Lung resistance and elastance in spontaneously breathing preterm infants: effects of breathing pattern and demographics

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1Department of Pediatrics, The Children's Regional Hospital at Cooper Hospital and Robert Wood Johnson Medical School, Camden 08103; 2Department of Pediatrics, Robert Wood Johnson Medical School, New Brunswick, New Jersey 08901; and 3Department of Pediatrics, Mercy Children's Hospital at St. Vincent Mercy Medical Center, Medical College of Ohio, Toledo, Ohio 43608

Pandit, Paresh B., Kee H. Pyon, Sherry E. Courtney, Sandra E. England, and Robert H. Habib. Lung resistance and elastance in spontaneously breathing preterm infants: effects of breathing pattern and demographics. J. Appl. Physiol. 88: 997–1005, 2000.—Reported values of lung resistance (RL) and elastance (EL) in spontaneously breathing preterm neonates vary widely. We hypothesized that this variability in lung properties can be largely explained by both inter- and intrasubject variability in breathing pattern and demographics. Thirty-three neonates receiving nasal continuous positive airway pressure (weight 606–1,792 g, gestational age (GA) of 25–33 wk, 2–49 days old) were studied. Transpulmonary pressure was measured by esophageal manometry and airflow by face mask pneumotachography. Breath-to-breath changes in RL and EL in each infant were estimated by Fourier analysis of impedance (Z) and by multiple linear regression (MLR). RLMLR (RLMLR = 0.85 × RLZ − 0.43; r² = 0.95) and ELMLR (ELMLR = 0.97 × ELZ + 8.4; r² = 0.98) were highly correlated to RLZ and ELZ, respectively. Both RL (mean ± SD; RLZ = 70 ± 38, RLMLR = 59 ± 36 cmH2O·s·l−1) and EL (ELZ = 434 ± 212, ELMLR = 436 ± 210 cmH2O/l) exhibited wide intra- and intersubject variability. Regardless of computation method, RL was found to decrease as a function of weight, age, respiratory rate (RR), and tidal volume (VT) whereas it increased as a function of RR·VT and inspiratory-to-expiratory time ratio (TI/TE). EL decreased with increasing weight, age, VT and female gender and increased as RR and TI/TE increased. We conclude that accounting for the effects of breathing pattern variability and demographic parameters on estimates of RL and EL is essential if they are to be of clinical value. Multivariate statistical models of RL and EL may facilitate the interpretation of lung mechanics measurements in spontaneously breathing infants.

impedance; multiple linear regression; frequency dependence; amplitude dependence

Babies with very low birth weight (VLBW) due to prematurity almost invariably require respiratory support because of surfactant deficiency, underdeveloped lungs, and/or immature respiratory control (6, 7, 16, 18–21, 27, 33). However, VLBW infants are increasingly being supported by administration of exogenous surfactant followed by less invasive respiratory support such as nasal continuous positive airway pressure (NCPAP; Refs. 7, 12). Allowing spontaneous ventilation while preventing alveolar collapse by NCPAP, as opposed to positive pressure mechanical ventilation, is believed to decrease lung barotrauma and allows easier access to the infant (8, 12).

Two important limitations of NCPAP-spontaneous ventilation support are 1) the possibility of failure, leading to intubation, and 2) the lack of a well-defined method to guide weaning neonates off this support. Instead, weaning is often a trial-and-error process that is highly variable among care providers. In theory, if reliable and reproducible, serial lung mechanics measurements probing the progression or regression of the underlying lung disease may provide a quantitative basis for weaning infants from NCPAP support. This approach, however, is hindered by the difficulty of interpreting these measurements given the large inter- and intrasubject variability of lung resistance (RL) and elastance (EL) estimates (1, 2, 6, 7, 10, 13, 15, 17–21, 27, 33).

We hypothesized that breathing pattern and demographic factors are responsible for a substantial portion of this variability. The main objectives of this study were to elucidate how breathing pattern parameters and patient demographics influence RL and EL in spontaneously breathing preterm infants and to examine whether these RL and EL dependencies are altered by the method used to compute these properties.

METHODS

Subjects

Lung mechanics measurements were performed on a total of 37 infants on NCPAP support in the neonatal intensive care nursery. Persistent leaks around the face mask did not allow for data analysis in four infants. The patient characteristics of the remaining 33 are shown in Table 1. The ethnic distribution was Caucasian: 15, African-American: 11, Hispanic: 6, and Asian: 1. At the time of measurements, the degree of respiratory distress in these infants was mild (median NCPAP = 5 cmH2O, median inspired O2 fraction = 8750-7587/00 $5.00 Copyright © 2000 the American Physiological Society 997
Table 1. Summary of patient characteristics (n = 33)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Birth weight, g</td>
<td>1041 g</td>
<td>606–1,792 g</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>20/13</td>
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<tr>
<td>Gestational age, wk</td>
<td>29</td>
<td>25–33</td>
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<tr>
<td>Age, days</td>
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<td>2–49</td>
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<tr>
<td>Corrected gestational age, wk</td>
<td>31</td>
<td>27–34</td>
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0.25). This study was approved by the Institutional Human Investigation Committee and was performed with parental consent.

Measurements and Protocol

Airway flow (Flow) was measured in preterm infants during quiet sleep with a calibrated neonatal fixed-orifice pneumotachograph (Novametrix, Wallingford, CT; dead space = 0.8 ml) via a neonatal face mask. Tidal volume (VT) was calculated by numerical integration of Flow. Leaks around the face mask were removed by repositioning the face mask until none was detected. Detection of airway leaks was possible from monitoring of VT obtained via real-time integration of Flow. In a few cases, petroleum jelly was used around the face mask to ensure that no leaks were present. Only stretches of breaths with no detectable leaks were considered for analysis.

Airway opening (Pao) and esophageal (Pes) pressures were measured with pressure transducers (Microswitch 743PC). For Pes measurement, each infant received a neonatal esophageal balloon catheter (Ackrad Laboratories, Cranford, NJ) inserted so that the balloon was, in the esophagus, at the level of the lower third of the trachea. Proper positioning of the esophageal balloon was checked by continuous on-line monitoring of Pes and adjusted until a high correlation ($r^2 > 0.90$) was obtained between Pao and Pes readings with the Esophagus occluded (5). To facilitate quiet sleep, infants were generally fed via a nasogastric tube after instrumentation was complete and before initiation of measurements. At completion of feeding, the nasogastric tube was withdrawn to avoid possible measurement artifacts.

Flow, Pao, and Pes were zeroed and calibrated at the beginning of each experiment. Their time signals during spontaneous breathing were then sampled at 100 Hz, monitored on-line, and stored on a computer (Ventrak, Novametrix) for later analysis. Data collection took place in stretches of 30–60 s, which were repeated when necessary to allow for variability in breathing patterns of individual subjects. Measurements were done with NCPAP and $O_2$ support discontinued.

Data Analysis

First, time domain data from each infant were examined, and all breaths with evidence of airway leaks around the face mask were excluded. Then, breath-to-breath estimates of $R_L$ and $E_L$ were derived in all infants from transpulmonary pressure ($Pt_p$; $Pt_p = Pao – Pes$), Flow, and VT data using two methods of calculation:

- Lung impedance. Before calculation of the breath-to-breath lung impedance ($Z$), the sampled time signals ($Pt_p$ and $Flow_o$) for each breath were processed as follows: 1) the mean $Pt_p$ and $Flow_o$ over the full breath were subtracted from $Pt_p$ and $Flow_o$, so that both signals were of zero mean; and 2) both $Pt_p$ and $Flow_o$ were then padded with zeros so that the number of points (N) is increased to the next higher power of two (m) so that $N = 2^m$. For example, the zero mean breath data corresponding to a respiratory rate (RR) of 60 min$^{-1}$ (or 100 samples given the 100 Hz sampling rate) would be padded with 28 zeros at the end of the breath to allow the use of 128-point fast Fourier transform (FFT). Lung resistance ($R_L$) and lung elastance ($E_L$) as determined by Fourier analysis (Matlab, The Math Works, Natick, MA) were then calculated as follows:

$$Z(f) = FFT(Pt_p)/FFT(Flow_o)$$

$$R_L = Real[Z(f_{k=1})]; k = 1 \ldots N$$

$$E_L = -2\pi f_{k=1} \cdot Imaginary[Z(f_{k=1})]$$

Where $R_L$ and $E_L$ are the lung mechanical properties at $f_{k=1}$ or the breathing frequency (3, 24).

- Multiple linear regression. Lung resistance ($R_{LMR}$) and elastance ($E_{LMR}$), as determined by multiple linear regression (MLR), were estimated by least squares fitting (Matlab, The Math Works) of the time domain $Pt_p$ data over the entire breath in terms of $Flow_o$, VT, and the elastic recoil pressure at end expiration ($P_o$) using a series resistance-elastance model of the lungs (16, 33):

$$Pt_p_{mod} = R_{LMR} \cdot Flow_o + E_{LMR} \cdot VT + P_o$$

Where $Pt_p_{mod}$ represents the MLR model (mod) estimate of $Pt_p$.

Multivariate Statistical Models of $R_L$ and $E_L$ in all multivariate modeling, all breath-to-breath estimates of $R_L$, $E_L$, $R_{LMR}$, and $E_{LMR}$ from all infants were considered in conjunction with their corresponding breathing pattern and demographic variables. The following breathing pattern variables were considered: RR, breath period (T), inspiratory time ($T_I$), expiratory time ($T_E$), VT (ml), 1/VT, effective minute ventilation ($V_{Eeff}$ = RR·VT; ml/min), mean inspiratory flow ($MIF = VT/T_I$; l/s), maximum inspiratory flow ($l/s$), and mean expiratory flow ($l/s$). Demographic parameters included in the analysis were birth weight (BW, kg), test weight (wt, kg), 1/WT, gestational age (GA, wk), age (wk), corrected gestational age (CGA, wk), and gender (male = 0, female = 1).

Multivariate linear models (SigmaStat, Jandel Scientific, San Rafael, CA) of the form $R_L/E_L = a \times wt + b \times wt + c \times age + d \times gest + e \times RR + f \times VT + g \times constant$ (where a–i represent the constants defined in Table 3) were used to determine the independent breathing pattern and demographic predictors of $R_L$ and $E_L$. $R_{LMR}$ and $E_{LMR}$. $P < 0.05$ was used for covariate retention in the final model.

RESULTS

Data from a representative example infant are illustrated in Fig. 1A. The breath-to-breath changes in pattern that are shown resulted in corresponding changes in the pressure-to-volume ($Pt_p$-to-$VT$) relationship, reflecting the alterations in the underlying mechanical properties (Fig. 1B).

A total of 450 breaths from all 33 infants were considered in the analysis. The number of breaths analyzed in each infant differed (5–18) mainly according to the degree of observed breathing pattern variability in each infant. Figure 2 illustrates the inter- and intrasubject variability in RR and weight-corrected VT (ml/kg), respectively. The range of measured VT and RR values shown for each infant indicated significant spontaneous breathing pattern variability in 28 of 33
infants. No trends were seen for RR and VT as a function of infant size. The average breathing pattern and lung mechanics data from all infants are summarized in Table 2.

Lung mechanical properties estimated by the impedance (RLZ, ELZ) and MLR (RLMLR, ELMLR) methods as a function of infant weight are graphically illustrated in Fig. 3. Both RL (Fig. 3A) and EL (Fig. 3B) showed a clear tendency to decrease (near hyperbolically) with increasing weight, independent of the method of calculation. Significant within-subject variability in both RL and EL, presumably due to changes in breathing pattern, is depicted by the range of values at each of the weight values. These variabilities were similar for both the Z and MLR methods of calculation.

The correlation and agreement between the mechanical properties (RLZ vs. RLMLR and ELZ vs. ELMLR) obtained with the two methods of calculation are presented and discussed in the APPENDIX.

Stepwise multivariate linear analyses indicated that RL and EL may be predicted from combinations of breathing pattern and demographic variables. Specifically, RL (cmH₂O·s·l⁻¹) is a function of weight, 1/wt, age, RR, Ti/Te, VT, Ve, and a constant k. Alternat-

Fig. 1. A: transpulmonary pressure (Ptp), volume, and flow shown for 9 breaths of varying pattern in an example infant (male, 1.15 kg, 12 days old). B: volume-Ptp curves corresponding to breaths 2, 5, and 8 spanning observed variability in respiratory rate (RR; 103–136 min⁻¹) and tidal volume (VT; 3.2–6.9 ml). Here, a substantial change in pressure-to-volume slope (elastance, E) and hysteresis area (resistance, R) indicates how changes in pattern lead to changes in between-breath estimates of lung R and E (RL and EL).

Fig. 2. Preterm infants’ breathing patterns show large variability in RR (A) and VT (B) both within as well as among subjects. Each weight value or line on these graphs represents an individual subject. There were no distinct tendencies for RR and VT variability with infant size.

Table 2. Summary of breathing pattern and lung mechanics in 33 infants

| RR, min⁻¹ | 81 ± 22 |
| VT, ml/kg | 7.3 ± 2.2 |
| RR × VT, ml·kg⁻¹·min⁻¹ | 575 ± 243 |
| RLZ, cmH₂O·s·l⁻¹ | 70 ± 42 |
| ELZ, cmH₂O/l | 434 ± 212 |
| RLMLR, cmH₂O·s·l⁻¹ | 59 ± 36 |
| ELMLR, cmH₂O/l | 436 ± 210 |

Values are means ± SD. RR, respiratory rate; VT, tidal volume; RLZ, ELZ, RLMLR, and ELMLR, lung resistance (RL) and lung elastance (EL) estimated by Fourier analysis of lung impedance (Z) and by multiple linear regression (MLR), respectively.
and

\[ E_{LZ} = 422 \times wt^{-1.28} - 30 \times \text{age} - 55 \times \text{gender} + 1.8 \times RR - 11 \times VT + 49 \times Ti/TE \]  

(4a)

\[ E_{LMR} = 421 \times wt^{-1.28} - 29 \times \text{age} - 57 \times \text{gender} + 1.8 \times RR - 10 \times VT + 39 \times Ti/TE \]  

(4b)

Through use of the above equations, simulations depicting the separate RR and VT dependence of RL and EL are illustrated in Fig. 4. Alternatively, because RR and VT are likely to change simultaneously, simulations showing the model-predicted effects of shallow-rapid, slow-deep, and intermediate breathing on RL and EL while minute ventilation was maintained are shown in Fig. 5.

**DISCUSSION**

Important pharmacological advances (e.g., exogenous surfactant) have improved survival and decreased mechanical ventilatory dependency of VLBW infants (7, 15, 25, 29). Indeed, a large percentage of

| Table 3. Multivariate models of RL and EL in terms of breathing pattern and demographic parameters: $R/E = a \cdot \text{wt}^b + c \cdot \text{gender} + d \cdot \text{age} + e \cdot RR + f \cdot VT + g \cdot V_{E_eff} + h \cdot Ti/TE$ |
|---------------------------------|-----------------|-------------|
| **Coefficient** | **t Statistic** | **P** |
| RLZ (r = 0.63) | | |
| a | 116 ± 13 | 8.81 | <0.001 |
| b | -0.81 ± 0.12 | -6.71 | <0.001 |
| c | 4.8 ± 1.3 | 3.64 | <0.001 |
| e | -0.68 ± 0.13 | -5.28 | <0.001 |
| f | 7.1 ± 1.3 | 5.61 | <0.001 |
| g | 76 ± 10 | 7.91 | <0.001 |
| i | 23 ± 4 | 5.73 | <0.001 |
| RLMLR (r = 0.59) | | |
| a | 100 ± 12 | 6.37 | <0.001 |
| b | -0.80 ± 0.12 | -6.49 | <0.001 |
| c | -55 ± 19 | -2.88 | 0.004 |
| d | -30 ± 6.5 | -4.59 | <0.001 |
| e | 1.8 ± 0.4 | 4.36 | <0.001 |
| f | -11 ± 2.7 | -4.04 | <0.001 |
| g | 49 ± 20 | 2.53 | 0.12 |
| i | 17 ± 4 | 4.63 | <0.001 |
| ELMLR (r = 0.68) | | |
| a | 422 ± 47 | 8.92 | <0.001 |
| b | -1.20 ± 0.19 | -6.47 | <0.001 |
| c | -57 ± 19 | -2.99 | 0.003 |
| d | -29 ± 6.6 | -4.36 | <0.001 |
| e | 1.8 ± 0.4 | 4.23 | <0.001 |
| f | -10 ± 2.7 | -3.70 | <0.001 |
| g | 39 ± 20 | 2.00 | 0.046 |

Coefficient values are means ± SE. $r =$ Correlation coefficient.
these infants are allowed to ventilate spontaneously while their lung volumes are maintained by NCPAP. A well-defined quantitative method to guide the weaning of infants from NCPAP remains elusive.

Use of serial lung mechanics measurements to guide weaning is a possible method. However, the wide variance in the reported RL and EL values in spontaneously breathing preterm infants (1, 2, 6, 7, 10, 13, 15, 17–21, 27, 34) casts doubt on its applicability. We postulated that a substantial component of this variability in RL and EL derives from differences in patient demographics and the significant breathing pattern variability characteristic of spontaneously breathing VLBW infants. Hence, quantifying these effects in multivariate models predicting RL and EL may facilitate their interpretation and enhance their clinical value. In this study, we confirmed that both RL and EL are altered significantly by breathing and demographic parameters, and we quantified these effects in the form of multivariate models. These models were essentially identical whether RL and EL were derived by the MLR or impedance method. Thus, from this point forward, the Z and MLR subscripts will be dropped for simplicity.

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**Fig. 4.** Simulated RL and EL based on multivariate models (Eqs. 3a and 4a). A: VT dependence of RL; B: RR dependence of RL; C: VT dependence of EL; D: RR dependence of EL. All simulations were done assuming age = 1 wk, male, Ti/Te = 1. Weight was varied between 0.6 and 1.8 kg, and effective minute ventilation (VE_{eff}) was computed as RR·VT.

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**Fig. 5.** Simulated RL (A) and EL (B) based on multivariate models (Eqs. 3a and 4a) with fixed VE_{eff} (RR·VT) and assuming varying breathing strategies: rapid shallow breathing (solid lines), slow deep breathing (dotted lines), and an intermediate pattern (dashed lines). All simulations were done assuming age = 1 wk, male, Ti/Te = 1. Weight was varied between 0.6 and 1.8 kg.
Multivariate Models of $R_L$ and $E_L$

The multivariate statistical models of $R_L$ and $E_L$ (Eqs. 3 and 4) indicate that both properties varied as a function of breathing pattern and demographic factors. These factors, however, did not account for all $R_L$ and $E_L$ variability in preterm infants as other factors affecting their estimation could not be controlled for. These include errors due to cardiogenic oscillations, extraneous noise (given that no averaging is possible), changes in absolute lung volumes and gas shunt effects within the face mask, as well as breath-to-breath changes in glottal geometry. Also, between-subject differences in 1) lung disease (albeit mild) and 2) sleep-wake state may have also added to the variability in $R_L$ and $E_L$. The sleep state is a major contributor to breathing pattern variability in both term and preterm infants (16). Hence, changes in the sleep state during measurements can consequently alter the underlying mechanical properties.

The gas volume within the face mask represents a gas flow shunt pathway that may cause some variability in the data, particularly among different subjects. This gas volume will vary on the basis of mask size and facial anatomy, which may have varied considerably among the infants we studied. If we assume similar gas volumes within the mask, the shunt compartment is more competitive to inspiratory flow in smaller compared with larger infants given their high vs. low downstream impedance. In this study, we minimized this effect by always using the smallest neonatal face masks with which leaks could be avoided.

Changes in absolute lung volumes [e.g., end-expiratory lung volumes (EELV)] may have occurred during measurements. Also, measurements from different infants may have been done at comparatively different lung volumes. Variations in EELV can alter $R_L$ and $E_L$ considerably, particularly if it is sufficiently low such that airway closure may have occurred (30, 32). Lung volumes in each of the infants we studied were maintained by NCPAP (4–6 cmH$_2$O) up to the point when we did our measurements. Also, the measurements were typically brief (30–60 s) and in no case did we observe substantial changes in pulse oximetry and electrocardiography that might indicate large changes in oxygenation during data acquisition. Also, inasmuch as P$_{ES}$ at end expiration reflects changes in lung volume, our measurements did not include gross changes in P$_{ES}$ at end expiration (see example in Fig. 1), and hence we do not expect that our measurements included large within-subject changes in EELV.

Neonates largely rely on their glottal aperture to maintain their functional residual capacity (8, 12). Thus it is possible that infants altered their glottal geometry during measurements and consequently changed the lung mechanical properties estimated at the airway opening. Changes in glottal aperture are greatest between inspiration (wide) and expiration (narrow) and are a main reason for the higher effective resistance during expiration. Therefore, to illustrate these effects, we compared the changes in resistance estimated from expiration ($R_{exp}$) to that estimated over the full breath ($R$). Breath-to-breath changes in $R_{exp}$ can be quite large, and the corresponding changes in $R$ computed over the entire breath are also evident but are relatively smaller (Fig. 6A). These smaller changes probably reflect the fact that $R$ is a weighted average of inspiratory and expiratory resistance, as well as reflecting the effects of other breathing pattern changes such as Te/Ti, RR, and Vt (Fig. 6B) that contribute to variability of the estimated mechanical properties.

Demographic variables. In preterm infants, $R_L$ and $E_L$ decreased with lung growth and maturity as indicated by their negative dependence on weight and age, respectively. These findings conform to previous studies of postnatal lung mechanics (3, 10, 15, 24). In infants and young children, Gerhardt et al. (18), Lancaster and Sly (26), and Galal et al. (17) independently demonstrated a negative size dependence of $R_L$ and $E_L$ as a function of lung volume, height, and weight, respectively.

The separate dependence of $R_L$ and $E_L$ on weight vs. age may also indicate that the effects of development during late gestation on lung mechanics are not simply a function of changes in lung size. Other maturational changes during the third trimester, reflected in the age parameter, such as increases in surfactant pool sizes (23) and alterations in alveolar architecture (11), may have also contributed.

$E_L$ also showed a gender dependence, that is, girls had a ~10% lower $E_L$ compared with boys (Eq. 4). Over

![Fig. 6. A: breath-to-breath changes in $R_L$ calculated from the full breath vs. expiration only in an example infant. Note 1) the larger expiratory resistance ($R_{exp}$) for any given breath at least partly reflecting the narrowed glottal aperture during expiration compared with inspiration and 2) the larger interbreath variability in $R_{exp}$ compared with a weighted average of both inspiratory and expiratory resistance ($R$). $R$ and $R_{exp}$ were computed by the MLR method. B: corresponding changes in Vt, RR, and Vt/Ti (relative to breath 1) that are perhaps related to changes due to glottal aperture and that also contribute to variability of $R$ and $E$.](http://jap.physiology.org/Downloadedfrom)
all infants, Rl estimates were ~15% less in girls vs. boys, but this difference did not prove significant in the multivariate model. These results are consistent with the studies by Stocks et al. (35) in preterm neonates and by Hanrahan et al. (22) in full-term babies that considered gender differences in lung mechanics.

Breathing pattern variables. Rl and El in preterm infants exhibited significant dependence on breathing pattern variables. Rl decreased with increasing RR (min⁻¹) and VT (ml/kg), whereas it increased with increasing V̇Eeff (ml·kg⁻¹·min⁻¹) and Ti/Te (Eq. 3). El decreased as Vt increased, but it increased for higher RR and Ti/Te ratio (Eq. 4). It is important to note that V̇Eeff is equal to RR × VT and that El is mathematically equivalent to the term (RR × VT)/(MIF − RR × VT), where MIF (ml/min) is the mean inspiratory flow rate. The breathing pattern dependence of both Rl and El can thus be narrowed to the same three variables (RR, VT, and MIF), but these effects are complex and differ for Rl compared with El.

As in previous studies in infants and young children (14, 17, 31), both Rl and El exhibited a negative VT dependence over the entire range of infant weights (Fig. 4). The degree of amplitude dependence, given a fixed RR and Ti/Te, seems to be more important in the larger babies. Such negative VT (or amplitude) dependence of El is similar to what Fletcher et al. (14) and Galal et al. (17) reported in infants and young children. This has also been reported in healthy and diseased lungs and is hypothesized to reflect either static hysteresis of lung tissues (28, 32) or nonlinear viscoelastic properties of RL with increasing RR has been described in older infants and children (17, 31). Also, a small but significant increase in El as a function of RR was reported in mechanically ventilated infants and young children (17). In the largest babies (~1.2 kg), the simulations in Fig. 4B show a reversal from negative to positive f dependence of Rl. Given the fixed Ti/Te = 1 for these simulated data, this reversal may indicate the effects of the necessary increase in MIF. Higher flows and larger airways can lead to higher airway resistance due to turbulence (17). This effect is manifested in Eq. 3 by the parameters Ti/Te and V̇Eeff.

Control of breathing is geared toward maintaining gas exchange and hence alveolar ventilation. We simulated (Fig. 5) how Rl and El are altered given a fixed V̇Eeff (500 ml·min⁻¹·kg⁻¹) that is achieved either by 1) rapid shallow breathing (VT = 5 ml/kg, RR = 100 min⁻¹), 2) slow deep breathing (VT = 10 ml/kg, RR = 50 min⁻¹), or 3) an intermediate pattern (VT = 7 ml/kg, RR = 71 min⁻¹). These indicated that El is systematically lower as VT increases and RR decreases, indicating that deeper and slower breathing is mechanically advantageous (Fig. 5B). This advantage is relatively more important in the larger infants. Rl changes were not systematic (Fig. 5A). A rapid shallow breathing strategy resulted in lower Rl (~15%) only in the smallest infants and was reversed for the larger neonates.

Clinical implications. Theoretically, Rl and El measurements can provide valuable insight to clinicians regarding the patient’s underlying lung function and perhaps about the changes in mechanics after treatments. The main contribution of this study is that we illustrate and quantify the effects of variability in breathing pattern and demographics on Rl and El estimates in spontaneously breathing preterm infants. These effects are a major obstacle hindering the routine use of such measurements clinically in infants whether intubated or not (1, 2, 6, 7, 10, 13, 15, 17–21). Indeed, given the magnitude of the variability in Rl and El, our results indicate that these properties must be adjusted (corrected) for changes in breathing pattern for proper interpretation to be possible.

In the presence of breathing pattern variability and changes in other aforementioned factors, it is difficult to know whether decreases in Rl and El really signal decreases in other aforementioned factors, it is difficult to know whether decreases in Rl and El really signal decreases in other aforementioned factors, it is difficult to know whether decreases in Rl and El really signal decreases in other aforementioned factors, it is difficult to know whether decreases in Rl and El really signal decreases in other aforementioned factors, it is difficult to know whether decreases in Rl and El really signal decreases in other aforementioned factors, it is difficult to know whether decreases in Rl and El really signal decreases in other aforementioned factors, it is difficult to know whether decreases in Rl and El really signal decreases in other aforementioned factors, it is difficult to know whether decreases in Rl and El really signal decreases in other aforementioned factors, it is 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sleep. These multivariate models may differ significantly in the presence of moderate and/or severe lung disease, as opposed to the mild lung disease in this group, due to associated changes in lung mechanics and breathing pattern, and 2) in awake infants or during different sleep states.

APPENDIX

Comparison of Lung Resistance and Elastance Estimated by MLR vs. Z Method

The RL and EL obtained by using either computational method were comparable to those previously reported in preterm infants of similar size and GA (5, 6, 23). Also, the inter- and intrasubject breathing pattern variability resulted in similar variability in RLZ and RLMRL (Fig. A1A) as well as for ELZ and ELMRL (Fig. A1B).

RLMLR (RLMLR = 0.85 × RLZ - 0.43; r² = 0.95) and ELMRLR (ELMMLR = 0.97 × ELZ + 8.4; r² = 0.99) were highly correlated to RLZ and ELZ, respectively (Fig. A1). These high correlations probably indicate that RL and EL estimates from both methods change in similar fashion with both breathing pattern and demographic variables. The 0.85 slope relating the two independent estimates of RL, however, indicates that RLMLR generally underestimates RLZ by ~15% (Fig. A1A). In contrast, the 0.97 slope relating ELMMLR and ELZ indicates that the lung elastance estimate is not significantly influenced by calculation method (Fig. A1B).

Consistent with the slopes relating the MLR- and Z-derived mechanical properties, analyzing the difference RLMRLR - RLZ (∆RL) relative to the mean RL reveals a 20% bias compared with minimal bias (3%) for ∆EL (Fig. A1C and D). Moreover, after accounting for the bias in each, the wider limits of agreement for ∆RL (Fig. A1C) compared with ∆EL (Fig. A1D) indicate a smaller variability due to method of calculation in EL vs. RL estimates. ELZ and ELMMLR were essentially identical (Fig. A1B) with little bias (3%) and a very high correlation (r² = 0.99) between them. These estimates were in close agreement over the entire range of measured ELZ and ELMMLR values as illustrated by the Bland-Altman (9) plot (Fig. A1D). Alternatively, RLMRLR generally underestimated RLZ by ~15% (Fig. A1A), but the two independent estimates were again highly correlated (r² = 0.95).

Even after the larger bias was accounted for, differences between RLZ and RLMRLR were generally larger (Fig. A1C) than those found between the corresponding EL estimates. These larger differences and underestimation of RLZ by RLMRLR may partly reflect the fact that RLZ is the effective resistance at the breathing frequency (fB) only. In contrast, the RLMRLR estimate is derived from the time data, which probably carry information from a wider range of frequencies (e.g., harmonics). RLZ at the harmonics of the fB is typically lesser in magnitude (4, 24, 31), and RLMRLR is perhaps closer to a weighted average of RLZ at the fB and all harmonics contributing significantly to the pressure and flow time domain data.

Another possible reason for the differences between RLZ and RLMMLR may be the edge effects on Fourier analysis. This is particularly possible because averaging could not be done when considering breath-to-breath variability. To minimize these effects in our analysis, pressure and flow data were always centered (so that both were of zero mean) before zero padding and application of the FFTs. Although we cannot discount the possibility of edge effects on RLZ and ELZ, we speculate that these effects should influence both the real and

Fig. A1. RL (A) and EL (B) estimated by MLR method agreed closely with those obtained from Z method as illustrated by linear regression comparisons. RLMMLR was generally less (~15%) than RLZ (A). EL estimates were essentially identical with both methods (B). Moreover, this agreement did not depend on breathing pattern. C and D: bias and limits of agreement (±2 SD) for RL and EL estimates, respectively, by the two methods.
imaginary components of impedance. Hence, the small bias and excellent agreement found for $\text{E}_\text{LZ}$ and $\text{E}_{\text{MLR}}$ suggest that edge effects are of secondary importance. This is also corroborated by the similarity of the effects of breathing pattern and demographic parameters on MLR- and impedance-derived properties (Fig. A1, A and B, Eqs. 3 and 4).

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