Effect of weight and age on respiratory complexity in premature neonates

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Engoren M, Courtney SE, Habib RH. Effect of weight and age on respiratory complexity in premature neonates. J Appl Physiol 106: 766–773, 2009; First published November 26, 2008; doi:10.1152/japplphysiol.90575.2008.—Very low-birth-weight premature infants often suffer from a variety of respiratory problems, including respiratory distress syndrome (RDS), hypopnea and periodic breathing, and apnea. These conditions are likely related to immaturity of the respiratory centers; yet how respiratory rhythms originating from these centers, including their complexity, relate to demographic measures of prematurity remains largely unknown. In 39 neonates with mild RDS (22 males, 28 ± 2 wk gestational age, 1,036 ± 234 g body wt), we derived the univariate association between complexity of two respiratory rhythms [respiratory rate (RR) and tidal volume (VT)] and postnatal age, gestational age, postconceptional age, and weight at time of study. RR and VT rhythm complexities were assessed using approximate entropy, sample entropy, base scale entropy, and forbidden words entropy estimated for 300 consecutive breaths determined from respiratory inductance plethysmography, irrespective of breathing effort rate or amplitude, collected during sleep while the neonates were exposed to nasal continuous positive airway pressure (4–6 cmH2O). RR and VT exhibited increased complexity with increased maturity, but only in terms of base scale entropy and forbidden words entropy, which are based on pattern matching, rather than approximate entropy and sample entropy, which are based on conditional probabilities. Specifically, RR complexity as measured by forbidden word entropy increased with increasing weight (r = 0.502), postconceptional age (r = 0.423), and gestational age (r = 0.493). As measured by base scale entropy, RR complexity increased with increasing weight (r = 0.488) and postconceptional age (r = 0.390). VT complexity, measured by base scale entropy, was greater with increased postnatal age (r = 0.428). Our results indicate that respiratory rhythms become more complex with increasing levels of maturity, as indicated by increased weight and several age parameters. This emphasizes the importance of the later weeks of gestation in the maturation of respiratory centers in the brain and suggests a promising use of entropy measures in exploring respiratory maturation in infants.

sudden infant death syndrome; respiratory control center; tidal volume; respiratory rate

PREMATURELY BORN INFANTS may suffer from a variety of respiratory problems, including respiratory distress syndrome, hypopnea, periodic breathing, and apnea. They are also more susceptible to sudden infant death syndrome (SIDS). Apneas, periodic breathing, and SIDS suggest abnormalities in respiratory control. The respiratory controllers in the brain stem and related rostral neurons involved in respiratory control receive inputs from a variety of feedback and primary sources. These respiratory centers undergo variable and nonlinear development and maturation during the weeks before full-term birth and during the 1st mo of life (10, 11, 14). Damage to these sources or their failure to develop leads to respiratory disturbances, increases the risk of death, and prevents development of a mature respiratory pattern (6–9, 15, 23, 24). The feedback and feedforward mechanisms that control respiration and produce homeostasis of blood gases and pH require stability and memory of the previous breaths (4). These memories, patterns, or physiological rhythms are complex nonlinear processes that reflect the underlying physiological state of the organs and controllers that produce the rhythm (18). Typically, these rhythms are studied by a variety of mathematical tools that measure the entropy, irregularity, or complexity of the rhythm (28, 32, 33).

Studies have examined respiratory pattern in neonatal animal models and adult humans. In human adults, approximate entropy, a statistical measure of complexity (where a complex series is more irregular, i.e., contains more information and is less predictable), has been shown to differentiate between patients with and without respiratory disease (16, 39). In neonatal animal models, peripheral chemodenervation had no effect on the phrenic neurogram in the full-term piglet at 3–7 days of age, but it produced decreased complexity when studied under hypoxic conditions in 10- to 16- and 25- to 31-day-old piglets (1). However, another study of full-term piglets showed that the vagus nerve did not contribute to variability as assessed by approximate entropy of the phrenic neurogram in decerebrate animals (2). Although we could find no studies evaluating the complexity of respiratory rhythms in human preterm neonates, several studies evaluated respiratory rhythms in healthy postterm infants and showed that the rhythms exhibit complexity (4, 12, 36). Baldwin et al. (4) studied healthy full-term infants at 1 mo of age and found that short-range memory of tidal volume (VT) increased after a sigh, but there was no long-term memory. Cernele et al. (12), in a study of healthy full-term infants at 36 ± 6 days of age, found long-term correlations in VT, but these were not associated with gestational or postnatal age. Small et al. (36), using correlation dimension, found that the breathing patterns in healthy infants at 1–6 mo of age exhibited low-dimensional behavior, suggesting that “regular breathing . . . is probably chaotic.”

Study of premature neonates may be more difficult than study of healthy human infants and animal models. Respiratory parameters must be measured between therapies and feedings

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that may perturb respiratory pattern or introduce artifacts. Therefore, the mathematical tools used to evaluate respiratory rhythms must be able to achieve results in very short time periods. Several mathematical tools have been described for evaluation of physiological rhythms and determination of their complexity.

The purpose of this study is to determine the association in premature neonates between complexity of respiratory rate (RR) or VT and infant age and weight. Specifically, we hypothesize that complexity will change with increasing age and weight.

**METHODS**

**Patients and Measurements**

The infant breathing pattern variability data analyzed in this study was derived from spontaneous breathing during variable-flow nasal continuous positive airway pressure (NCPAP). The data were collected as part of two separate trials comparing work of breathing in premature infants during variable-flow NCPAP (13, 22, 29). The demographics of the subjects were similar, and the data were collected with the same device. Preterm infants (<1,500 g birth wt) requiring NCPAP for mild respiratory distress (≤0.40 inspiratory O2 fraction, to ensure tolerance of study procedures) were eligible for study. Those with airway anomalies, other major anomalies, or >35 wk postmenstrual age were excluded. The protocol was approved by the North Shore Long Island Jewish Health System Institutional Review Board, and consent was obtained from both parents before the study.

**Instrumentation and Data Collection**

NCPAP was administered in standard fashion using the Infant Flow NCPAP (Viasys Health Care, Conshohocken, PA). Spontaneous breathing was measured from chest wall and abdominal movements recorded using respiratory inductance plethysmography (RIP, Respiband Plus Neonate/Infant and Respiritrace QDC, Viasys Health Care). After 5–10 min of stabilization on continuous positive airway pressure (4–6 cmH2O), data were collected continuously using a computerized data acquisition system (model MP100, Biopac Systems, Goleta, CA) at 1,000 samples per second per channel. Collected data were filtered using a digital low-pass filter [−92 dB (Blackman); Acknowledge version 3.7.2 software (BioPac Systems)] with a cutoff frequency of 5 Hz to minimize nonphysiological noise.

**Determination of Breath-to-Breath Data**

Data collected during periods of infant agitation and crying were excluded from consideration. In each infant, a period of continuous comfortable breathing or quiet sleep was identified, and the corresponding summed rib cage and abdominal data (VT measured by RIP) were used to determine breath-to-breath variations in RR and tidal ventilation (Fig. 1). In 3 of 39 infants, major artifacts were present in one of the bands; in these cases, the breathing data were based on a single RIP band. A Matlab computer program that was adapted from the peak-detection algorithm of Peng et al. (31) and met international standards (17) was used to determine the peak-to-peak intrabreath interval (pIBrI, in s; Fig. 2). Next, we determined the valley-to-valley intervals (in s). Breath size or VT of each breathing effort [VT(k)] was calculated as the difference between the peak RIP-measured VT and the average of the two valley values on either side of the peak (Fig. 2). For our analysis, RR [RR(k), in min⁻¹] was determined as the ratio 60 divided by the corresponding pIBrI(k).

**Complexity Analysis**

**Entropy measurements.** Breath data (RR and VT) were analyzed initially using means and standard deviations. To determine complexity, six measures of entropy were calculated: approximate entropy (ApEn) (32), sample entropy (SpEn) (35), base scale entropy (BsEn) (28), forbidden words entropy (FwEn) (28, 38), cross-ApEn (29) with the modification proposed by Richman and Moorman (35), and cross-SpEn (35). Briefly, these six measures of entropy attempt to determine the complexity of a series of numbers. All have the following advantages: they are computationally fast, and they require short data sets of ~300–1,000 points. However, they differ in the manner in which they handle nonstationary, noisy signals, which are the normal characteristics of physiological rhythms.

ApEn was calculated as shown in steps 1–6, SpEn as shown in steps 7–13, and BsEn as shown in steps 14–18. ApEn and SpEn are...
the conditional probabilities that two sequences within a tolerance \( r \) for 2 points remain within \( r \) of each other at the next point. BzEn and FwEn transform a time signal to a symbol signal and denote the uncertain occurrence of \( m \) consecutive points of the form \( \pi \).

They predominantly differ from ApEn and SpEn, in that they evaluate only the local information contained in the \( m \) consecutive points, whereas ApEn and SpEn compare the local vectors with all vectors in the series. By restricting their (BzEn and FwEn) evaluations to only \( m \) consecutive points at a time, Li and Ning (28) proposed that nonstationary data are better handled by BzEn and FwEn than by ApEn and SpEn.

**ApEn.** For ApEn (32), \( N \) is the number of points in the series and \( m \) (pattern length) = 2 for calculation of pairs of points and 3 for triplets of points.

We varied \( r \) from 1 to 300% of the standard deviation of the series of points; 20% was used in **RESULTS**.

In step 1, we constructed \( N - m + 1 \) vectors, labeled \( x_i \) for each \( 1 \leq i \leq N - m + 1 \), of length \( m \) consisting of each consecutive pair (triplet) of points in the time series.

In step 2, we defined the distance \( d \) as \( \max(x_j - x_k) \), where \( d \) represents the maximum difference between their scalar components.

In step 3, we divided the frequency of \( d \leq r \) by \( (N - m + 1) \) for each vector of paired (triplet) points \( x_i \) compared with every other pair (triplet) of consecutive points \( x_j \) and call it \( C^m(\cdot) \), which is the number of vectors within the tolerance \( r \) scaled for the number of possible vectors.

In step 4, we defined \( \phi^m(\cdot) = (N - m + 1)^{-1} \sum C^m(\cdot) \) from \( i = 1 \) to \( N - m + 1 \), when \( m = 2 \).

In step 5, we repeated steps 1–4 using \( m = 3 \) for triplets of points to produce \( \phi^m(\cdot) \).

**SpEn.** SpEn (35) is similar to ApEn, in that both look for matches within tolerance \( r \), but SpEn differs from ApEn by avoiding self-matches, that is, \( i \neq j \), and is largely independent of series length. For SpEn, \( N \) is the number of points in the series; \( B \), the probability that two sequences (pairs of points) are within tolerance \( r \), was calculated using \( m \) (pattern length) = 2, and \( A \), the probability that two sequences (triplets of points) are within tolerance \( r \), was calculated using \( m \) (pattern length) = 3.

We varied \( r \) from 1 to 300% of the standard deviation of the series of points; 20% was used in **RESULTS**.

In step 7, we constructed \( N - m + 1 \) vectors, labeled \( x_i \) for each \( 1 \leq i \leq N - m + 1 \), of length \( m \) consisting of each consecutive pair (triplet) of points in the time series.

In step 8, we defined the distance \( d \) as \( \max(x_j - x_k) \), where \( d \) represents the maximum difference between their scalar components.

In step 9, the number of length \( m \) = 2 vectors \( x_m(i) \) occurring within \( r \) of \( x_m(i) \), scaled by the total number of vectors, was then calculated as \( B \), i.e., \( B = (N - m + 1)^{-1} \sum_{i=1}^{N-m+1} |\delta| \).

In step 10, this was summed over all \( i \), i.e., \( B(\cdot) = (N - m)^{-1} \sum_{i=1}^{N-m+1} |\delta| \).

In step 11, we defined \( A \) as the number of length \( m = 3 \) vectors \( x_m + 3(i) \) occurring within \( r \) of \( x_m + 3(i) \) scaled by the total number of vectors: \( A(\cdot) = (N - m + 1)^{-1} \sum_{i=1}^{N-m+1} |\delta| \).

In step 12, this was summed over all \( i \), i.e., \( A = (N - m)^{-1} \sum_{i=1}^{N-m+1} |\delta| \).

In step 13, SpEn is the negative natural logarithm of the number of length \( m = 3 \) vectors within \( r \) divided by the number of length \( m = 2 \) vectors within \( r \) : \( \ln[A(\cdot)/B(\cdot)] \).

**BsEn.** For BsEn (28), \( N \) is the number of points in the time series \( u, m \) (pattern length) = 3 or 4 for calculation of triplets or quartets or points, \( m = 3 \) was used in **RESULTS**, and \( \alpha \) is a filter, similar to tolerance \( r \) used in ApEn and SpEn. If \( \alpha \) is too large, information will be lost; if \( \alpha \) is too small, BsEn will reflect noise, and not data.

In step 14, we embedded the time series \( m \)-dimensional space and construct \( (N - m + 1) \) vectors \( x(i) = [u(i), u(i + 1), u(i + 2)] \), consisting of every set of \( m \) consecutive points.

In step 15

\[ Z_{BS}(i) = \left( \sum_{j=1}^{m-1} [u(i + j) - u(i + j - 1)]^2 / (m - 1) \right)^{1/2} \]

Then, in step 16, we transformed each \( m \)-dimensional vector \( x(i) \) into a symbolic sequence \( S_x(x(i)) = [s(i), s(i + 1), \ldots, s(i + m - 1)] \), on the basis of the alphabet \( \chi \). The values of \( \chi \) (0, 1, 2, 3) are symbols and should not be construed as numbers

\[ S_x(x(i)) = 0, \text{ if } U_i < u(i + k) \leq U_i + \alpha Z_{BS} \]

\[ = 1, \text{ if } u(i + k) > U_i + \alpha Z_{BS} \]

\[ = 2, \text{ if } U_i - \alpha Z_{BS} < u(i + k) \leq U \]

\[ = 3, \text{ if } u(i + k) \leq U_i - \alpha Z_{BS} \]

where \( i \) (each sequential breath in the time series) = 1, 2, 3, \ldots, \( N - m + 1 \); \( k \) (each of the \( m \) breaths in the pattern being compared) = 0, 1, or 2 if \( m = 3 \) and \( k = 0, 1, 2 \), or 3 if \( m = 4 \); \( U_i = [u(i) + u(i + 1) + \ldots + u(i + m - 1)] / m \); and \( U \) is the arithmetic mean of each set of \( m \) consecutive points. Here, we compared the value of \( u(i + k) \) with the mean value \( U_i \) and the filter \( \alpha Z_{BS} \) and assigned a symbol 0, 1, 2, or 3 to their relationship depending on whether \( u(i + k) \) was above the mean but below the mean + the filter (assigned the symbol 0), greater than the mean + the filter (symbol 1), below the mean but above the mean − the filter (symbol 2), or below the mean − the filter (symbol 3). This characterized the relation between the particular value in the time series \( u(i + k) \) and the mean value \( U_i \) (of the local 3 consecutive points) and noise, which was expressed as the filter \( \alpha Z_{BS} \).

In step 17, the symbols of \( \chi \) can be combined in \( m^2 \) different forms, 64 forms if \( m = 3 \), and 256 forms if \( m = 4 \). For \( m = 3 \), for each \( \chi \) (000, 001, 002, 003, 010, 011, \ldots, 332, 333), we determined its frequency. For \( m = 4 \), for each \( \chi \) (0000, 0001, \ldots, 3332, 3333), we determined its frequency.

In step 18, for \( m = 3 \), we calculated BsEn = \(-\sum_{\pi=0}^{3} p(\pi) \log_2(\pi)\), where \( p(\pi) \) is the number \( \{i 1 \leq i \leq N - m + 1 | u(i), \ldots, u(i + m - 1) \} \) and has form \( \chi/(N - m + 1) \).

[Note that BsEn renormalizes the delay vectors and extracts the wave characteristics of the time series but ignores the amplitude of the wave.]

**FwEn.** For FwEn (28,38), in a regular series, only a few of the symbol combinations from step 16 occur (38). A more complex series will have many symbol combinations occur. The symbol combinations that do not occur are called forbidden words; hence, low forbidden words indicate greater complexity. However, the convention for entropy is that higher numbers indicate greater complexity, so we subtracted the number of forbidden words from the number of possible symbol combinations and termed this FwEn.

**Sensitivity Analysis**

To choose the appropriate filter sizes, \( r \) and \( \alpha \), we first randomized the individual data series by shuffling them (12) and calculated ApEn, SpEn, cross-ApEn, and cross-SpEn with \( r = 1\)–300% of the standard deviation for each data set and calculated FwEn and BsEn for \( \alpha = 0.01\)–3. We also varied \( m \), the number of points in each vector, in calculating FwEn and BsEn from 3 to 4. (We did not perform a sensitivity analysis of \( m \) for ApEn, SpEn, cross-ApEn, and cross-SpEn, because the number of breaths was insufficient.) Increasing \( m \) by 1 for comparison of triplets (\( m = 3 \)) and quadruplets (\( m = 4 \)) of breaths requires 1,000–10,000 breaths (31). We then chose the filters, \( r \) and \( \alpha \), that were in an area of stability. For final analysis, we chose \( r = 20\% \) of the standard deviation to calculate ApEn and SpEn and \( \alpha = 0.5 \) with \( m = 3 \) to calculate FwEn and BsEn.
Cross-Entropy Measurements

RR and VT are not independent rhythms but, rather, are inversely related to produce a constant minute volume to maintain arterial PCO2 at a constant level. We therefore examined the complexity of the linkage of RR and VT as measured by cross-ApEn and cross-SpEn. Conceptually, cross-ApEn and cross-SpEn are similar to ApEn and SpEn. To calculate cross-ApEn and cross-SpEn, we first normalized the RR and VT series by setting the normalized vector \( x_i = [x_i - \text{mean}(x)] / \text{standard deviation of } x \) (32, 35). This produced normalized series of equal means and standard deviations. Where both ApEn and SpEn compare each vector within the series with every other vector within the same series, e.g., each pair of consecutive VT measurements is compared with every other pair of VT measurements; cross-ApEn and cross-SpEn compare each pair of vectors within a series with every pair of vectors within the other series, e.g., each pair of consecutive normalized VT values is compared with every pair of consecutive normalized RR values. Further calculation of cross-ApEn and cross-SpEn follows the calculations for ApEn (with the suggested correction) (32, 35) and SpEn (35). Whereas ApEn and SpEn evaluate complexity within one physiological rhythm, cross-ApEn and cross-SpEn evaluate complexity within the relationship between two related physiological rhythms (32, 35). Whereas cross-SpEn is nondirectional, cross-ApEn is directional: the cross-ApEn of comparing normalized VT with normalized RR is not necessarily equal to the cross-ApEn of comparing normalized RR with normalized VT; hence, we computed cross-ApEn in both directions.

Higher values of all the entropy measures, ApEn, SpEn, BsEn, FwEn, cross-ApEn, and cross-SpEn, indicate greater complexity. Entropy values were then graphed against postnatal age, postmenstrual age, gestational age, and weight, and the correlation coefficients were calculated. All entropy calculations were done using FORTRAN Powerstation (Microsoft, Redlands, WA), SPSS 16.0 (SPSS, Chicago, IL) was used to calculate correlations (Pearson’s r) and means ± SD. \( P < 0.05 \) was considered significant.

RESULTS

We studied 39 preterm neonates (Table 1) for 306–1,107 breaths (mean ± SD = 571 ± 244 breaths), but we used only the first 300 breaths for analysis. Using the shuffled data sets, we found that the correlations between the entropy values and weights and ages were close to zero. However, the correlations for the actual breath sets varied little from one value to the next value of \( r \) or \( \alpha \) (Fig. 3). Using \( r = 20\% \) of the standard deviation for ApEn, SpEn, cross-ApEn, and cross-SpEn, we found no association between these entropy statistics and weight or ages. Using \( \alpha = 0.5 \) and \( m = 3 \), FwEn and BsEn showed statistically significant increases in complexity with increasing weights and ages (Table 2). Specifically, complexity of the RR as measured by FwEn increased with increasing weight, gestational age, and postconceptional age (Fig. 4), and complexity of the RR measured by BsEn increased with increased weight and postconceptional age (Fig. 4). However, VT complexity as measured by BsEn was only associated with postnatal age as measured by BsEn (Fig. 5).

DISCUSSION

We found that complexity of the respiratory system, measured by FwEn and BsEn, but not ApEn, SpEn, cross-ApEn, and cross-SpEn, increased with increasing ages and weight. This increased complexity was more apparent in the RR rhythm but was still present in the VT rhythm. Higher complexity or a more irregular pattern has previously been associated with more mature and healthier systems (21, 28, 33, 35).

Table 2. Correlation coefficients

<table>
<thead>
<tr>
<th>Respiratory Parameter</th>
<th>Body wt</th>
<th>Postnatal age</th>
<th>Gestational age</th>
<th>Postconceptional age</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>0.123</td>
<td>−0.015</td>
<td>0.151</td>
<td>0.150</td>
</tr>
<tr>
<td>SD of RR</td>
<td>0.179</td>
<td>0.111</td>
<td>0.127</td>
<td>0.147</td>
</tr>
<tr>
<td>ApEn of RR</td>
<td>0.069</td>
<td>0.113</td>
<td>−0.191</td>
<td>−0.115</td>
</tr>
<tr>
<td>SpEn of RR</td>
<td>0.088</td>
<td>0.189</td>
<td>−0.213</td>
<td>−0.082</td>
</tr>
<tr>
<td>FwEn of RR</td>
<td>0.502†</td>
<td>−0.173</td>
<td>0.493†</td>
<td>0.423*</td>
</tr>
<tr>
<td>BsEn of RR</td>
<td>0.488†</td>
<td>0.184</td>
<td>0.243</td>
<td>0.390*</td>
</tr>
<tr>
<td>Cross-ApEn of RR</td>
<td>0.057</td>
<td>0.121</td>
<td>−0.178</td>
<td>−0.090</td>
</tr>
<tr>
<td>Cross-ApEn (reversed) of RR</td>
<td>0.129</td>
<td>0.166</td>
<td>−0.129</td>
<td>−0.008</td>
</tr>
<tr>
<td>Cross-SpEn of RR</td>
<td>0.006</td>
<td>0.117</td>
<td>−0.220</td>
<td>−0.144</td>
</tr>
<tr>
<td>Vt</td>
<td>0.207</td>
<td>0.241</td>
<td>−0.273</td>
<td>−0.133</td>
</tr>
<tr>
<td>SD of Vt</td>
<td>0.158</td>
<td>−0.011</td>
<td>0.104</td>
<td>0.101</td>
</tr>
<tr>
<td>ApEn of Vt</td>
<td>0.048</td>
<td>0.122</td>
<td>−0.129</td>
<td>−0.035</td>
</tr>
<tr>
<td>SpEn of Vt</td>
<td>−0.055</td>
<td>0.089</td>
<td>−0.231</td>
<td>−0.174</td>
</tr>
<tr>
<td>FwEn of Vt</td>
<td>0.073</td>
<td>0.202</td>
<td>0.014</td>
<td>0.153</td>
</tr>
<tr>
<td>BsEn of Vt</td>
<td>0.095</td>
<td>0.428†</td>
<td>−0.180</td>
<td>0.141</td>
</tr>
<tr>
<td>Cross-ApEn of Vt</td>
<td>0.129</td>
<td>0.166</td>
<td>−0.129</td>
<td>−0.008</td>
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<td>−0.144</td>
</tr>
</tbody>
</table>

ApEn, approximate entropy; SpEn, sample entropy; FwEn, forbidden words entropy; BsEn, base scale entropy. \( *P < 0.05 \). \( †P < 0.01 \).

Table 1. Demographics and respiratory characteristics of neonate subjects

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body wt, g</td>
<td>1,036</td>
<td>234</td>
<td>525–1,446</td>
</tr>
<tr>
<td>Postnatal age, days</td>
<td>11</td>
<td>11</td>
<td>1–58</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>28</td>
<td>2</td>
<td>23–33</td>
</tr>
<tr>
<td>Postmenstrual age, wk</td>
<td>29</td>
<td>2</td>
<td>26–34</td>
</tr>
<tr>
<td>RR, min⁻¹</td>
<td>76.5</td>
<td>20.0</td>
<td>40.0–124.2</td>
</tr>
<tr>
<td>VT, V</td>
<td>0.354</td>
<td>0.121</td>
<td>0.09–0.64</td>
</tr>
</tbody>
</table>

Data are from 39 neonates. RR, respiratory rate; VT, tidal volume.
38). By better handling of physiological input, the more complex system may be better able to maintain homeostasis and avoid problems following perturbations. We found that BsEn and FwEn were more likely than ApEn and SpEn to find statistically significant evidence of increased complexity. Li and Ning (28) showed that BsEn, which incorporates forbidden words into its computation of complexity, is a more sensitive indicator of complexity and better than ApEn and SpEn at separating normal from abnormal cardiac rhythms in patients with heart failure. Conversely, we cannot exclude a type I error, where BsEn and FwEn found spurious associations and the complexity does not change over the time period and weights studied. There are several other possible explanations for our failure to detect an increased complexity with ApEn and SpEn and our ability to detect an increased complexity with BsEn and FwEn. 1) The ranges of ages and weights may have been too small for detection of a subtle change in complexity. 2) The length of the time series ($n =$...
300) may have been too short for separation of signal from noise. For calculations, we chose 300 breaths, which was the minimum achieved by all neonates, and previous study in adult intensive care unit patients showed similar predictive accuracy when 300 or 1,000 breaths were used to identify respiratory failure (16). Although SpEn is independent of series length, all the other complexity statistics increase with increasing series length, thus prohibiting comparisons between series of different lengths. However, the sensitivity of BsEn and FwEn was sufficient to find differences in series of only 300 breaths. J) Complexity does not change with neurological development. However, this explanation would be inconsistent with studies by Akay et al. (1–3), who found that complexity measured by ApEn increased with developmental age. More intriguingly, the differences in sensitivity may imply a difference in complexity over different numbers of breaths. ApEn and SpEn in our study compared the complexity between pairs and triplets of breaths, whereas BsEn and FwEn analyzed the
complexity over triplets of breaths, which suggests that as the respiratory controllers mature, the memory of previous breaths extends over a greater number of breaths. This length of memory effect agrees with a study in adults that showed that the number of breaths with autocorrelated RR is affected by experimental endotoxemia (34). Although ApEn and SpEn can evaluate triplets of points, many-fold more breaths (1,000–10,000) would be required to produce valid results (32, 35).

Our results that respiratory rhythms increase in complexity with age are consistent with a report of Akay (1) that ApEn increased with increasing natal age in a piglet model but are inconsistent with another model that showed a U-shaped relationship between ApEn of RR and natal age. Our study differed from the studies of Akay, in that we used noninvasive measurements of VT and RR, rather than exposure of the phrenic nerve via cervical dissection. We also used preterm human neonates, rather than full-term piglets. There may be interspecies differences in timing of neurological development. Additionally, Akay’s use of vagotomy and chemodenervation may produce results different from those found in a neurologically intact subject.

Our results are similar to those of Cernelc et al. (12), who found long-term correlations in VT values. In contrast to their finding of no association with postnatal age, we found that increased postnatal age was associated with increased complexity, measured by BsEn, of the VT series. This difference may be related to the use of healthy postterm infants in the study of Cernelc et al. compared with our use of premature neonates with mild respiratory distress in the present study. This may suggest that once a given level of maturity, as manifested by healthy postterm infants, is achieved, the respiratory controllers are also mature and no longer exhibit any differing effects based on weight or ages.

We also found that complexity of RR rhythm as measured by FwEn and BsEn increased with increasing weight. Weight may act as a surrogate for physiological maturity in premature neonates. This finding is consistent with reports that lower birth weight, independent of age, is a predictor of respiratory problems and abnormal neurodevelopment (21, 30, 37).

One strength of the present study is that we used several measures of complexity and found differences between results determined by the pattern-matching methods, FwEn and BsEn, and the measures that used conditional probability, ApEn and SpEn. ApEn, SpEn, BsEn, and FwEn have shown separation determined by the pattern-matching methods, FwEn and BsEn, and the measures that used conditional probability, ApEn and SpEn. ApEn, SpEn, BsEn, and FwEn have shown separation between diseased and healthy states over short data sets (16, 28, 32, 35). Another strength is that we found results with only 300 breaths, compiled over 2.4–7 min. This short time period helps minimize disturbances in care and lessen the chances that the neonate may leave one sleep state and progress to another with possible changes in respiratory pattern (19).

One limitation of the present study is that only premature neonates with mild respiratory distress were studied. Study of neonates with moderate and severe respiratory distress, as well as neonates without respiratory problems, may show differences in complexity based on severity of disease state. In adults, ApEn showed changes in complexity between intensive care unit patients with and without respiratory failure (16). One possibility is that neonates without respiratory failure may have more developed respiratory and brain stem systems, whereas neonates with respiratory distress may have less developed systems, and studies of these normal and more severely impaired neonates may show levels of complexity different from those shown by our subjects.

Another limitation is that heart rate or cardiogenic noise may have influenced the accuracy of peak-to-peak detection, with perhaps small effects on the variability. Although the sleep stage was not evaluated in these subjects, they appeared to have been in quiet sleep, and Larsen et al. (27) showed that sleep stage had no effect on RR fractality in infants.

Additionally, although the infants appeared to be resting comfortably with NCPAP, we cannot exclude subtle interactions with NCPAP that may affect complexity of the respiratory rhythm. Nevertheless, since the purpose of the present study was to evaluate respiratory complexity in neonates with mild respiratory distress, it would not have been possible to study them without some form of support.

Until the present study, we did not know whether any entropy measure may be useful in detecting maturational effects in breathing patterns of preterm infants. Our results are promising and invite the exploration of other methods, such as fast Fourier transforms and detrended fluctuation analysis. Our results also suggest that complexity measures may be useful to more fully understand the effects of pharmacological (surfactant and caffeine) and ventilatory support (NCPAP) interventions in this patient population and, perhaps, help in dosing or titration of such support to more closely approximate normal breathing patterns. Also, comparison of complexity between preterm and full-term infants may allow a better understanding (quantification) of the degree of prematurity of respiratory centers controlling breathing patterns. For example, does increasing or decreasing positive distending pressures, such as with NCPAP, affect breathing pattern complexity differently in preterm vs. full-term infants, or at varying levels of prematurity? With use of a variety of entropy measures to better delineate respiratory complexity, future studies should compare preterm with postterm and healthy with ill infants and follow the subjects longitudinally to evaluate the effect of the disease and its resolution on complexity.

In conclusion, we found that complexity of the VT and RR time series increased with increasing postnatal, postmenstrual, and gestational ages and weight in premature neonates, indicating more complex breathing pattern with maturation and development of respiratory control centers.

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