Spectral characteristics of airway opening and chest wall tidal flows in spontaneously breathing preterm infants

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Habib, Robert H., Kee H. Pyon, Sherry E. Courtney, and Zubair H. Aghai. Spectral characteristics of airway opening and chest wall tidal flows in spontaneously breathing preterm infants. J Appl Physiol 94: 1933–1940, 2003.—We compared the harmonic content of tidal flows measured simultaneously at the mouth and chest wall in spontaneously breathing very low birth weight infants (n = 16, 1,114 ± 230 g, gestation age: 28 ± 2 wk). Airway opening flows were measured via face mask-pneumotachograph (P-tach), whereas chest wall flows were derived from respiratory inductance plethysmography (RIP) excursions. Next, for each, we computed two spectral shape indexes: 1) harmonic distortion (k_d, k_d,P-tach, and k_d,RIP, respectively) defines the extent to which flows deviated from a single sine wave, and 2) the exponent of the power law (s, s,P-tach and s,RIP, respectively), describing the spectral energy vs. frequency. P-tach and RIP flow spectra exhibited similar power law functional forms consistently in all infants. Also, mouth (s,P-tach = 3.73 ± 0.23% (95% confidence interval), k_d,P-tach = 38.8 ± 4.6%) and chest wall (s,RIP = 3.51 ± 0.30%, k_d,RIP = 42.8 ± 4.8%) indexes were similar and highly correlated (s,RIP = 1.17 × s,P-tach + 0.85; r^2 = 0.81; k_d,RIP = 0.90 × k_d,P-tach + 8.0; r^2 = 0.76). The corresponding time to peak tidal expiratory flow-to-expiratory time ratio (0.62 ± 0.08) was higher than reported in older infants. The obtained s and k_d values are similar to those reported in older and/or larger chronic lung disease infants, yet appreciably lower than for 1-mo-old healthy infants of closer age and/or size; this indicated increased complexity of tidal flows in very low birth weight babies. Importantly, we found equivalent flow spectral data from mouth and chest wall tidal flows. The latter are desirable because they avoid face mask artificial effects, including leaks around it, they do not interfere with ventilatory support delivery, and they may facilitate longer measurements that are useful in control of breathing assessment.

harmonic distortion; control of breathing; power law; respiratory mechanics; respiratory inductance plethysmography

Frey and colleagues (11) recently argued that tidal flow is an integrated output of the neural respiratory oscillator in the brain stem, which, in turn, reflects the processing of interacting chemo- and stretch-receptor feedback mechanisms in addition to lung and chest wall passive mechanics. This viewpoint is premised on prior findings that inspiratory and expiratory phases are interdependent and are determined by multiple factors, including respiratory mechanics (e.g., Refs. 2, 3, 6, 7, 9, 15, 20), postinspiratory respiratory drive (13, 25, 26), peripheral chemoreceptors (24), and sleeping patterns (23). Accordingly, they proposed that such complex neuromechanical respiratory control is better characterized by considering the entire periodic tidal flow waveform (TFW), as opposed to simple indexes derived from a limited number of points (2, 20), e.g., time to peak tidal expiratory flow-to-expiratory time ratio (TPTEF/TE).

To characterize flows, Frey et al. (11) quantified the harmonic content of the TFW power spectrum in terms of two related spectral shape indexes: 1) k_d, a harmonic distortion index that defines, irrespective of spectral shape, the extent to which a periodic signal deviates from a single sine wave; and 2) s, the exponent of the power law describing the flow spectral energy vs. frequency. The latter index was justified by their finding that the TFW harmonics of both healthy (longitudinally at 1, 6, and 12 mo) and diseased lungs do indeed follow a power law functional form. They also found that 1) s was significantly lower in chronic lung disease (CLD) infants compared with healthy subjects, 2) k_d was significantly increased with maturation in healthy infants between 1 and 6 mo, and 3) s and k_d exhibited less breath-to-breath variability compared with TPTEF/TE in all infant groups and may, consequently, provide more robust noninvasive means to assess lung pathophysiology and maturational changes.

Very low birth weight (VLBW) preterm babies are a challenging population in whom widely accepted noninvasive methods to assess respiratory mechanics and control remain lacking (1, 18). These infants often suffer from significant lung mechanical dysfunction due to their surfactant deficiency, substantial chest wall distortion and asynchrony during breathing, and incomplete airway and alveolar development (8, 17). Moreover, given their prematurity, it is likely that their receptor-feedback mechanisms are immature. Indeed, because of these VLBW infant characteristics, noninvasively deriving tidal flow s and k_d indexes may...
The primary aims of this study were 1) to test whether, like older infants, tidal flow harmonics of VLBW infants also followed a power law functional form, and 2) to determine whether equivalent \( s \) and \( k_d \) data may be obtained from distal measurements of tidal flow at the chest wall [respiratory inductance plethysmography (RIP); \( s_{\text{RIP}} \) and \( k_{d,\text{RIP}} \), respectively] compared with proximal measurements at the mouth [face mask pneumotachography (P-tach); \( s_{\text{P-tach}} \) and \( k_{d,\text{P-tach}} \), respectively]. Tidal flows measured distally are desirable for avoiding the potential artificial and variable effects of face mask placement and manipulation on the infant’s breathing pattern and, consequently, on TFW indexes, for avoiding the frequently occurring and difficult-to-control air leaks around the mask, and for facilitating less intrusive, longer term measurements.

**METHODS**

**Subjects**

This study was approved by the Institutional Human Investigation Committee and was performed with parental consent. A total of 18 VLBW infants were studied in the neonatal intensive care unit. Infants were receiving nasal continuous positive airway pressure (NCPAP) support at the time of study was an average NCPAP of 5–5 cmH\(_2\)O and inspired oxygen fraction (FIO\(_2\)) of 28% (5 were 8% (5 were 6% (5 were room air). Patient diagnosis was that of varying respiratory distress syndrome (RDS) (1 resolving RDS, 7 mild RDS, 8 RDS). Apnea of prematurity was also documented in five of the infants. A summary of breathing pattern data and corresponding lung mechanical properties during measurements are detailed in Table 1.

**Measurements and Protocol**

Tidal flow measurements were obtained simultaneously 1) at the airway opening via a face mask P-tach system and 2) at the chest wall by using RIP. Neonatal rib cage (RC) and abdominal (Abd) RIP bands (Respiband Plus, SensorMedics, Yorba Linda, CA) were fitted and secured in place in standard fashion (8, 17), and tidal excursions of the chest wall were recorded (Somnostar, SensorMedics). Importantly, the effective length of the RC and Abd bands was determined by the corresponding (i.e., where it was placed) body section circumference at end expiration. Effective length was typically between 80 and 90% of body section circumference (i.e., ensuring a baseline stretched condition) and was maintained constant throughout measurements. Based on prior experience (8, 17, 18), under these band placement conditions, one typically finds excellent agreement between distally and proximally measured flow and volume data via RIP and P-tach, respectively.

Airway opening flow (Vao) was measured by using a neonatal screen P-tach (Hans Rudolph, Kansas City, MO) attached to a neonatal face mask. Leaks around the face mask were removed by repositioning the face mask until none were apparent. Monitoring of tidal ventilation was obtained by real-time integration of Vao. In a few cases, petroleum jelly was used around the mask to ensure that no leaks were present.

Airway opening (Pao) and esophageal pressures (Pes) were measured by using pressure transducers (MP45, Validyne, Northridge, CA). To measure Pes, 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 one-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 \((r^2 > 0.90)\) between Pao and Pes tracings with the airway occluded was obtained (12, 18).

Linearity of the P-tach was verified, and the frequency response was flat upwards of 12 Hz. Flow, Pao, and Pes were zeroed and calibrated at the beginning of each experiment. RIP tidal ventilation data were estimated from both RC and Abd data, and an absolute calibration was obtained by direct matching to corresponding P-tach flow-volume data, as previously described (8, 17).

All signals were sampled during spontaneous breathing at 100 Hz, monitored on-line (MP 100, BioPac Systems, Santa Barbara, CA), and stored on a computer for later analysis. Data were collected in stretches of 30–60 s. 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. Measurements were done with NCPAP and oxygen support discontinued. Respiratory rate, heart rate, and oxygen saturation were continuously monitored at the bedside.

**Data Analysis**

Tidal flow indexes. The primary aim of this study was to compare three tidal flow indexes from airway opening (TPTEF/Te, \( k_a \), and \( s \)) and RIP (\( k_d \) and \( s \)) tidal ventilation data. Stretches of 10–15 consecutive spontaneous P-tach and RIP TFW data were chosen from each infant for analysis. RIP flow was estimated from the derivative of RIP volume. These

**Table 1. Summary of infant demographics, ventilation parameters, and respiratory mechanics**

<table>
<thead>
<tr>
<th>Category</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, g</td>
<td>1,114</td>
<td>230</td>
<td>1,120</td>
<td>658</td>
<td>1,567</td>
</tr>
<tr>
<td>Study weight, g</td>
<td>1,107</td>
<td>230</td>
<td>1,190</td>
<td>667</td>
<td>1,485</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>28.0</td>
<td>0.9</td>
<td>28.2</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>PNA, days</td>
<td>4.8</td>
<td>0.9</td>
<td>4.7</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>NCPAP, cmH(_2)O</td>
<td>4.7</td>
<td>0.9</td>
<td>4.7</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>FIO(_2), %</td>
<td>27.8</td>
<td>8.0</td>
<td>30.3</td>
<td>25</td>
<td>43</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>85</td>
<td>20</td>
<td>87</td>
<td>41</td>
<td>115</td>
</tr>
<tr>
<td>Tidal volume, ml/kg</td>
<td>3.7</td>
<td>1.0</td>
<td>3.7</td>
<td>1.7</td>
<td>4.9</td>
</tr>
<tr>
<td>Minute ventilation, ml(\text{-kg}^{-1}\text{-min}^{-1})</td>
<td>307</td>
<td>101</td>
<td>302</td>
<td>155</td>
<td>508</td>
</tr>
<tr>
<td>Rt, cmH(_2)O(^{-1})/s</td>
<td>27.9</td>
<td>9.8</td>
<td>24.5</td>
<td>9.0</td>
<td>12.6</td>
</tr>
<tr>
<td>El, cmH(_2)O/(\text{liter}^{-1})</td>
<td>502</td>
<td>401</td>
<td>564</td>
<td>90</td>
<td>1,724</td>
</tr>
</tbody>
</table>

Diagnosis: 1 resolving respiratory distress syndrome (RDS), 7 mild RDS (4 with apnea), 8 RDS (1 with apnea). Min and Max, minimum and maximum values, respectively; PNA, postnatal age; NCPAP, nasal continuous positive airway; P\(_{\text{O}}\), inspired oxygen; Rt, lung resistance; El, lung elastance.
data were specifically chosen such that they were free of air leak around the mask (confirmed off line) and free of gross artifact for all measured signals (Pes, Pao, Vao, RC, and Abd). We determined TPTEF/TE from the expiration phase of each of the P-tach-measured TFW (2, 20).

The two harmonic content tidal flow indexes \((k_d \text{ and } s)\) were derived in similar fashion for RIP and P-tach data along the lines described by Frey et al. (11). Briefly, to determine the tidal flow power spectrum, we too applied the discrete Fourier transform (DFT; MATLAB, 6.0, MathWorks) to avoid the spectral smearing and leakage problems associated with applying the fast Fourier transform to breath data exhibiting variable (within- and between-subject) breathing frequencies \((f_b)\). No filtering or windowing of the data was used to maintain spectral content. Power spectra of the individual breaths were calculated, and the two tidal flow shape indexes were calculated. Data for individual subjects were averaged, and the within-subject variability was calculated.

**Harmonic distortion.** The deviation from a pure \(f_b\) sinusoid can be quantified as \(k_d\) and is defined as the square root of the relative power in the tidal flow above the fundamental or \(f_b\) (22, 27). Accordingly, a sine wave would have \(k_d = 0\%\), whereas increasingly higher values of \(k_d\) would indicate the presence of stronger higher frequency content.

**Power law analysis.** If the spectral harmonics of tidal flows follow a power law functional form, then the frequency dependence of TFW harmonics will be characterized by a linear decrease as a function of frequency \((f)\) when plotted on log-log scales. This is mathematically defined by the following

\[
\log |Vao(f)| = c - s \times \log(f)
\]

where Eq. 1 is the logarithm of the power law equation \(Vao(f) = A \times f^{-s}\) with \(A = \log(c)\). Note, a smaller (larger) value of \(s\) indicates greater (lower) content of harmonics at higher frequencies, resulting in less (more) single sinusoidal shape of the TFW.

**Statistical methods.** For each infant, breath-to-breath TFW from the entire flow signal were used to determine TPTEF/TE, \(f_b\) (in breaths/min), tidal volume (VT; in ml/kg), and the associated lung mechanical properties. Least squares (MATLAB, The MathWorks, Natick, MA) estimates of lung resistance (Rt) and elastance (EL) were derived by multiple-regression analysis. Here, the time \((t)\) domain pulmonotary pressure (Pt(p = Pao – Pes)) data over the entire breath were described in terms of Vao(t), Vt(t), and the elastic recoil pressure at end expiration (P0) via a series resistance-elastance model of the lungs (8, 18); i.e., Pt(p) = Rt \times Vao(t) + EL \times Vt(t) + P0.

Next, the individual breath power spectra were calculated for both proximal (P-tach) and distal (RIP) flow measurements, and the corresponding breath-to-breath \(s\) and \(k_d\) were derived. Group means [and 95% confidence interval (CI)] for all parameters were calculated. RIP vs. P-tach-based parameter estimates [and percent respiratory cycle variability (RCV%)] were compared via paired t-tests.

**RESULTS**

We studied 16 VLBW infants [8 boys and 8 girls, gestational age: 28 wk (median); birth weight: 1,114 g (median)] with varying severities of RDS (with or without apnea of prematurity) between postnatal days 1 and 14 (median = 4 days; Table 1). All babies were on NCPAP support (4–6 cmH2O) with FiO2 varying from room air (21%) up to 43%.

Figure 1 shows an example of TFW and corresponding Vt data measured directly at the mouth by using a P-tach compared with the RIP-derived flow and volume data. Respiratory rate (median: 87 breaths/min), Vt (median: 3.7 ml/kg), and TPTEF/TE (median: 0.61) varied substantially among the infants (Tables 1 and 2). Their estimated lung mechanical properties (Rt: median 24.5 cmH2O l−1s and EL: median 564 cmH2O/I) varied appreciably also (Table 1).

A total of 202 individual breaths was analyzed in all patients (10–15 breaths per subject). The overall mean ± 95% CI of TPTEF/TE was 0.62 ± 0.08. We found a consistent power law behavior of the breath-to-breath TFW harmonics in all infants. The averaged TFW spectra vs. frequency in individual subjects are shown in Fig. 2. Importantly, the power law functional form was similar when derived from direct flow measurements at the mouth (Fig. 2, top) or indirectly through Vt excursions measured distally at the chest wall (Fig. 2, bottom).

The mean and 95% CI of TFW indexes derived from all infants and their observed RCV% are summarized in Table 2. The \(s\) and \(k_d\), derived separately from measurements at the mouth \(s_{P-tach} \approx 3.73 ± 0.23%\) (CI) and \(k_d_{P-tach} = 38.8 ± 4.6\%\) and the chest wall \(s_{RIP} = 3.51 ± 0.30\%\) and \(k_d_{RIP} = 42.8 ± 4.8\%\) were of comparable value (Table 2; means of both indexes were similar by unpaired t-test) and were closely correlated (Fig. 3). Yet small but systematic between-method dif-
ferences in the values of both indexes were statistically significant (paired t-test). Linear regressions illustrating the high correlations between the power law exponent ($s$) derived from measurements at the chest wall ($s_{\text{RIP}}$) vs. $s$ derived from measurements at the mouth ($s_{\text{P-tach}}$) and harmonic distortion index ($k_d$) derived from measurements at the chest wall ($k_d_{\text{RIP}}$) vs. $k_d$ derived from measurements at the mouth ($k_d_{\text{P-tach}}$) are shown in Figure 3. Comparison of infant-averaged RIP vs. P-tach derived spectral indexes (shaded triangles) is shown with corresponding linear regression fit (solid line).

Whereas $s$ and $k_d$ did not exhibit any dependence on either infant weight or age, both showed considerable within- and between-patient variations (Fig. 3). The variability was similar, irrespective of flow measurement method (RIP vs. P-tach) when quantified in terms of the breath-to-breath or RCV% (Table 2). These results showed relatively lower $s$ RCV% ($s_{\text{P-tach}}$: 16.2 ± 8.1%; $s_{\text{RIP}}$: 13.1 ± 2.9%) compared with both $k_d$ ($k_d_{\text{RIP}}$: 23.6 ± 13.0% vs. $k_d_{\text{P-tach}}$: 18.8 ± 5.3%) and TPTEF/TE (P-tach: 22.2 ± 9.5%), whose RCV% were statistically similar (Table 3). The fact that $s$ had the lowest variability was consistent with findings of Frey et al. (11), but, unlike their data in larger infants, TPTEF/TE in VLBW babies did not exhibit significantly greater breath-to-breath variations compared with $k_d$.

Fig. 2. Averaged P-tach (top) and RIP (bottom) derived flow power spectra shown for each infant (shaded lines) on a log-log plot. Note, for each infant, frequencies were normalized to the corresponding breath frequency ($f_{\text{br}}$) or fundamental such that $f_{\text{br}} = 1$. The mean ± SD flow power spectra for all infants are represented by the symbols and error bars.

Fig. 3. Breath-by-breath comparison of RIP vs. P-tach derived spectral indexes from all infants (open circles): power law exponent ($s$) derived from measurements at the chest wall ($s_{\text{RIP}}$) vs. $s$ derived from measurements at the mouth ($s_{\text{P-tach}}$) (top) and harmonic distortion index ($k_d$) derived from measurements at the chest wall ($k_d_{\text{RIP}}$) vs. $k_d$ derived from measurements at the mouth ($k_d_{\text{P-tach}}$) (bottom). Comparison of infant-averaged RIP vs. P-tach derived spectral indexes (shaded triangles) is shown with corresponding linear regression fit (solid line).

Table 2. Summary of tidal flow waveform parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Group 95% CI</th>
<th>Respiratory Cycle Variability CV, % (group means ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPTEF/TE</td>
<td>0.62</td>
<td>0.08</td>
<td>22.2 ± 9.5</td>
</tr>
<tr>
<td>$k_d_{\text{P-tach}}$</td>
<td>38.8</td>
<td>4.62</td>
<td>23.6 ± 13.0</td>
</tr>
<tr>
<td>$k_d_{\text{RIP}}$</td>
<td>42.8</td>
<td>4.75</td>
<td>18.8 ± 5.3</td>
</tr>
<tr>
<td>$s_{\text{P-tach}}$</td>
<td>3.73</td>
<td>0.23</td>
<td>16.2 ± 8.1</td>
</tr>
<tr>
<td>$s_{\text{RIP}}$</td>
<td>3.51</td>
<td>0.30</td>
<td>13.1 ± 2.9</td>
</tr>
</tbody>
</table>

CI, confidence interval; CV, coefficient of variation; TPTEF/TE, time to peak tidal expiratory flow-to-expiratory time ratio; P-tach, pneumotachograph; RIP, respiratory inductance plethysmography; $s$, power law exponent; $k_d$, harmonic distortion index; $s_{\text{P-tach}}$ and $s_{\text{RIP}}$, respectively, derived from measurements at the mouth; $k_d_{\text{RIP}}$ and $k_d_{\text{P-tach}}$, $k_d$ and $s$, respectively, derived from measurements at the chest wall. Despite similarity of the absolute mean values of $s$ and $k_d$ (all were similar by unpaired t-test), both of these parameters ($s_{\text{P-tach}}$ vs. $s_{\text{RIP}}$: $P = 0.004$, $k_d_{\text{P-tach}}$ vs. $k_d_{\text{RIP}}$: $P = 0.005$) were statistically significantly different by paired t-test because of small but mostly systematic differences in these parameters across flow-measuring methods (see Figure 3).
DISCUSSION

A primary finding of this study is that tidal flow harmonics in VLBW infants follow a power law functional form similar to that described in older and/or larger infants (11). Also, tidal flow spectra are essentially similar, as are, consequently, their corresponding $s$ and $k_d$ indexes, if derived from direct face mask P-tach flows measured at the airway opening or indirectly via distal RIP (Figs. 2 and 3).

The averaged $s$ (mean $s_{P-tach}$: 3.73%) and $k_d$ (mean $k_d,P-tach$: 38.8%) values of VLBW babies were similar to those reported (11) in older and/or larger babies with CLD (CLD: 3.84 and 44.3%, respectively). Yet the $s$ and $k_d$ of VLBW babies differ appreciably from the corresponding values (4.24 and 26.2%, respectively) reported in healthy 1-mo-old infants (11), despite being of closer age and size.

TPTEF/TE, a simple, noninvasive tidal flow index derived from spontaneous breathing time domain expiratory flow data, has been shown to convey information regarding airway mechanics in infants (2, 3, 6, 7, 20) and has also linked to inspiratory drive (13, 25) and postinspiratory respiratory muscle drive (26). In our VLBW infants, TPTEF/TE values were noticeably greater than those reported in older infants, whether healthy or diseased. Indeed, when combined with the data of Frey et al. (11), TPTEF/TE data indicate 1) a systematic decrease in this parameter up to ~6 mo postnatal age, and 2) little or no effect of CLD and reactive airway disease on this parameter (Fig. 4). This is rather in contrast to $s$ and $k_d$ values that

<table>
<thead>
<tr>
<th>Compared Parameters</th>
<th>$t$ Statistic</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_d,P-tach$ vs. $s_{P-tach}$</td>
<td>-3.07</td>
<td>0.008</td>
</tr>
<tr>
<td>$k_d,P-tach$ vs. TPTEF/TE</td>
<td>-0.29</td>
<td>ns</td>
</tr>
<tr>
<td>$s_{P-tach}$ vs. TPTEF/TE</td>
<td>-3.02</td>
<td>0.009</td>
</tr>
<tr>
<td>RIP measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_d,RIP$ vs. $s_{RIP}$</td>
<td>-3.29</td>
<td>0.005</td>
</tr>
<tr>
<td>$k_d,RIP$ vs. TPTEF/TE</td>
<td>-1.04</td>
<td>ns</td>
</tr>
<tr>
<td>$s_{RIP}$ vs. TPTEF/TE</td>
<td>-3.28</td>
<td>0.005</td>
</tr>
<tr>
<td>RIP vs. P-tach</td>
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<td></td>
</tr>
<tr>
<td>$k_d,RIP$ vs. $k_d,P-tach$</td>
<td>0.90</td>
<td>ns</td>
</tr>
<tr>
<td>$s_{RIP}$ vs. $s_{P-tach}$</td>
<td>0.47</td>
<td>ns</td>
</tr>
</tbody>
</table>

In each infant, we computed the percent respiratory cycle variability (RCV%) for all breaths relative to the mean value of each parameter with each method. Next, we calculated the group mean values for all parameters. Within-method and across-method RCV% comparisons were done using paired $t$-test. ns, Not significant. Power of analysis was >0.8 in all cases. TFW, tidal flow waveform.

Table 3. Comparison of respiratory cycle variability of TFW-derived parameters expressed by its coefficient of variations

![Fig. 4. Mean (±95% confidence interval) time to peak tidal expiratory flow-to-expiratory time ratio (TPTEF/TE; top), $s$ (middle), and $k_d$ (bottom) of 5 infant groups of varying size [left; weight (Wt) in kilograms] and age [right; post conception age (PCA) in weeks]. All data points except for VLBW (solid triangles) were based on values reported by Frey et al. (11). Open circles, averaged longitudinal data from 10 healthy infants at 1, 6, and 12 mo after birth (an average PCA of 40 wk at birth was assumed for these babies); shaded squares, averaged data from 10 chronic lung disease infants (postnatal age: 8.1 ± 7.2 mo) who were premature at birth (gestational age: 27.7 ± 2.4 wk).]
seemed to differ more with health status, as opposed to maturation. Hence it appears that the time-domain expiratory phase parameter, TPTEF/Te, may provide different and possibly complementary information to that available from the two spectral (or frequency-domain) indexes, s and k_d.

It has been suggested that significantly lower breath-to-breath s and k_d variability relative to that of TPTEF/Te indicated increased robustness of these spectral indexes, perhaps making them more useful as clinical parameters (11). Our results in preterm infants did not fully duplicate their within-subject RCV% findings. We, instead, found that 1) VLBW babies exhibited greater TPTEF/Te, s, and k_d variability compared with older infants; and 2) RCV% was lowest for s and was similar for k_d and TPTEF/Te. A variety of factors can potentially influence RCV% of TFW indexes. The possibility that the greater RCV% in the VLBW babies data that we present here is a characteristic of prematurity cannot be discounted, particularly given the variations in the underlying disease severity (see Table 1). However, the limited study population and study design do not allow for definitive conclusions.

A notable measurement-related difference between our study and that by Frey et al. (11) is that our infants were studied during quiet sleep but without sedation. The potential effects of sedation on the derived parameters are unknown to us, but such effects are possible, particularly as these indexes vary with sedation-related breathing pattern changes. Breathing pattern may also be modified by each infant’s response to the unavoidable manipulation associated with face mask flow measurements. Tolerance of such manipulation may differ in sedated compared with nonsedated babies. These artificial effects attest to the potential benefits of distal or chest wall flow measurements, which our data indicated will provide an equivalent, yet non-intrusive, surrogate to face mask flow data.

Overall, the breathing pattern that we measured in VLBW infants was characterized by a somewhat high breathing rate (f_br) and low Vr (in ml/kg). Also, both f_br and Vr showed significant within- and between-patient variations (Table 1). As discussed above, these values may have been partly due to the intrusive nature of face mask measurements and may have been tolerated differently among subjects. We examined the effects of varying f_br and Vr on s and k_d and found no systematic effects of Vr on either index. Alternatively, we found a significant trend of increasing s at higher f_br (r^2 = 0.36; P < 0.001), a trend similar for mouth and chest wall flow measurements (Fig. 5, top). Then, expectedly, k_d tended to decrease with increasing f_br, albeit less steeply (r^2 = 0.13; P < 0.001; Fig. 5, bottom). We found no evidence that any of the TFW indexes exhibited age and/or size dependence for the range of values (see Table 1) in the studied VLBW baby population.

While not reported in their paper (11), Frey and colleagues did not find systematic changes in s and k_d estimates with breathing pattern (personal communication). Importantly, their data also did not include high respiratory rates (>60 breaths/min) and were collected in sedated babies who are less likely to alter their breathing pattern during the measurements. Alternatively, such rates are rather common in preterm infants in respiratory distress, particularly when removed from their NCPAP support and with the placement of the face mask for measurements. Therefore, for respiratory rates characteristic of VLBW babies, changes in breathing pattern may contribute to observed variations in spectral indexes and hence should be considered when interpreting tidal flow s and k_d data in this population.

A potential limiting or confounding factor in our analysis is the fact that the measurements were done in VLBW babies shortly after discontinuing their NCPAP support, with or without supplemental FIO2 (see Table 1). Moreover, the levels of distending pressure and oxygen support could have varied among infants, as did the time between support interruption and the actual analyzed breath data. Possible consequences of these factors are that measurements may have been done at differing 1) effective lung volumes and 2) oxygenation levels among the different babies.
In fact, even for the same subject, the rate of lung volume derecruitment and possible changes in oxygenation after discontinuing NCPAP could have varied, depending on the extent of underlying RDS, level of support, and duration of face mask measurements. Note that babies were not allowed to drop their oxygen saturation <90 at any time during the measurements. One expects that varying lung volume and oxygenation will alter respiratory control (and hence the tidal flow characteristics) through the stretch- and chemoreceptor feedback mechanisms feeding into the respiratory oscillator (4, 13, 16, 19).

An important result of our study is that we found that accurate flow measurements with essentially equivalent flow spectral information are possible by distal flow measurements obtained at the chest wall via inductance plethysmography. To illustrate, this approach would allow characterization of tidal flows in its clinically relevant form, i.e., while NCPAP and FiO2 support is maintained and airway opening conditions are not artificially altered. Infant breathing is also known to exhibit long-range correlations (5, 10, 14, 21), which means that very long time series of tidal flow indexes such as s and k_d are needed to accurately and more fully characterize their underlying control of breathing. This too is greatly facilitated by the fact that s and k_d can be equivalently derived from noninvasive chest wall measurements that are less likely to modify breathing pattern, interrupt ventilatory support, or introduce additional and/or altered imposed work of breathing load.

In the smallest VLBW babies, the immature chest wall may lead to excessive chest wall distortion and possibly paradoxical breathing. In such instances, use of RIP flows (particularly if combining RC and Abd signals) to assess TFW spectral characteristics may be problematic. It is unclear whether using RC or Abd movement alone would yield satisfactory results in such situations and should be investigated in future studies. In this study, we did not encounter cases of excessive chest wall distortion, which may have partly been due to the fact that babies were on NCPAP support until shortly before the measurements, as well as because of the relative short duration of data collection.

In conclusion, our study reports for the first time a three phase model of respiratory rhythm generation. Further studies should hence determine whether a similar (or modified) dependence is present in healthy and diseased older infants, as well as explore its effects on interpreting s and k_d.

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