Estimating patient-specific maximum recruitable volume in neonatal lungs

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Abstract: This research aims to improve mechanical ventilation therapy in the neonatal intensive care unit (NICU). Mechanical ventilation (MV) settings in this vulnerable cohort are currently clinically determined based on experience, estimation and patient response. Modelling the lung mechanics of each specific patient may aid as a setting guide for clinicians, and provide a deeper indication of patient status. This study presents a novel method for estimating the maximum remaining recruitable lung volume, V_m, of a neonate. Current methods for determining patient lung volume are invasive, costly and disruptive to care, so are not often performed. The method proposed is non-invasive and uses data readily available through bedside monitoring. An optimal V_m value was determined for each patient. When compared to patient mass, a strong linear relationship was determined. The variability of results reflects the inter-patient variability amongst this cohort and reinforces the need for patient-specific treatment solutions utilising novel, non-invasive metrics to provide better, more personalised care.

Keywords: Mechanical Ventilation; Respiratory Mechanics; Neonate; Lung volume; Non-Invasive; Patient-specific.

1.0 INTRODUCTION

Mechanical ventilation (MV) is a critical support therapy in the neonatal intensive care unit (NICU). It aims to maintain blood oxygenation and decrease the work of breathing for patients experiencing respiratory distress syndrome (RDS). Current NICU practices and treatment are highly variable (Wanger et al 2005 Gupta et al 2019; van Kaam et al 2010) due to a lack of clear insight into patient status and internal pulmonary mechanics (Gupta 2019). Optimal treatment is patient-specific and time-varying, as each patient has different requirements (Kim et al 2019; Kim et al 2020). Sub-optimal ventilation settings place the patient at risk of insufficient oxygenation, or ventilator induced lung injury, (VILI), which increase patient length of stay and cost, as well as reducing outcomes both directly and indirectly (Kneyber et al 2014; Albaiceta & Blanch 2011; Attar and Donn 2002; Gattinoni et al 2018; Chen et al 2018; Dreyfuss 1992; Major 2018).

A personalised care approach could better address variable ventilation requirements due to significant inter- and intra-patient variability (Sundaresan and Chase 2012; Morton et al 2019, Chase et al 2018). Current research approaches this problem by combining simple bed-side models with clinical data to create personalised and predictive models (Morton et al 2018; Morton et al 2019; Morton et al 2020; Langdon et al 2017; Langdon et al 2017; Sun et al 2020; Zhou et al 2021). However, virtually all of these models are focused on adult intensive care unit (ICU) patients, rather than NICU patients, where there are some significant differences (Sweet et al 2007; Brown and DiBlasi 2011).

The simplest pulmonary model describes the lungs as a single compartment where the airway pressure is a linear function of airway resistance and lung wall elastance (Bates 2009). This model was adapted to MV and altered to contain a time-variant lung elastance to optimise the peak end expiratory pressure (PEEP) in adult intensive care patients (Chiew 2011; Chiew 2015), and further adapted to successfully predict patient response at varying PEEP (Morton et al 2018; Morton et al 2019; Morton et al 2020; Zhou et al 2021). Kim et al adapted and applied the model to neonatal data to find and describe patient-specific elastance in a cohort of premature and term infants (Kim et al 2019; Kim et al 2020).

The maximum recruitable volume of the lung, V_m, is a pulmonary parameter with significant clinical and modelling implications for tidal volume and PEEP, and their relationship with VILI. In adults, V_m = 1L as an upper limit is a good approximation in highly predictive models of PEEP change (Morton et al 2018; Morton et al 2019; Morton et al 2020). However, because neonatal gestational age and weight can vary significantly, the maximum volume is also expected to vary. Thus, maximum recruitable lung volume is expected to be much smaller in infants, with more interpatient variation due to the variation in infant size, and the resulting lung development and maturity, which prevents the choice of a fixed parameter and could significantly impact model performance in monitoring and guiding care.

This research presents the non-invasive model-based identification of this patient-specific V_m in neonates, with the added goal of assessing its variability over time and in relation to patient specific variables. This outcome would improve clinical care by providing clinicians with an internal parameter to assess patient status such as severity of disease, alveoli development, and response to treatment, and act as an indicator for setting tidal volume. Knowledge of patient-specific parameters and their relationship to

patient characteristics will improve understanding of neonatal pulmonary mechanics in the context of care.

2.0 METHODS

2.1 Patients and data

This research presents a retrospective analysis using observational data collected from N=9 patients at the Christchurch Women's hospital neonatal intensive care unit (NICU). The neonates received invasive mechanical ventilation (MV) treatment using a SLE5000 ventilator (SLE Ltd, UK). The ventilation was in the form of patient triggered ventilation (PTV) with the SLE specific Targeted Tidal Volume (TTV) mode. Airway pressure and flow data was observed and collected at a sampling rate of 125 Hz for up to 24 hours under informed parental consent, while receiving standard, clinically determined treatment. This trial was approved by the New Zealand Northern B health and disability ethics committee (study ref: 16/NTB/16).

Patients were ventilated at a constant PEEP, with varying breath-to-breath driving pressure and tidal volume as specified by the ventilation mode. Pressure was measured in cmH2O and flow was measured in L/min, these units remain consistent throughout the study.

The patients were neonates, and thus too small to sedate. The data collected showed significant breath-to-breath variability in peak inspiratory pressure (PIP) and inspired tidal volume. This variability is asynchrony and spontaneity in breaths, and is likely a result of unsedated ventilation. Asynchrony occurs when the patients' respiratory effort is out of phase with the ventilator, resulting in uncharacteristically high or low captured data, and spontaneous breathing occurs when the baby cries, coughs, is interacted with by the clinician, or during other movement which causes the baby to vary from a regular breathing pattern, resulting in interrupted or elongated breaths. Breaths that were not standard were removed during the data processing stage.

2.2 Model and Identification

The commonly used single compartment model parameterizes lung mechanics in terms of the constant values elastance, E, and resistance, R, (Bates 2009).

$$P(t) = EV(t) + RQ(t) + PEEP \quad (1)$$

Where $P(t)$ is ventilator delivered airway pressure (cmH2O), $V(t)$ is tidal volume (mL), $Q(t)$ is flow (L/min), and PEEP is positive end expiratory pressure.

A recent study in sedated adult ICU patients replaced the constant E and R terms from Eq. (1) with basis functions to capture non-linear changes in elastance with recruitment and distension, and changes in resistance with laminar and turbulent flow (Sundaresan and Chase 2012; Morton et al 2018; Morton et al 2019; Morton et al 2019; Zhou et al 2021). This model can be applied to neonates, where the elastance term describing lung distension can be removed because neonates are ventilated at a low pressure and lung distention is very unlikely (Kim et al 2019; Kim et al 2020). In addition, all resistance terms can be replaced with the resistance of the endotracheal tube, because in this type of invasive ventilation, the endotracheal tube provides much more resistance than the airways.

The entire model is thus defined:

$$P(t) = E_1\varphi_1 V(t) + \Delta P_{ETT} + PEEP \quad (2)$$

The elastance component in this instance encompasses all respiratory elastance. Its basis function, φ_1, is defined:

$$\varphi_1 = \left(1 - \frac{V_t}{V_m}\right)^2 \quad (3)$$

Where V_t is tidal breathing volume for a breath and V_m is the maximum possible tidal volume to be identified and analysed in this study.

The pressure drop across the endotracheal tube (ETT) is defined (Jarreau et al 1999):

$$\Delta P_{ETT} = L(0.0203D)^{-4.25}Q(t)^{1.5} \quad (4)$$

Where L and D are the length and diameter of the ETT.

2.3 Data Processing and Analysis

The first step in this analysis removed asynchronous breaths and separated inspiration and expiration data. Inspiration was defined by positive flow, while expiration was defined by the start of negative flow. Because of small pressure/flow fluctuations in the pause between expiration and inspiration, additional criteria for the onset of inspiration required an increase in pressure above PEEP + 1 cmH2O, a positive average flow over inspiration, and inspiratory time greater than 0.3 seconds. Breaths not meeting these criteria were typically asynchronous or partial breaths, and were removed.

The lung mechanics model in Equations (2)-(4) was applied to inspiratory pressure and flow data for every breath, and a breath-to-breath lung elastance, E_1, was identified. A filter was applied to remove breaths resulting in (non-physical) zero valued elastance, or a tidal volume less than 0.25, or greater than 1.75, times the ventilator target tidal volume. These cases point to additional asynchrony or atypical breaths missed in the initial filtering of breathing data, and are well outside the range of typical and intended volume delivery.

2.4 Identification of V_m

Lung elastance, E_1, in this model, captures the passive tissue stiffness characteristics of the lung, airways, and chest wall (Chiew et al 2015). Breath-to-breath, these tissue characteristics are not expected to vary significantly. Thus, when applying the overarching model to data in which both the PIP (peak inspiratory pressure) and tidal volume vary breath-breath, it is expected E_1 will remain constant.

However, if V_m is changed from an overall population constant, the value of E_1 changes and can be much more variable across breaths. This variability does not match the assumption of relatively constant elastance across limited sets of breaths and relatively very short times. Thus, this study hypothesises the optimal value of V_m is defined by having the most stable, or least variable identified E across all breaths for a patient at a given driving pressure.

In particular, one complicating factor in this analysis is breath-to-breath variability in patient effort, and the negative inspiratory pressure it causes, resulting in variability in PIP. This patient effort is not directly accounted for in the passive mechanics model, and consequently, the identified elastance value, E, is affected. To account for the effects of spontaneous breathing, breaths are binned by driving pressure, in bins of 1 cmH20, where driving pressure is $P_{drive} = PEEP - PIP$. If driving pressure is assumed to be correlated with inspiratory drive, breaths with similar driving pressure can be assumed to have similar underlying inspiratory drive and overall lung mechanics for the purposes of this analysis.

Data from the most common driving pressure of each patient was iteratively applied to the lung mechanics model of Equations (2)-(4), varying V_m = 1-35 mL in steps of 1 mL. Per the Hypothesis, the optimum V_m is identified as the value where E is the least variable across breaths for all tidal volumes for a patient. The lognormal distribution of breath-to-breath elastance was assessed at each trialled V_m, and the value with the lowest multiplicative σ^*term was considered the optimal V_m . Plots of E vs tidal volume show a flat line at the optimal V_m (Figure 1).. The slope of the line of best fit was also calculated, to check the lowest variance represented this approximately horizontal line. Finally, V_m is plotted against patient weight to assess whether higher weight and thus greater maturity is related, as expected, to a larger lung volume.

3.0 RESULTS

A total of 205.9 hours of data was processed. The breath separation filter separated this data into inspirations and expirations, while filtering out unfit breaths. A total of 368,438 out of 535,428 breaths were kept (68%) after filtering. A patient-specific V_m and associated average elastance was found for each patient.

Figure 1 displays the elastance plotted against the tidal volume of every examined breath for different values of V_m, for every patient. Figure 2 displays an expanded view of these same results for patient 7 (who was arbitrarily selected). New datasets are plotted in different colours for increments of V_m, and the optimal V_m value is plotted in black. The physical properties of the chest wall should not change on a breath-to-breath basis. Thus, the lowest elastance variance, and therefore the straightest E_1 vs V_t line indicates the most accurate V_m.

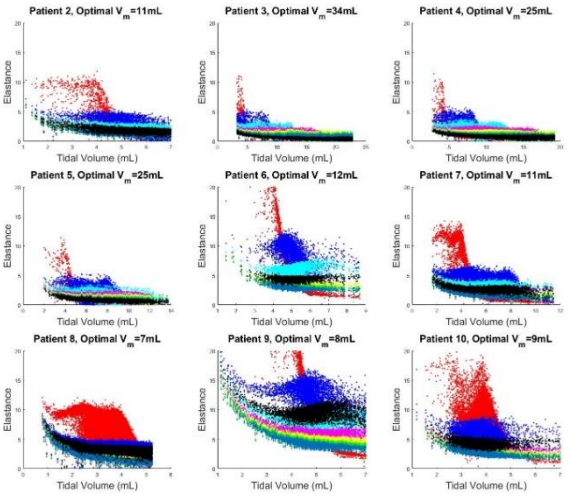

Figure 1. All results from all patients. Comparison of $E_1 - V_t$ curve as V_m is changed over selected values. Optimum V_m is plotted in black.

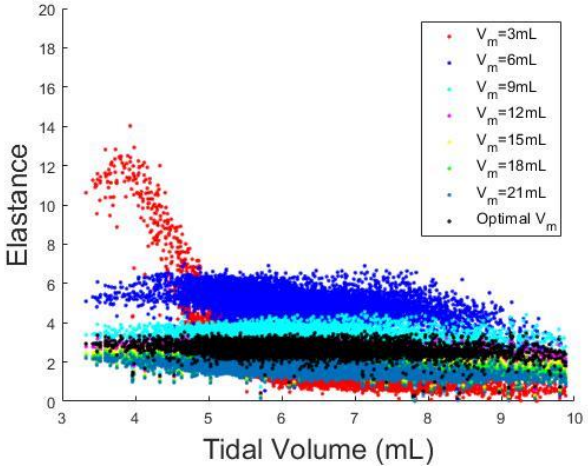

Figure 2: Patient 7 comparison of E_1-V_t curve as Vm varies over selected values in the range analysed. The optimal Vm is 11 mL and shown in black.

The maximum volume, V_m, found for each patient was compared to the patient-specific physical property of birth weight, shown in Figure 3. The results in Figure 3 confirm the expected strong linear relationship to weight (R^2=0.94).

These results additionally show the presence of sex differences in neonatal elastance, where males are typically less developed and therefore have lower elastance, conforming to previous studies (Kim et al 2018). Figure 3 also shows the values for V_m range from 7 mL to 34 mL, where this 4x range is similar to the weight range, further validating the results in Figure 1.

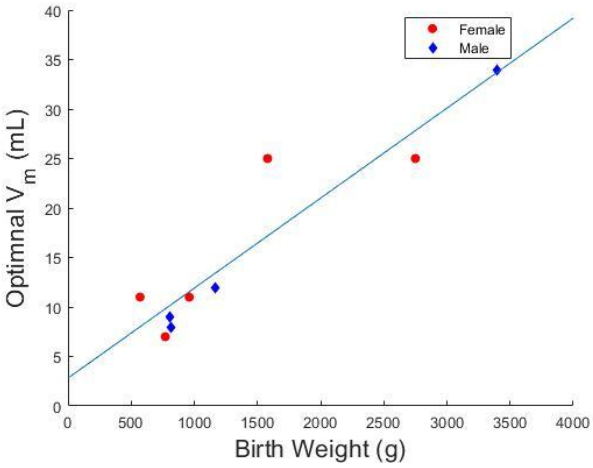

Figure 3: All patients, comparison of V_m and weight, differentiated by sex. A strong linear relationship holds $R^2 = 0.87$

4.0 DISCUSSION

4.1 Identification of remaining recruitable lung volume, V_m

The well-known single compartment pulmonary model was applied to active breathing for 368,438 breaths in 9 neonates. A novel patient-specific remaining maximum recruitable volume, $V_{m.}$, was identified parametrically. The identification of this value also results in the identification of a stable, consistent breath-to-breath lung elastance, E, in Equation (2) for equivalent driving pressure in the presence of spontaneous breathing effort. Overall results enable non-invasive estimation of remaining recruitable lung volume in mechanically ventilated premature infants.

The optimum V_m was found by observing the relationship between elastance, E_1, and tidal volume, V_t, at a range of V_m values. It is assumed elastance is a function of lung and chest wall tissue properties, and thus should not typically vary breath-to-breath. At non-optimal V_m the E_1-V_t curve is nonlinear, implying significant breath-breath change in elastance. As V_m nears its optimal value, the curve linearizes and flattens, so the magnitude and gradient decrease until a saturation point is reached. The optimum V_m is the value giving the most stable and flat E_1-V_t curve. The flatness of the curve is assessed using lognormal variance (σ^*) of patient-specific and breath-to-breath elastance values identified, where a lower variance relates to a flatter curve in these plots, as illustrated in Figures 1 and 2.

Optimum identified V_m is plotted against weight for each patient in Figure 3, producing a strong linear relationship (R^2=0.87). The relationship between the lung volume and body size in infants, children and adults is relatively constant (Cook et al 1958) and Rao et al shows, experimentally, lung volume in infants increases linearly with body length (Rao et al 2010). The modelled results thus match relationships found in the literature and which are well known in the field, further validating the physiological relevance of the optimum V_m values identified from clinical data in this study.

Methods of quantifying neonatal lung volume have previously been developed. Plethysmography is a common method for finding lung volume in both children and adults (Coates et al 1997; Edberg et al 1991). Standard plethysmography requires patient co-operation and is not suitable for infants. However, the equipment can be adapted for a sleeping or sedated infant by fitting them with a face mask or using a plethysmograph which does not enclose the infant's face (Edberg et al 1991). Overall, this method is not clinically feasible at the bedside, and not compatible with MV life support therapies in this fragile cohort. It also cannot provide any form of clinically relevant continuous monitoring, as the model-based method presented can.

Another method previously used to assess infant lung volume is nitrogen washout, where the patient is ventilated with 100% oxygen for one or several breaths, and the concentration of residual nitrogen expired is used to determine the functional residual capacity of the lung (Sjöqvist et al 1991; Gerhardt et al 1985). Other methods are helium dilation and tomography (Wanger et al 2005). All of these existing methods for finding infant lung volume are invasive, disruptive to normal clinical care, and require additional resources or equipment, and are thus not regularly employed in clinical practise. The novel model-based method of identifying infant lung volume presented in this paper is non-invasive and requires no additional resources beyond monitoring the data obtained during standard mechanical ventilation. It can also quickly adapt to new data, allowing the clinician to monitor patient progress without disrupting care.

4.2 Limitations

This study has only nine participants due to the difficulty in recruiting neonatal patients for research trials. However, a large amount of data was recorded from each patient. A total of 482,379 breaths were fit to the pulmonary model in this study, enabling sufficient data density to establish trends in V_m and E_1

The model was developed to assess the underlying lung mechanics of an adult during passive breathing. However, in this study, it is applied to active, spontaneously breathing patients resulting in large fluctuations in the time, volume and pressure of each breath. The difference is accounted for by removing obvious asynchronies and separating the data by driving pressure. Differences in driving pressure due to changes in spontaneous breathing effort typically result in elastance scaling, without changing the shape of the $E_1 - V_t$ relationship. Thus, selecting a single driving pressure in this analysis enables comparison of 'like' breaths in terms of breathing effort. Only the most common driving pressure of each patient was analysed, but further research should examine a range of driving pressures in the available data.

No other methods of lung volume determination were carried out during the trials, so there are no measured volume values to compare to the computed results. Volume

measurement tests were not considered for this study because they are invasive, disruptive to care, and were unnecessary for patient care, thus increasing patient burden. The computed results have been compared to other patient metrics, namely weight, and returned a very strong linear correlation ensuring the results are in reasonable agreement with other common measures.

4.3 Clinical implications

This research presents a new non-invasively determined lung mechanics measurement, which can be regularly updated and monitored in real time. The maximum recruitable volume of the lung could be used as a guide for the targeted tidal volume, particularly when there are changes in MV settings such as PEEP. In this study, the TTV applied to a patient during ventilation averaged 43% of their computed V_m and all values were between 30-50%. This range shows the variability of standard care, but also shows there is a possible relationship between V_m and V_t. Further research is required to determine whether a generalised ideal TTV to V_m ratio exists.

Lung volume in an infant may aid in determining the progress of lung development or presence of disease (Delgado et al 2020, Kavvadia et al 1998). Lung volume grows linearly with body size in infants and toddlers (Cook et al 1958; Rao et al 2008), the value of V_m found here conforms to this relationship as seen in Figure 3. Individuals who vary significantly from this linear relationship may have additional pulmonary issues in their pre-term development. Knowledge of patient-specific parameters could aid in diagnosis and monitoring of pulmonary issues.

The V_m value can be updated regularly as new data is presented, or PEEP is changed. An adaptive filter could be developed to display the progression of V_m over time or weight, giving a quantifiable value to assess the efficiency of ventilation in a clinical setting. It may thus present new and novel clinical monitoring opportunities.

This research, and the continued development of the pulmonary model applied to various demographics of patients and modes of respiratory care, aims to contribute to the development of a generalisable virtual patient for this cohort. A virtual patient is a computer-based model representation of an individual real patient (Morton et al 2018; Chase et al 2018; Zhou et al 2021). A virtual patient is programmed with models, such as the one presented in this study (Equation 2), identified with patient data to find patient specific parameters, and forward predict patient response to treatment to safely guide and optimise care. The method of finding V_m could be used in a clinically applied virtual patient to predict patient response to treatment before it is applied, allowing the clinician to select the best ventilation settings for the individual patient.

5.0 CONCLUSIONS

This retrospective observational study estimated a previously unobtained parameter of neonatal pulmonary mechanics, which cannot be readily or non-invasively measured. The remaining maximum recruitable lung volume, V_m, was identified in 9 neonatal patients, with values ranging from 7mL-34mL, which increased with mass (R^2 = 0.87). The large range in identified values reflects significant and expected inter-patient variability in lung mechanics, highlighting the need for patient-specific MV approaches. Clinically, this value could provide further useful information to guide selection of ventilator settings and tidal volume targets.

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