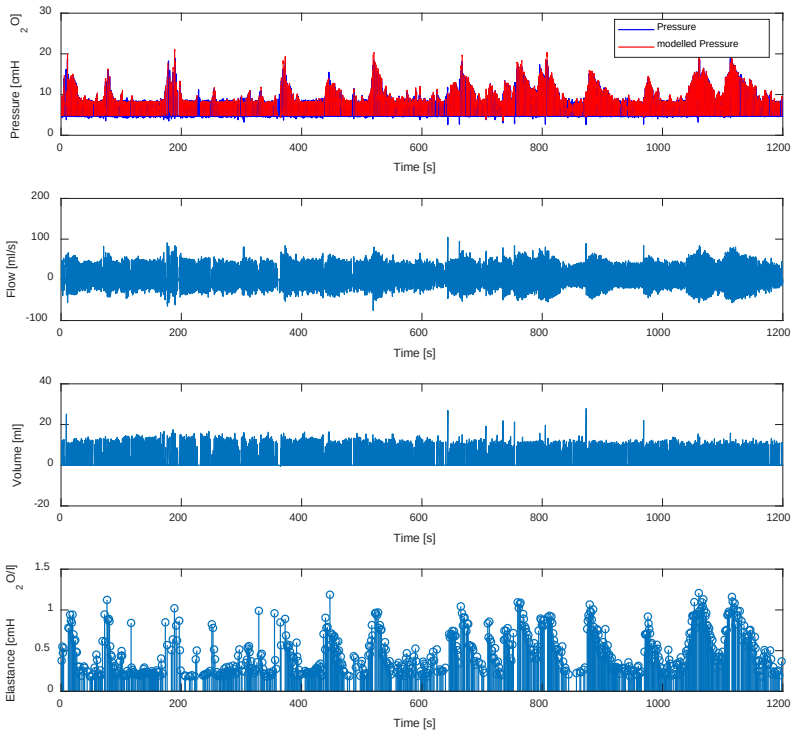


*Fig. 7. Raw data from 20minutes of ventilation in Patient 4 showing significant and periodic increases in PIP.*

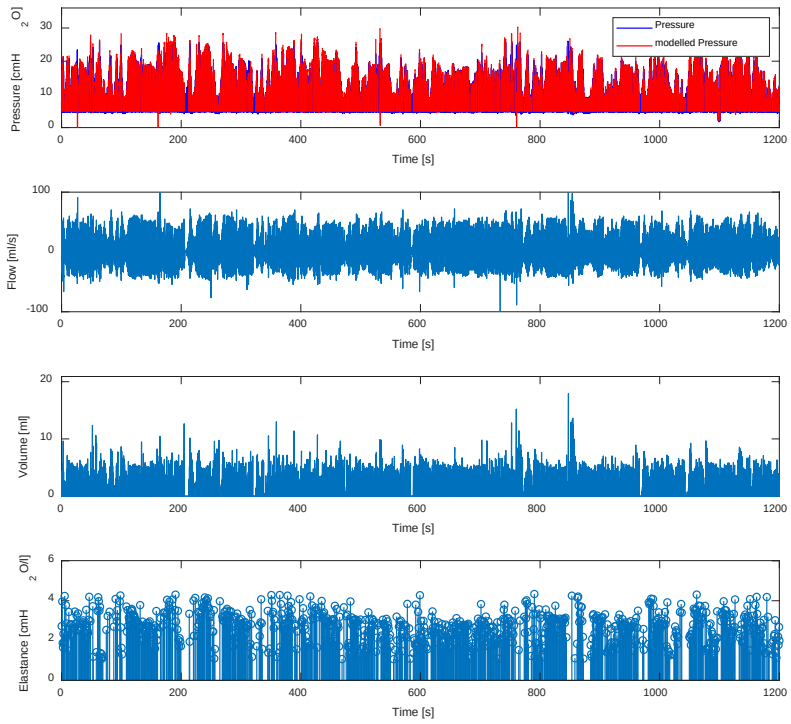


*Fig. 8. Raw data from 20 minutes of ventilation in Patient 9 showing significant and periodic increases in PIP.*

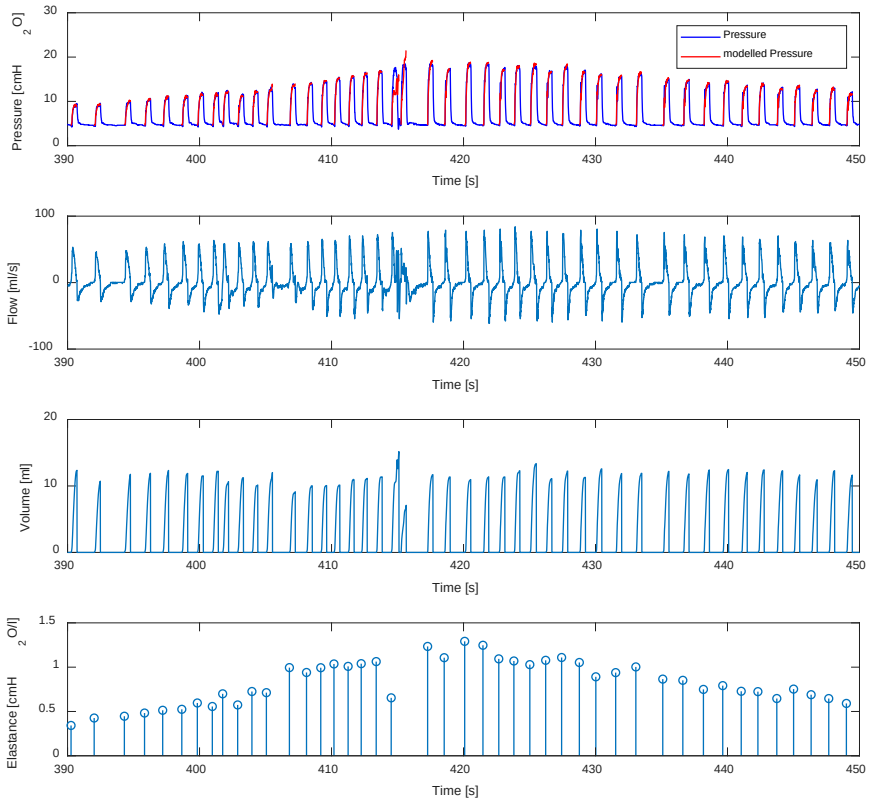


*Fig. 9. PIP increase and decrease over period of 60 seconds for Patient 4 in hour 8 of recording.*

Underlying intra-patient variability is large. As shown in Table 5, both intra- and inter- patient elastance ($E_{rs}$) differs largely over a 24 hour period. Large inter-patient variability is expected, as patients have different birth weights degrees of prematurity and clinical diagnoses and co-morbidities. However, the observed intra-patient elastance ($E_{rs}$) is shown to be unexpectedly variable, in comparison to adult MV [46].

Some patients were observed (Table 5) to have zero model-fit resistance ($R_{rs}$ = 0) due to the fact that the $\Delta P_{ETT}$ term captures the main contribution to resistance without any additional requirement for an additional resistance term. For this reason, resistance values shown in Table 5 are all relatively small or effectively zero. This result may be due to the assumed ETT length. A shorter length than assumed, if used, would have lower $\Delta P_{ETT}$ and thus it would capture lower resistance pressure drops. Equally, the Jarreau equation approximation used in $\Delta P_{ETT}$ in Equation 2 could be too large in some cases [37]. However, as $R_{rs}$ is constrained to change more slowly than elastance, it does not significantly affect trends in $E_{rs}$

## 4.3. Subgroup Analyses

Patients who received surfactant treatment had lower specific elastance (99% CI difference in medians: -0.49 [-0.48 -0.48] $cmH_2O.kg/ml$) compared to those that did not (Patients 5 & 8 vs Patients 2, 3, 4, 6, 7, 9, & 10) with $p \leq 0.01$. This result matches expected behaviour as surfactant lowers the surface tension, thus lowering the pressure required to keep alveoli and airways open [6,47,48].

Elastance decreased with increasing patient weight. This result reflects the fact that all patients are receiving the similar PEEP levels with similar driving pressure. Therefore, increases in tidal volume (with increasing in weight) would decrease elastance and thus, this result is expected [40]. Equally, the more premature the infant, the less developed the lung [5,49], with lack of surfactant production and fewer underdeveloped alveoli [45], and an overall lower body. Thus, the model effectively captures this expected physiological difference, as desired, demonstrating its ability to assess underlying pulmonary mechanics in this cohort.

## 4.4. Elastance and Resistance Comparison to Literature

Bhutani et al. (1988) used the single compartment model to fit specific compliance to data from 22 neonates [18]. The specific compliance median IQR for Bhutani et al. (1988) was 0.40 [0.34 - 0.57] $ml/cmH_2O/kg$ [18]. The specific compliance median IQR for our study was 0.61 [0.42 - 0.95] $ml/cmH_2O/kg$. The median and range of IQR for specific compliance for this study is slightly higher than the results from Bhutani et al (1988), of the same order of magnitude with overlapping ranges.

There are several different factors that may cause the slightly higher results in this study. Bhutani et al (1988), performed their analyses in 1988 using external pneumotachometer and pressure transducer, and size of the data was limited to 20-40 breaths per patient in comparison to this study, where ventilator data was retrieved with ~20,000 breaths per patient in this study. Patient weight is higher in Bhutani et al (1988), with lowest weight being 1.51 kg, in comparison to 0.81 kg in this study, so per our results in Fig. 6, this lower elastance for the Bhutani et al (1988) cohort is expected. Other factors such as respiratory rate and ventilator mode also differed.

### 4.5. Limitations

This study has small patient numbers (n=9), but very large numbers of recorded breaths (535,428 breaths). After removing asynchronies from all potential cases, 422,475 (79%) breaths were successfully fit using the single compartment model with ETT compensation term (Equation 1). Overall, the results indicate the model captures fundamental, underlying patient-specific elastance and resistance within these limitations.

The results from subgroup analysis also provide preliminary indication the model captures expected clinical outcomes. This latter point is critical for any model used in clinical monitoring or care. This is a proof of concept paper to apply model-based method to clinical infant data to assess underlying pulmonary mechanics and therefore the small number of patients was deemed less important than the very large number of breaths (422,475) captured for analysis.

Patients have different lengths of recording period and different number of breaths used in analyses. As described in methods, some infants had their recording cut short due to technical difficulties. However, given that the minimum number of breaths used per patient is 10,000 breaths there are sufficient number of data for this analyses. Comparing different subgroup with widely different number of breaths does not change the results either as the minimum of 60,000 breaths were present per subgroup.

### 4.6. Comparison to adult MV

Compared to elastance values of adult ICU patients [15,36], neonates have significantly higher elastance. This result confirms that neonates cannot be treated like small adults in managing MV. It also suggests they have different lung mechanics [50]. However, the underlying model appears to translate cohorts well. Neonates have a high spontaneous breathing or clinical interaction affecting breaths (~21%). Infants also have high intra- and inter- patient variability. Such behaviour is different in comparison to adults as adult ICU patients are sedated [31,51–54].

## 4.7. Future Work

Future work is required to use model-based method to capture patient-specific lung mechanics in NICU clinical settings in real time. CURE Soft [24] allows monitoring of patient-specific lung mechanics in adult ICU in real time. CURE Soft can be modified to be used in NICU settings. 21% of the data were considered as asynchronous or severe spontaneous breathing effort. In adult patients, methods such as pressure reconstruction, allows adjusting asynchronous or spontaneous breath and be able to quantify them [27,29]. Therefore these methods can be implemented be able to apply model-based methods using the single compartment model to approach neonatal MV.

## 5.0. Conclusions

This study is the first-indepth (535,428 breath) study of NICU pulmonary mechanic quantifying neonatal elastance, which shows unique behaviours including major inter- and intra- and breath-to-breath patient variability. This study showed that there is asynchrony rate of 21% which other literature could not evaluate.

The model fit was good and captured the respiratory mechanics well in this cohort using $\Delta P_{ETT}$ term. This model was further validated by comparing the sub-cohorts with known differences in elastance, as well as comparison to adults and another NICU study.

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