Mechanically Ventilated Premature babies have sex differences in specific elastance: A pilot study

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Abstract

Objectives: A pilot study to compare pulmonary mechanics in a NICU cohort, specifically, comparing lung elastance between male and female infants in the neonatal ICU (NICU).

Hypothesis: Anecdotally, male infants are harder to ventilate than females. We hypothesise that males have higher model-based elastance (converse: lower specific compliance) compared to females, reflecting underlying stiffer lungs.

Study design: A clinically validated, single compartment model is used to identify specific elastance (inverse of specific compliance) and resistance for each breath. Specific elastance accounts for weight differences when comparing male and female infants. Relative percent breath-to-breath variability (%ΔE) in specific elastance is also compared. Level of asynchrony was determined.

Patient-subject selection: 10 invasively mechanically ventilated patients from Christchurch Women's Hospital.

Methodology: Airway pressure and flow data from 10 invasive MV infants from Christchurch Women's Hospital Neonatal Intensive Care Unit, New Zealand was prospectively recorded under standard MV care. Model-based specific elastance and resistance are identified for each breath, as well as relative percent breath-to-breath variability (%ΔE) in specific elastance.

Results: Male infants overall had higher specific elastance compared to females infants ($p \leq 0.01$), with median [interquartile range (IQR)] for males of 1.91[1.33-2.48]cmH2O.kg/ml compared to 1.31[0.86-2.02]cmH2O.kg/ml in females. Male infants had lower variability with %ΔE of -0.03[-7.56 – 8.01]% versus female infants of -0.59[12.56 – 12.86]%. Males had 14.75% asynchronous breaths whereas females had 17.54%.

Conclusion: Overall, males had higher specific elastance and correspondingly lower breath-to-breath variability. These results indicate male and female infants may require different MV settings, modes and monitoring.

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Consent

This study was an observational study where no intervention procedure was performed. All patients were ventilated and treated on standard care practice. Therefore parental informed consent was obtained prior to data recording. Ethical approval was granted by the New Zealand Northern B Health and Disability Ethics Committee (ref: 16/NTB/16).

1.0. Introduction

Respiratory distress syndrome (RDS) commonly occurs in neonates due to premature birth and lack of surfactant [1,2], and is a major cause of morbidity and mortality among newborns [3–7]. Clinically, RDS is treated using MV and postnatal surfactant therapy [1,2,5]. Surfactant therapy can improve mortality and morbidity [1,8]. In particular, it reduces the surface tension inside lung alveoli, helping prevent alveolar collapse and mitigating the impact of RDS [9].

Newborn male infants have a higher incidence of RDS, morbidity, and mortality than females at similar birth weight [3,10]. In utero, male fetuses are less developed than females at the same gestational age by 1.5-2 weeks [3]. Thus, premature male infants produce less surfactant in comparison, and are more likely to receive invasive MV [11]. Anecdotally, male infants are harder to ventilate, but no studies have yet quantified any differences in lung stiffness or mechanics to support this observation.

It is well documented that model-based methods can be used to identify patient-specific lung mechanics [12–14] and enable better understanding of patient specific condition using existing bedside measurements. A simple model comprising of a single compartment has been used to describe lung mechanics in adults [12,14,15], and is currently used in a MV trial to guide PEEP selection [14]. In this model the lungs are treated as a single volume expanding against a spring-stiffness with pressure losses in the airways due to flow resistance. This model has also been applied to retrospective neonatal MV data to describe lung elastance and its differences between infants and changes over time.

This study is a pilot study which analyses MV data to quantify patient-specific elastance, and inter- and intra- patient variability between male and female neonates. The model is fit to clinical data from 9 NICU infants of varying prematurity and condition who were invasively ventilated. Specific elastance is used to factor out weight and size, thus allowing fairer comparison between infants of different maturities. Male infants have stiffer lungs [16] and are thus hypothesized to have higher model-based elastance and lower intra-patient variability. This analysis of specific elastance and its variability aims to provide further insight

on differences in response between sexes in NICU MV. Also the level of asynchrony is determined.

2.0. Methods

2.1. Patient Data and Data acquisition

Airway pressure and flow data from 10 invasively ventilated patients was collected from Christchurch Women's Hospital NICU during an observational and non-interventional study with informed parental consent. Up to 24 hours of MV data per patient recording session was recorded under standard care. Eligibility criteria included the expectation MV would continue for the entire 24 hours, and clinical equipoise. Ethical approval was granted by the New Zealand Northern B Health and Disability Ethics Committee (ref: 16/NTB/16).

MV modes and settings were clinically determined as part of standard care. Patients received either conventional ventilation (CV) or high frequency oscillatory ventilation (HFOV) on a SLE5000 neonatal Ventilator (SLE, UK). Most patients received Patient Triggered Ventilation (PTV), although some were treated with more than one mode. Targeted Tidal Volume (TTV) is an "add on" specific to SLE, where pressure control is adapted breath-to-breath to improve attempts to meet tidal volume targets.

None of the infants were sedated over the trial period, though some received morphine, which can have a sedative effect [17]. In cases where an infant was re-intubated after weaning 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. In this paper, only conventional ventilation (CV) data is analysed, as HFOV exhibits very different dynamics with different time constants [18]. Therefore, data from Patient 1, who only received HFOV, was excluded. Patient characteristics and relevant demographic data are shown in supplement material 1.

Patient data was collected using a computer with MediCollector software (MediCollector, USA) from a Philips Healthcare MP70 bedside monitor (Philips Healthcare, Netherlands) connected via a M1032A Vuelink respiratory module (Philips Healthcare, Netherlands) to the SLE5000 ventilator (SLE, UK). Data was sampled at 125Hz, the output frequency from the ventilator. Further details of data acquisition can be found in preliminary study [19].

2.2. Model Fitting

A linear single compartment model with Jarreau's equation for pressure loss across endotracheal tube (ETT) is used to estimate patient specific lung elastance and resistance [12,15,20]. The equation used has been previously defined in NICU populations [19]. The model is fit using linear regression to every breath to find inspiratory elastance (E_{rs}) and airway resistance (R_{rs}). The linear single compartment model with extra added term to compensate for pressure loss across ETT is defined:

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

Where Q and V are the clinical inputs of flow (ml/s) and volume (ml) respectively, and P_{aw} is the resulting airway pressure. Patient specific parameters are lung elastance, E_{rs}, (cmH_2O/ml) and airway resistance R_{rs}, (cmH_2Os/ml), where E_{rs} captures the degree of stiffness of the lung, and R_{rs} pressure losses in the airways and lung units due to flow. E_{rs} is the inverse of compliance. ΔP_{ETT} is used to capture the pressure drop over the ET tube which is defined according to Jarreau's equation [19,20].

2.3. Male Infants Vs Female Infants

Specific elastance based on infant weight is used to account for patient weight as a marker for maturity. It is useful when comparing infants with large variations in weight as larger infants typically have larger (and more developed) lungs. Larger lung volumes result in different apparent elastances for a given underlying tissue stiffness [19,21]. Specific elastance ($E_{specific}$) is the reciprocal of specific compliance, which is a metric used to measure the intrinsic elasticity of the lung tissue independent of lung volume, as previously described [19,22].

In this study, specific elastance ($E_{specific}$) and airway resistance (R_{rs}) are compared in male and female infants. Females are hypothesised to have lower specific elastance as male infants are typically sicker and less developed [3,4,6]. Resistance is hypothesised to be similar between males and females.

Statistical comparisons for specific elastance and resistance are made using non-parametric statistics due to non-Gaussian distributions and large data sets (422,475 breaths total) [23]. To assess the overall central tendency of behaviour we analyse the 90% range of results for each infant. Bootstrapping medians was used as the most robust and fundamental means of evaluating statistical comparisons [23], Avoiding the problem of unrealistically low p-values that can arise when data sets used in more traditional comparison tests are very large (N > 10,000) [24].

Bootstrapping compared medians from 10,000 breaths with replacement, repeated 10,000 times. 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 $p \leq 0.01$. This choice of p value significance was made to be more conservative than $p \leq 0.05$, because of multiple comparisons [24].

2.4. Variability Analysis and Comparison

Preliminary analysis showed large variability between and within patients. This underlying inter- and intra- patient variability is quantified using percentage difference in breath to breath specific elastance (%ΔE). The percentage difference in elastance is determined by current specific elastance (current breath, $E_{specific}(N)$) and forward specific elastance (next breath, $E_{specific}(N+1)$), defined:

$$\%\Delta E = \frac{E_{Specific}(N) - E_{Specific}(N+1)}{E_{Specific}(N+1)} \times 100 \quad (2)$$

The standard box plot is used to show the overall distribution of specific elastance and its variability for each patient. This plot clearly compares patients and sexes by overall distribution.

The variability in the cohorts of male and female infants is quantified. It is hypothesised male neonates will have much lower intra- and inter- patient variability, as stiffer lungs are harder to inflate and less responsive to small changes in flow-volume input. Overall variability is calculated using the interquartile range (IQR; 75^{th}-25^{th}) of specific elastance and its percentage change over the distribution. As an indication of the relative size of the variability between patients, the IQR is also divided by the median.

2.5. Asynchrony

Ventilator asynchrony occurs when the particular ventilator mode and settings do not match patient breathing efforts. High incidence of ventilator asynchrony can lead prolonged MV duration [25].

The level of incidence of patient ventilator asynchrony was quantified, and the percent asynchronous breaths calculated per patient. The asynchrony incidence between male and female infants are compared. The purpose of this comparison is to show the patient-ventilator interaction while comparing the difference in sex. This result would give more context to how a patient is responding to MV.

3.0. Results

3.1. Male infants Vs Female Infants

Patient clinical data are shown in supplement material 1. Male infants had higher specific elastance compared to females, as seen in Figure 1 and Table 1. The median [IQR] of specific elastance for male infants was 1.91[1.33-2.48] $cmH_2O.kg/ml$ and higher than female infants at 1.31[0.86-2.02] $cmH_2O.kg/ml$ ($p<0.01$). The median [IQR] resistance was 0.00[0.00-0.02] and 0.02[0-0.05] cmH_2Os/ml for males and females, respectively ($p<0.01$).

The higher elastance in males matches the hypothesis as male infants are anecdotally harder to ventilate [6]. The difference in resistance, while statistically significant, is not likely clinically significant. Equally, it could reflect increased resistance in more developed lung structures with a greater number of branches and alveoli, if female infants are more developed in comparison to males.

3.2. Variability

Variability within and between patients is large. The median [IQR] for specific elastance and breath-to-breath %ΔE of each patient and sex is shown in Table 1. The median [IQR] of breath-to-breath %ΔE across all patients is -0.20[-9.40 - 9.63]%, with absolute IQR range of 19.03% indicating a progression towards lower elastance over time. The minimum per-patient IQR range is 10.96% and the maximum is 67.97%, showing large intra-patient variability, as well as large inter-patient variability in this metric.

Figure 2 shows box plots of specific elastance for all patients. Figure 2 and Table 1 show Patient 3 has the lowest median specific elastance while Patient 5 has the narrowest IQR range for specific elastance as seen in Figure 2 but Patient 6 has the lowest IQR range/Median($E_{specific}$). The per-patient IQR range as a percentage of the median value (IQR Range/Median($E_{specific}$)) also varies considerably.

Figure 1 and Table 1 also show males have consistently higher specific elastance than females, barring Patient 3 who was near term and relatively large. They also show the hypothesized lower intra- patient variability for males versus females, seen in narrower IQR boxes in Figure 2 and values in Table 1. Excepting patient 3, the same holds for the IQR range of %ΔE, breath-to-breath.

Figure 3 plots median specific elastance against the IQR range of %ΔE per patient, assessing breath-to-breath variability as a function of specific elastance. This plot shows a hyperbolic relationship with $R^2 = 0.73$. Eliminating the outlier at (0.5, 68%; Patient 3 [male]) changes to $R^2 = 0.71$. This relationship shows that the median specific elastance and IQR range of breath-to-breath %ΔE per patient are strongly related. It also shows as median specific elastance rises, breath-to-breath (%ΔE) variability falls. This plot shows variability in a function of E_{rs}, not sex. It just happens that males have higher E_{rs}.

3.3. Level of Asynchrony

Asynchronous and outlying breaths were detected. Using criteria shown in Figure 4, a consort diagram shows breaths as either asynchronous and/or outlying. Breaths filtered based on perturbations from a well-accepted model of typical lung dynamics and the relationship between flow-volume and pressure. These breaths total up to 112953 (21%) of the total 535428 breaths.

The percentage asynchrony per patient is shown in Table 2. Patient 3 was highly asynchronous. This may be a function of his clinical diagnoses (seizures) or the fact that he was ventilated using SIMV mode, whereas other patients were on PTV. Male infants (excluding Patient 3) have lower incidence of asynchrony in comparison to female infants, although this is not likely to be statistically significant. The chi-squared test is inappropriate

here because large data sets results in p of 0. Patient 6 had lowest occurrence of ventilator asynchrony with 11.24% and Patient 4 had the largest asynchrony with 19.13%.

4.0. Discussion

4.1. Specific Elastance

Males have higher specific elastance compared to females ($p \leq 0.01$). This behaviour matches the hypothesis, and is supported by anecdotal and literature evidence that male infants are harder to ventilate and tend to have longer ventilation period compared to females [4,26]. Thus, a single compartment model is able to quantify established trends, and capture MV behaviour in neonates. Patient 3 was an outlier, in that it was a male with the lowest overall elastance. However, it was a full-term infant with weight of 3400g, and is likely more mature in terms of lung structure and function. This infant was also ventilated for reasons unrelated to lung function due to severe hypoxic ischemic encephalopathy. Overall, these results match observations that male premature infants are less developed with stiffer lungs [4,16], which may require a different approach to MV for this cohort.

The results show an initial finding that male infants have stiffer lungs, creating a hypothesis for a larger, more controlled study. The authors feel this result would still hold true for larger and more controlled studies recruiting only preterm infants with similar weight and gestational age. In particular, such a study would exclude Patient 3 who was near term and much larger, but also reduced the apparent sex differences seen. Thus, from these results, we would hypothesize a larger controlled study would deliver the same differences with greater statistical power.

4.2. Variability

There was large intra- and inter- patient variability across the cohort. The lowest breath-to-breath IQR range of the percentage change in elastance (%ΔE) was 11%, and highest was 68%. The overall elastance distribution of breath-to-breath %ΔE varied. Breath-to-breath variability can differ significantly. Patient-specific elastance changes hourly, and breath-to-breath changes can be relatively large.

The results show male infants have higher specific elastance, but lower variability, as seen in the IQR range of $E_{specific}$ and breath-to-breath %ΔE. If excluding the more mature Patient 3, males have significantly lower IQR range/median values compared to female neonates (Table 1). This outcome is expected as male infants have higher elastance in the results, excepting Patient 3. Figure 3 indicates that variability in elastance in a function of median elastance, rather than sex. This makes sense as higher elastance means stiffer lungs, which are thus less responsive to pressure-flow inputs compared to lungs with lower elastance, and thus less likely to vary given similar ventilator settings.

In Fig 3, the hyperbola shape is chosen because this line does not cross zero, thus making physical sense. The correlation of determination (R^2 = 0.73) value does not change much if the outlying first data point is removed. It overall suggests that variability is primarily a function of median specific elastance. Such large distributions in variability across the patients shows the potential need to change MV modes more frequently. Equally, it may show a need for better MV modes to account for patient variability in the NICU environment.

4.3. Asynchrony

A total of 112,953 (21%) of breaths were counted as either asynchronous or significantly outlying, and are not representative of typical MV supported breaths. These 21% of breaths are either asynchronous, or breaths with relatively very large spontaneous breathing efforts, resulting in extreme elastance values or poor model fit to a well-accepted model. Infants are not cuffed or sedated during MV, although morphine is given, which has sedative effects [17]. Therefore neonates are more prone to ventilator asynchrony. Patient-ventilator asynchrony severely interfere with MV [25,27–29] and is associated with prolonged MV [25]. For this reason, it can be much harder to detect and/or reduce ventilator asynchrony in the NICU setting in comparison to adult ICU [25,28]. Neonates may thus require much closer and more frequent attention to ventilator settings and response for this reason as well to minimise asynchrony and further enhance patient-ventilator interaction.

Not accounting for Patient 3, who was on solely on SIMV mode, male neonates have lower asynchrony rates. The male and female infants all shared similar ventilator modes,

settings, and approach as per standard care. However, given females had much higher ventilator asynchrony occurrences, they may require different ventilator settings for this reason, as well as due to differences in lung mechanics and variability.

4.4. Overview

This analysis used specific elastance, a measure which accounts for patient weight [22]. Other studies indicate lung development and volume are strongly associated with weight [19,21]. However, the high variability between patients seen here is likely a function of infant injury or disease state and associated complications. Males were seen to have higher elastance and less variability overall and breath-to-breath.

These results suggest MV management for infant males should be different to infant females as male neonates have stiffer lungs and are thus less variable in response to MV. They may also pose a greater risk for over inflation (barotrauma) or under recruitment/oxygenation. In contrast female neonates showed greater variability associated with lower specific elastance, and thus may likely need more frequent observation and/or changes in MV settings.

The identified resistance values for the model are very low due to the ΔP_{ETT} term added to the model and used in this analysis. The ETT is the single largest resistor in patient breathing. This term thus captures most of the flow resistance behaviour observed in the data. Calculating it separately, as in this analysis, leaves relatively little further flow resistance to be identified from the model term. Therefore, the (added) identified airway resistance, R_{rs}, is relatively low.

4.5. Limitations

The major limitation of this study is small patient numbers (n= 9). However, the number of recorded breaths are large (535,428 breaths). This large number of breaths and the robust statistics used help ensure the validity of the results for this initial observational cohort. Despite the small patient numbers, the male vs female neonates comparisons showed the hypothesized trends in elastance, which can be further verified in larger studies.

The model itself is simple, and analyses lungs as a combined volumetric unit. It is therefore unable to independently describe differences in MV properties between the lungs or lung

units (heterogeneity), but presents an overall average description of their combined behaviour. This model has been successfully applied to adults [12], and has the advantage in that it can be built using readily available bedside data with no additional measurements.

The single compartment model is structurally simple compared non-linear models. Non-linear models might be able capture more specific differences and insight in lung mechanics properties. However, such models are far less identifiable and often not practically identifiable [30], meaning unique parameter values may not be able to be found with the clinical data available without invasive and burdensome added procedures or measurements not typically available for this cohort. There is thus a trade-off of ease of use and detail [31].

5.0. Conclusion

We examined the difference between mechanically ventilated male and female infants in terms of specific elastance, inter- and intra- patient variability. Male neonates had higher specific elastance than female neonates. Females had greater intra-patient and breath-to-breath variability, which increased with declining specific elastance. These results indicate male and female infants should be ventilated differently, where higher variability in females show they may require more frequent observation and changes during MV. In contrast, males may require different ventilation modes and/or settings than females.

6.0. References

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