Preprints of the 21st IFAC World Congress (Virtual)
Berlin, Germany, July 12-17, 2020

# Physiological sex differences in mechanically ventilated premature neonates: A pilot study

**Kyeong Tae Kim*, Jennifer Knopp*, Bronwyn Dixon**, J.Geoffrey Chase***

*Centre for Bioengineering, University of Canterbury, Christchurch, New Zealand (email: kyeong.kim@pg.canterbury.ac.nz).
** Neonatal Intensive Care Unit, Christchurch Women's Hospital, Christchurch, New Zealand (email: Bronwyn.Dixon@cdhb.health.nz).

Abstract: Mechanical ventilation (MV) is commonly used in neonatal intensive care units (NICUs) to support breathing. Anecdotally, male infants are harder to ventilate than females. In this study, the pulmonary mechanics of 10 invasively mechanically ventilated neonates from Christchurch Women's Hospital, recorded during an observational trial with no protocolised change to care, are compared. We hypothesise males have higher specific lung elastance (elastance corrected for weight) than females, due to stiffer and less developed lungs. The specific elastance and resistance is identified for every breath using a single compartment model with a pressure loss term added to compensate for endotracheal tube resistance. Variability is determined by relative percent breath-to-breath variability (%ΔE) in specific elastance. Male infants had higher specific elastance compared to females ($P \leq 0.01$) with median [interquartile range] of 1.91[1.33-2.48] cmH2O.kg/ml and 1.31[0.86-2.02] cmH2O.kg/mL respectively. Males also had lower %ΔE median IQR of -0.03 [-7.56 - 8.01] and females had 0.59[-12.56 - 12.86]. The results validates our hypothesis that boys have higher elastance than girls. These results also suggests males and females should be ventilated differently.

*Keywords:* Physiological model, respiratory mechanics, elastance, model-based, NICU

## 1. INTRODUCTION

Mechanical ventilation (MV) is commonly used in neonatal intensive care units (NICUs) to support breathing (Brown and DiBlasi, 2011; Liggins and Howie, 1972; Sweet et al., 2013) . It is a core therapy for pre-term neonates due to their underdeveloped lungs, respiratory distress syndrome (RDS) is due to surfactant deficiencies (Brown and DiBlasi, 2011; Griese, 1999; Kribs et al., 2015; Torday and Nielsen, 1987).

Male infants are reported to have higher incidence of RDS, morbidity, and mortality than females at similar birth weight (Hislop et al., 1986). Anecdotally, males are also harder to ventilate than females (Peacock et al., 2012; Torday and Nielsen, 1987). Thus, there is a need for greater analysis around sex differences in these cohorts and its potential impact on therapy delivery.

Model-based methods can be used to identify pulmonary mechanics. It can be used to further enhance understanding of patient condition (Sundaresan et al., 2011). A single compartment linear lung model (Bates, 2009; Greenspan et al., 1988; Kim et al., 2019) can reliably identify patient's lung condition and have been applied to retrospective neonatal MV data (Kim et al., 2019).

This pilot study aims to determine patient-specific elastance and, inter- and intra- patient breath-to-breath variability between male and female neonates using the single compartment model. The hypothesis of this study is males will have higher specific elastance (stiffer lungs) and lower variability.

## 2. METHODS

### *2.1 Patient data and data acquisition*

Data recorded from 10 neonates in Christchurch Women's Hospital NICU were collected, under observational and non-interventional settings. Informed parental consent was obtained prior to recruitment and up to 24 hours of airway pressure and flow waveforms were recorded. Ethics approval was granted by New Zealand Northern B Health and Disability Ethics Committee (ref: 16/NTB/16).

Patients were ventilated under standard care and with high-frequency oscillatory ventilation (HFOV) or conventional ventilation (CV) on a SLE5000 neonatal ventilator (SLE, UK). Some patients received MV under more than one mode, but most received patient triggered ventilation (PTV) with targeted tidal volume, a SLE specific mode. Where a patient received a different MV mode within a day of a data recording, parental consent was obtained to undertake a second recording. Patient details are given in Table 1. Data from Patient 1, who only received HFOV is excluded, as HFOV exhibits very different dynamics.

Patient data was recorded at sampling rate of 125 Hz. MediCollector (MediCollector, USA) software was connected to a Philips Healthcare MP70 bedside monitor connected to a SLE5000 via a M1032A Vuelink respiratory module was used to capture the data. Further data acquisition details can be found in (Kim et al., 2019).

Copyright lies with the authors

**Table 1:** Patient Demographics and ventilation settings, males are highlighted rows

| Patient | Ventilation mode | Sex | Weight (g) | | Gestational Age at birth (weeks) | Post Natal Age (days) | Day of MV | PEEP (cmH2O) | Target Tidal Volume (ml) | Surfactant therapy | Hours of Recording | Steroids | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Birth | Study | | | | | | | | | |
| 2-2 | PTV +TTV | F | 570 | 770 | 25 | 31 | 23 | 5 | 4 | N | 2 | Pr/Po | Severe RDS, CNS Sepsis. |
| 2-3 | PSV + TTV | F | | 890 | | 21 | 27 | 5 | 4 | N | 3 | Pr/Po | PPHN |
| 3 | SIMV + TTV | M | 3400 | 3400 | | 23 32 | 3 | 5 | 13 | Y | 21 | Po | Severe Hypoxic Ischemic Encephalopathy, Seizures |
| 4 | PTV +TTV | F | 2750 | 2750 | 41.5 | 2 | 2 | 5 | 11 | Y | 19.3 | - | PPHN |
| 5 | PTV +TTV | F | 1580 | 1580 | 37 | 0 | 1 | 5 | 7.9 | N | 8.2 | Pr | MCDA twin, Maternal Pre-eclampsia Toxaemia |
| 6 | PTV +TTV | M | 1170 | 1170 | 29.9 | 2 | 1 | 5 | 5 | Y | 21 | Pr | Oesophageal atresia, post op from surgery |
| 7 | PTV +TTV | F | 960 | 1990 | 27.4 | 45 | 5 | 5 | 6.6 | N | 23.6 | Pr | Abdominal surgery |
| 8 | PTV +TTV | F | 770 | 770 | 28.1 | 2 | 2 | 5 | 3 | N | 22 | | RDS |
| 9 | PTV +TTV | M | 820 | - | 25.7 | 4 | 5 | 5 | 4 | Y | 24.6 | Pr | RDS |
| 10 | PTV +TTV | M | 810 | 810 | 25.3 | 4 | 1 | 5 | 4 | N | 42.8 | Pr | RDS |

*Pr is pre-natal, Po is post-ntal. 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.*

**Table 2.** Median IQR of specific elastance and breath-to-breath percentage difference in specific elastance.

| Patient # | Sex | Hours of Recording | Median [IQR] Specific Elastance [cmH2O/ml/kg] | IQR Range ($75^{th}$-$25^{th}$) [cmH2O/ml/kg] | IQR Range of specific E/median [cmH2O/ml/kg] | Median [IQR] %ΔE [%] | IQR Range of %ΔE [%] |
|---|---|---|---|---|---|---|---|
| 2 | F | 5 | 0.86 [0.57 - 1.70] | 1.13 | 1.32 | -1.60 [-17.83 - 16.16] | 33.99 |
| **3** | **M** | **21** | **0.50 [0.36 - 0.72]** | **0.36** | **0.74** | **-1.45 [-29.84 - 38.13]** | **67.97** |
| 4 | F | 19.3 | 1.12 [0.69 - 1.86] | 1.17 | 1.05 | -0.88 [-14.40 - 15.11] | 29.51 |
| 5 | F | 8.2 | 0.67 [0.59 - 0.82] | 0.23 | 0.35 | -0.31 [-11.55 - 12.61] | 24.16 |
| **6** | **M** | **21** | **2.53 [2.24 - 2.97]** | **0.73** | **0.29** | **-0.05 [-5.33 - 5.63]** | **10.96** |
| 7 | F | 23.6 | 2.07 [1.46 - 2.59] | 1.13 | 0.55 | -0.54 [-10.58 - 10.36] | 20.94 |
| 8 | F | 22 | 1.29 [1.01 - 1.72] | 0.71 | 0.55 | -0.47 [-12.99 - 13.55] | 26.54 |
| **9** | **M** | **24.6** | **2.28 [1.84 - 2.57]** | **0.73** | **0.32** | **-0.02 [-9.53 - 9.65]** | **19.18** |
| **10** | **M** | **42.8** | **1.43 [1.17 - 1.65]** | **0.48** | **0.34** | **0.07 [-6.60 - 7.24]** | **13.84** |
| All* | | 187.5 | 1.65 [1.08 - 2.37] | 1.29 | 0.77 | -0.20[-9.40 - 9.63] | 19.03 |
| Males* | | | 1.91 [1.33 - 2.48] | 1.15 | 0.60 | -0.03 [-7.56 - 8.01] | 15.57 |
| Females * | | | 1.31 [0.86 - 2.02] | 1.16 | 0.89 | -0.59[ -12.56 - 12.86] | 25.42 |

* These categories are weighted by the contributing number of breaths from each patient

### *2.2 Model Fitting*

A linear single compartment lung model with Jarreau's equation (Jarreau et al., 1999) to compensate for pressure loss across the endotracheal tube (ETT) is used to identify patient-specific lung elastance and resistance and is defined:

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

Where $Q$ is flow (ml/s) and $V$ is volume (ml), $P_{aw}$ is the resulting airway pressure ($cmH_2O$). The identified parameters are lung elastance, $E_{rs}$ (cmH2O/ml) and airway resistance, $R_{rs}$ cmH2O.s/ml. $\Delta P_{ETT}$ is the term to capture pressure loss across the ETT. This equation has previously been validated in (Kim et al., 2019) and uses the empirical equation 2 (Kim et al., 2019).

In this study, patients vary in weight, and gestational age. Therefore, direct comparison in elastance for boys and girls is not possible. Specific elastance ($E_{Specific}$) incorporates weight as marker for maturity and allows direct comparison between patients. $E_{Specific}$ is the reciprocal of the specific compliance, a metric used previously to measure the intrinsic elasticity of the lung tissue independent of lung volume (Kannangara et al., 2018). $E_{specific}$ is calculated by:

$$E_{specific} = E_{rs} * weight = \frac{1}{C_{specific}} = \frac{weight}{C_{rs}} \quad (2)$$

Breaths were defined by checking for inspiration and expiration. Positive airflow with overall increase in flow and pressure is determined as inspiration. Expiration is determined as first negative airflow with overall decrease in flow. Breaths are also filtered if maximum inspiratory volume or peak inspiratory pressure was small as such breaths does not represent a proper breath.

### *2.3 Male infants vs female infants*

The hypothesis is that females have more developed, and therefore have more compliant lungs (lower elastance) than male infants, as males are typically sicker and less developed (Peacock et al., 2012; Stevenson et al., 2000; Torday et al., 1981; Torday and Nielsen, 1987). Thus, it is expected the $E_{specific}$ is higher for male infants than female infants and airway resistance is hypothesised to be similar between the two cohorts.

Due to large number of breaths in this study (422,475 breaths), standard statistical comparison tests are not applicable. Instead bootstrapping methods are used to compare the medians from 10,000 breaths with replacement, repeated 10,000 times. A 99% confidence interval (CI) for the difference in median specific elastance value are created. If the CI does not cross zero, then the differences in medians are statistically significant with $P \leq 0.01$ (Motulsky, 2015). The choice of 99% CI ($P \leq 0.01$) was made to be more conservative than 95% CI ($P \leq 0.05$), due to multiple comparisons.

### *2.4 Variability analysis and comparison*

Preliminary study showed large intra- and inter- patient variability. 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 and forward specific elastance, defined:

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

A box plot is also used to show the overall distribution of $E_{specific}$ for all patients. It is hypothesized that female cohort will have (hypothesised) higher intra- and inter- patient variability, as they have more compliant lungs and thus are easier to inflate in comparison to stiffer lungs of male cohort. It should also be noted more compliant lungs are much more responsive to changes in small flow-volume input.

The overall variability is calculated using median interquartile range (IQR:25$^{th}$ -75$^{th}$) of specific elastance and its breath-to-breath change over the distribution.

## 3.0 RESULTS

### *3.1 Specific Elastance: Male vs Female infants*

The male cohort had higher specific elastance than the female cohort, as seen in Fig. 1. The median [IQR] of specific elastance for male cohort was 1.91 (1.33-2.48) cmH2O.kg/mL compared to the female median [IQR] of 1.31 (0.86-2.02) cmH2O.kg/mL ($P < 0.01$). The median [IQR] resistance was 0.00 (0.00-0.02) and 0.02 (0-0.05) cmH2Os/mL for males and females, respectively ($P < 0.01$), where this low reistance implies the primary resistive loss is to the ETT tube, as captured by $\Delta P_{ETT}$ in Equation 1. Comparison of specific elastance and resistance values are statistically significant, ($P < 0.01$) between male and female infants, but the resistance values are likely clinically insignificant and thus not equivalent. Alternatively, more developed lungs may have increased resistance due to greater numbers of branches and alveoli, and thus the female cohort has overall higher elastance median and IQR.

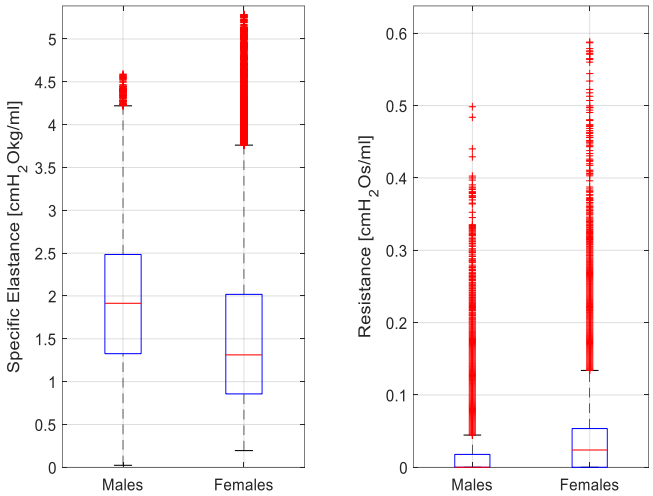


Fig. 1. Boxplot of $E_{Specific}$ and resistance of two cohorts.

Fig. 2 and Table 2 shows males have overall consistently higher specific elastance than females. However, Patient 3 has the lowest specific elastance and variability. This male patient was a near term baby and intubated for different reasons.

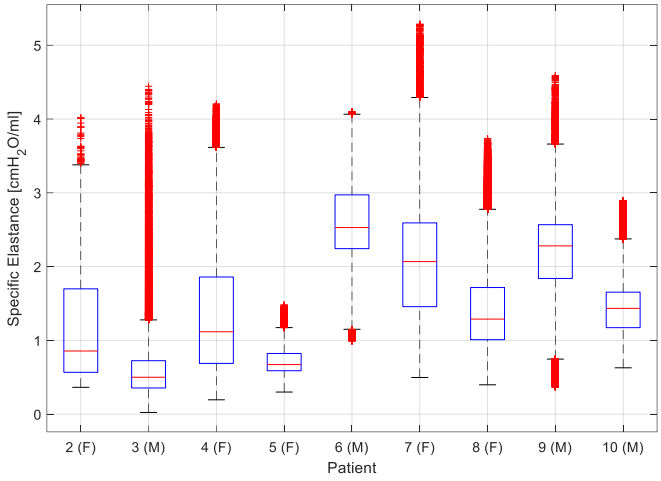


Fig. 2. Boxplot of $E_{Specific}$ for all patients

### 3.2 *Variability*

The inter- and intra- patient variability in Table 2 of specific elastance is large. Table 2 and Fig. 2 shows the median IQR specific elastance and breath-to-breath %ΔE is higher in females than makes, and the IQR range ($75^{th}$ – $25^{th}$) of breath-to-breath variability is also higher for females at 25.42% versus 15.57% for males.

Fig. 3 plots median specific elastance against the IQR range of %ΔE. It shows a hyperbolic relationship with $R^2$ = 0.73. Eliminating the outlier at (0.5,68%; Patient 3, Male), results in $R^2$ = 0.71. Thus, there is strong relationship between lung function and breath-to-breath variability. It also shows stiffer lungs result in lower breath-to-breath variability as the lungs are less compliant to ventilator drive, as hypothesised.

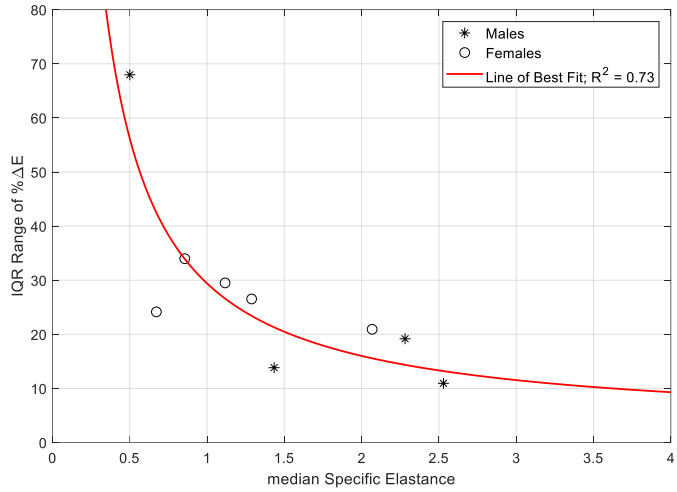


Fig. 3. Relationship between median specific elastance and IQR range of *%ΔE*

## 4. DISCUSSION

### 4.1 *Male vs Female infants*

Anecdotally, male infants are harder to ventilate than females. This anecdote matches these results, where males show stiffer lungs with higher elastance compared to females (P≤ 0.01). This key result also indicates the single-compartment model is able to capture and describe trends in MV physiology.

The outlier to this trend was Patient 3, ventilated for reasons unrelated to lung function due to severe hypoxicischemic encephalopathy. This patient was also a full-term infant with weighing 3400g and thus, had a fully developed lungs. Thus, as a term and non-lung function compromised infant, their lung dynamics are expected to differ from the rest of the infants in Tables 1 and 2.

The identified resistance values were extremely small. This result is due to the term added to compensate for pressure loss across ETT. ETTs used in the NICU have small diameter and are thus the largest resistance in patient breathing. When calculating the pressure loss across the ETT, this term absorbs most of the resistive component in the observed dynamics. Patients in this cohort had ETT diameter between 2.5-4mm based on their weight (Kim et al., 2019).

### 4.2 *Variability*

Intra- and inter- patient variability was large. The highest breath-to-breath percentage difference in specific elastance was 68% by Patient 3 (M) and lowest was 11% by Patient 6 (M). The *%ΔE* distribution can vary significantly across patients.

The median IQR of $E_{specific}$, *%ΔE*, and boxplot shows both intra- and inter- patient variability is large. However, overall, the female cohort has higher variability compared to male cohort. This outcome matches the hypothesis in this study, as males are expected to have stiffer lungs and thus, lower variability, as their lungs are much less responsive to ventilator input

The hyperbola in Fig. 3, shows high correlation between median specific elastance and IQR range of breath-to-breath variability with $R^2$ = 0.73. This value does not change much if the outlier Patient 3 is removed at (0.5, 68%). The hyperbola shape makes physical sense, as specific elastance increases (gets stiffer), the breath-to-breath variability decreases (less variations/ due to stiffer lungs), but never reaches zero.

### 4.3 *Clinical considerations*

Specific elastance is a measure of patient lung condition when accounting for patient weight and development. Patients with higher weight are associated with stronger lung development and increased lung volume (Hislop et al., 1986). At greater lung volume, lung elastance is expected to be lower due to

scaling considerations (Kannangara et al., 2018). The patients in this study were not the smallest infants, but did tend to be the most premature (Table 1). Thus, it seems likely that overall lung dynamics do differ between the sexes. Specifically, a higher in specific elastance in males indicates stiffer lungs than females after accounting for weight. In addition, females were more variable as a result.

The difference in specific elastance results suggests MV management should be differentiated. Males have stiffer lungs and thus are less responsive to MV, which poses a greater risk of injury or under recruitment. Females have higher variability, and likely need frequent changes of MV mode and observations.

### *4.4 Limitations*

The study is limited by the small patient numbers (N = 9), but the number of recorded breaths are very large (422,475 breaths). The results are validated by large data set and robust statistics and matches with the initial hypothesis. The male vs female comparison can be further validated with larger studies.

The model itself is simple, and analyses lungs as a combined volumetric unit. Therefore, it is 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 (Chiew etal., 2011; Sundaresan et al., 2011; van Drunen et al., 2013), and has the advantage in that it can be identified using readily available bedside data with no additional measurements (Szlavecz et al., 2014).

The single-compartment model is structurally simple compared nonlinear models. Nonlinear 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 (Docherty,et al., 2011) 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 (Chase et al., 2018).

## 5. Acknowledgement

The project has received funding from EU H2020 R&I programme (MSCA-RISE-2019 call) under grant agreement #872488 — DCPM

## 6. CONCLUSION

There was noticeable difference in specific elastance between two cohorts, male and female infants. The intra- and inter-patient variability was also significantly different. Both result matched initial hypotheses. That males have higher specific elastance than females and therefore lower overall variability. These initial findings show males and females should be ventilated differently in NICU.

## REFERENCES

Bates, J.H.T., 2009. Lung Mechanics. An Inverse Modeling Approach.

Brown, M.K., DiBlasi, R.M., 2011. Mechanical Ventilation of the Premature Neonate. Respir. Care 56, 1298–1313. https://doi.org/10.4187/respcare.01429

Chase, J.G., Preiser, J.C., Dickson, J.L., Pironet, A., Chiew, Y.S., Pretty, C.G., Shaw, G.M., Benyo, B., Moeller, K., Safaei, S., Tawhai, M., Hunter, P., Desaive, T., 2018. Next-generation, personalised, model-based critical care medicine: A state-of-the art review of in silico virtual patient models, methods, and cohorts, and how to validation them. Biomed. Eng. Online 17, 1–29. https://doi.org/10.1186/s12938-018-0455-y

Chiew, Y.S., Chase, J.G., Shaw, G.M., Sundaresan, A., Desaive, T., 2011. Model-based PEEP optimisation in mechanical ventilation. Biomed. Eng. Online 10, 111. https://doi.org/10.1186/1475-925X-10-111

Docherty, P.D., Chase, J.G., Lotz, T.F., Desaive, T., 2011. A graphical method for practical and informative identifiability analyses of physiological models: a case study of insulin kinetics and sensitivity. Biomed. Eng. Online 10, 39. https://doi.org/10.1186/1475-925X-10-39

Greenspan, J., Abbasi, S., Bhutani, V., 1988. Sequential changes in pulmonary mechanics in the very low birth weight (≤1000 grams) infant. J. Pediatr. 113, 732–737. https://doi.org/10.1016/S0022-3476(88)80391-3

Griese, M., 1999. Pulmonary surfactant in health and human lung diseases: State of the art. Eur. Respir. J. 13, 1455–1476. https://doi.org/10.1034/j.1399-3003.1999.13f36.x

Hislop, A.A.A., Wigglesworth, J.S.S., Desai, R., 1986. Alveolar development in the human fetus and infant. Early Hum. Dev. 13, 1–11. https://doi.org/10.1016/0378-3782(86)90092-7

Jarreau, P.H., Louis, B., Dassieu, G., Desfrere, L., Blanchard, P.W., Moriette, G., Isabey, D., Harf, a, 1999. Estimation of inspiratory pressure drop in neonatal and pediatric endotracheal tubes. J. Appl. Physiol. 87, 36–46.

Kannangara, O., Dickson, J.L., Chase, J.G., 2018. Specific compliance: is it truly independent of lung volume? IFAC-PapersOnLine 51, 299–304. https://doi.org/10.1016/j.ifacol.2018.11.625

Kim, K.T., Knopp, J., Dixon, B., Chase, G., 2019. Quantifying neonatal pulmonary mechanics in mechanical ventilation. Biomed. Signal Process. Control 52, 206–217. https://doi.org/10.1016/j.bspc.2019.04.015

Kribs, A., Roll, C., Göpel, W., Wieg, C., Groneck, P., Laux, R., Teig, N., Hoehn, T., Böhm, W., Welzing, L., Vochem, M., Hoppenz, M., Bührer, C., Mehler, K., Stützer, H., Franklin, J., Stöhr, A., Herting, E., Roth, B., 2015. Nonintubated surfactant application vs conventional therapy in extremely preterm infants: A

randomized clinical trial. JAMA Pediatr. 169, 723–730. https://doi.org/10.1001/jamapediatrics.2015.0504

Liggins, G.C., Howie, R.N., 1972. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 50, 515–525.

Motulsky, H.J., 2015. Common misconceptions about data analysis and statistics. Br. J. Pharmacol. 172, 2126–2132. https://doi.org/10.1111/bph.12884

Peacock, J.L., Marston, L., Marlow, N., Calvert, S.A., Greenough, A., 2012. Neonatal and infant outcome in boys and girls born very prematurely. Pediatr. Res. 71, 305–310. https://doi.org/10.1038/pr.2011.50

Stevenson, D.K., Tyson, J.E., Korones, S.B., Bauer, C.R., Stoll, B.J., Papile, L.A., Verter, J., Fanaroff, A.A., Oh, W., Ehrenkranz, R.A., Shankaran, S., Donovan, E.F., Wright, L.L., Lemons, J.A., 2000. Sex differences in outcomes of very low birthweight infants: The newborn male disadvantage. Arch. Dis. Child. Fetal Neonatal Ed. 83, 182–185.

Sundaresan, A., Chase, J.G., Shaw, G.M., Chiew, Y.S., Desaive, T., 2011. Model-based optimal PEEP in mechanically ventilated ARDS patients in the intensive care unit. Biomed. Eng. Online 10, 64. https://doi.org/10.1186/1475-925X-10-64

Sweet, D.G., Carnielli, V., Greisen, G., Hallman, M., Ozek, E., Plavka, R., Saugstad, O.D., Simeoni, U., Speer, C.P., Vento, M., Halliday, H.L., 2013. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants-2013 update. Neonatology 103, 353–368. https://doi.org/10.1159/000349928

Szlavecz, A., Chiew, Y.S., Redmond, D., Beatson, A., Glassenbury, D., Corbett, S., Major, V., Pretty, C., Shaw, G.M., Benyo, B., Desaive, T., Chase, J.G., 2014. The Clinical Utilisation of Respiratory Elastance Software (CURE Soft): a bedside software for real-time respiratory mechanics monitoring and mechanical ventilation management. Biomed. Eng. Online 13, 140. https://doi.org/10.1186/1475-925X-13-140

Torday, J.S., Nielsen, H.C., 1987. The sex difference in fetal lung surfactant production. Exp. Lung Res. 12, 1–19. https://doi.org/10.3109/01902148709068811

Torday, J.S., Nielsen, H.C., Fencl, M. de M., Avery, M.E., 1981. Sex differences in fetal lung maturation. Am. Rev. Respir. Dis. 123, 205–208. https://doi.org/10.1164/arrd.1981.123.2.205

van Drunen, E.J., Chiew, Y.S. hiong, Chase, J.G., Lambermont, B., Janssen, N., Desaive, T., 2013. Model-based respiratory mechanics to titrate PEEP and monitor disease state for experimental ARDS subjects. Conf. Proc. ... Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE Eng. Med. Biol. Soc. Annu. Conf. 2013, 5224–5227. https://doi.org/10.1109/EMBC.2013.6610726