Correlation properties of tidal volume and end-tidal O₂ and CO₂ concentrations in healthy infants

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Cernelc, Mateja, Béla Suki, Benjamin Reinmann, Graham L. Hall, and Urs Frey. Correlation properties of tidal volume and end-tidal O₂ and CO₂ concentrations in healthy infants. J Appl Physiol 92: 1817–1827, 2002. First published December 21, 2001; 10.1152/japplphysiol.00675.2001.—We investigated whether breath-to-breath fluctuations in tidal volume (VT) and end-tidal O₂ and CO₂ exhibit long-range correlations and whether parameters describing the correlations can be used as noninvasive descriptors of control of breathing. We measured VT and end-tidal O₂ and CO₂ over n = 352 ± 104 breaths in 26 term, healthy, unsedated infants (mean age ± SD: 36 ± 6 days) and calculated the detrended fluctuation function [F(n)]. The F(n) of the breath-to-breath time series of VT, O₂, and CO₂ revealed a linear increase with a breath number on log-log plots with a slope that was significantly different from 0.5 (random) and thus consistent with scale-invariant behavior. Long-range correlations were stronger for O₂ than for VT and CO₂. The F(n) of many individual signals exhibited a crossover behavior indicating that control mechanisms regulating fluctuations of VT, O₂, and CO₂ may be different on different time scales. Thus breathing has a memory up to at least 400 breaths that can be characterized by the simple indicator α. The breathing pattern of infants is highly irregular. Patterns of regular breathing interrupted by periods of insufficient breathing (hypopneas) or quiescence (apnea) are commonly observed even in healthy neonates. Although certain age-related variability is a physiological feature of infancy (19), the exaggeration of this variability might be interpreted in terms of a delayed maturation of control of breathing (12) and higher risk for hypopneas and apneas in infants. This is particularly true for premature infants and infants with increased risk for sudden infant death syndrome. The size, shape, and timing of each breath are controlled by a neural oscillator, which drives the respiratory muscles (28). A variety of feedback and feed-forward mechanisms have been proposed to explain matching of the tidal volume (VT), oxygen (O₂), and carbon dioxide (CO₂) outputs from the lungs with changes in airway mechanics and variations in total body O₂ consumption and CO₂ production (9, 35).

It has been proposed that, in infants, breathing can be considered as the output of a regulatory system that is attracted to a steady state (12). In other words, regulation of breathing may be a homeostatically controlled process. However, recent works in neurorespiratory and other biological regulatory systems have emphasized the nonlinear and dynamic nature of such feedback controls (6, 11, 16, 31, 32). The interactions among the various complex feedback and feed-forward mechanisms often result in weak but correlated fluctuations of the physiological quantity in question (6, 16). In general, correlations imply that successive values of the physiological variable are not independent of each other. Past values of variables describing the control system will have an influence on the future values of the variable. In other words, the system exhibits memory. When the correlations extend over at least one order of time decade, the variable is said to have long-range correlations. If the correlation function follows a power-law functional form, the correlations are also said to exhibit scaling behavior. Such scaling behavior has been found in heart rate variability (1, 25), in fluctuations in breath intervals (14), in firing rate of respiratory related neurons (20), in variations in lung volume (10), in transport of ions and molecules across biological membranes (21), and in the time intervals between crackle sounds (2).

The aim of this paper was to test whether correlations and, in particular, long-range correlations exist in the fluctuations of the breath-to-breath VT and end-tidal O₂ and CO₂ in infant breathing and whether they can be described by simple mathematical parameters, potentially useful to characterize immature breathing in infants. Furthermore, if correlations existed, we also aimed to determine whether control mechanisms regulating fluctuations of breathing parameters are different on different time scales and how these correlations may change with age.
METHODS

Study Design

We have quantified the breath-to-breath variability and ordering, or correlations, in VT, O2, and CO2 by measuring tidal breathing time series in 26 healthy, unsedated infants in quiet sleep.

First, robustness of the methodology was studied by using numerical simulations to investigate the effects of finite record length on data analysis. Second, we aimed to establish whether long-range correlations exist in tidal breathing in infants and to examine whether these correlations could be characterized by a simple parameter as a descriptor of control of breathing in infants. Analysis of breath-to-breath fluctuations in VT and end-tidal O2 and CO2 was done by using detrended fluctuation analysis (DFA) (24). The existence of long-range correlations in individual time series was then established by detecting differences in ordering compared with the randomized surrogates of the original time series. Third, we investigated whether the ordering properties of the VT and end-tidal O2 and CO2 fluctuations were different from each other. Last, age dependence of long-range correlations in VT, O2, and CO2 was studied to explore the maturational differences in the control of breathing in infants of different age.

Subjects

We measured breath-to-breath tidal breathing parameters in 26 term, healthy, unsedated, quiet-sleeping infants with a mean age of 36 ± 6 (SD) days and gestational age of 40.1 ± 1.0 wk. None of the infants had respiratory infections. The study was approved by the ethics committee of the University Hospital of Berne, and parental consent was also obtained for each study. Parents were usually present at the time of measurement.

Measurements

Infants were measured in the supine position with the head in the midline position. Quiet sleep was defined as Prechtl state I (26), meaning closed eyes, regular respiration, and absence of eye and gross body movements. O2 saturation and heart rate were monitored throughout the measurements (model Biox 3700, Datex-Ohmeda, Helsinki, Finland). A total of 10 min of recordings [352 ± 104 (SD) breaths] of VT, O2, and CO2 was assessed by using a measurement set up (Exhalyser, EcoMedics, Switzerland), which is in accordance with the recent specifications for tidal breathing measurements in infants (15). The dead space of the flow-, O2-, and CO2-measuring equipment was 3 ml. A compliant silicon infant face mask (infant mask, size 0; Homedica, Cham, Switzerland) was placed over the infant’s nose and mouth. The dead space of the mask had a total volume of 15 ml (measured by water displacement). Hence, the effective dead space of the measurement head was 10.5 ml (50% contribution of the face mask dead space).

Flow, O2, and CO2 were measured during tidal breathing by using commercially available infant lung function equipment (Exhalyser, EcoMedics). Flow measurements were assessed by using an ultrasonic flowmeter (Spiroson model M30.8001, EcoMedics) connected to a bias flow of 14 l/min. Flow-volume loops were inspected for a leak before starting measurement. VT were calculated from the flow signal. End-expiratory O2 concentration was measured by using a side-stream laser diode O2 sensor with visible-spectrum absorption spectroscopy analysis with a resolution of 0.02%, accuracy of ±0.2% in air mixtures and a response time of 100 ms (Oxygraf).

All tidal breathing signals were sampled at a rate of 200 Hz with the use of a 12-bit analog-to-digital converter. Flow, O2, and CO2 signals were corrected for the time delay due to sampling. Analysis of the signals was carried out by using a custom-written analysis package (MATLAB, Mathworks).

Analysis

Theoretical background. DFA. First, the end-expiratory values of VT, O2, and CO2 were assessed from the original time series as a function of breath number (n). Next, breath-to-breath time series of VT, O2, and CO2 were created by plotting the end-expiratory values of VT, O2, and CO2 as a function of n. Finally, the DFA introduced by Peng et al. (24) was applied to each time series as follows.

DFA is a technique suitable to quantify the correlation properties of nonstationary time series. Accordingly, this method can detect intrinsic correlation properties of a complex physiological signal and avoids the detection of false correlations due to the nonstationarity nature of the time series. According to Peng et al. (24), the DFA method estimates the fluctuation function of a time series as follows

\[
F(n) = \left(1/N \sum_{k=1}^{N} (y(k) - y_{ave})^2 \right)^{1/2} \tag{1} \]

where \(F(n)\) is the root-mean-square fluctuation of the integrated and detrended time series of \(y(k)\). To calculate \(F(n)\) of VT, O2, and CO2, the time series containing \(N\) data points, were first integrated

\[
y(k) = \sum_{i=1}^{k} (x(i) - x_{ave}) \tag{2} \]

where \(x(i)\) is one of the VT, O2, or CO2 time series, and \(x_{ave}\) is the corresponding average of the time series. The time series of \(y(k)\) was then divided into nonoverlapping windows of equal length (n). A linear regression line was fit through the data points of \(y(k)\) in each window. The regression line \(y_n(k)\) established the local trend in that window. The time series \(y(k)\) was then detrended by subtracting the local trend, \(y_n(k)\), from the data in each window. The calculation of \(F(n)\) was repeated for different window length of observation (n) and plotted as a function of n on a log-log plot for all breathing parameters (VT, O2, and CO2).

If the \(F(n)\) shows a linear increase with increasing n on a log-log plot, then \(F(n)\) is said to follow a power-law functional form

\[
F(n) = An^\alpha \tag{3} \]

where \(\alpha\) is the exponent and A is the amplitude of the power-law fluctuation function. These parameters can be obtained as the slope and intercept, respectively, of a straight line fit through the data plotted on a double logarithmic graph. It is the numerical value of \(\alpha\) that characterizes the correlation properties of the original time series \(x(i)\).

For a random process, \(\alpha\) takes the value of 0.5. For a positively correlated signal (large fluctuations are likely to be followed by large fluctuations), \(\alpha\) is >0.5, and for an anticorrelated signal (large fluctuations are likely to be followed by
small fluctuations, $\alpha$ is between 0 and 0.5 (25). If $F(n)$ follows a power law over at least an order of magnitude time scales with an $\alpha$ different from 0.5, the corresponding variable is said to exhibit long-range correlations or scale-invariant behavior. For example, $\alpha = 1$ corresponds to $1/f$ noise and $\alpha = 1.5$ corresponds to Brownian noise.

To ascertain that the correlations in breath-to-breath fluctuations of $V_T$, $O_2$, and $CO_2$ are real, we randomized (shuffled) the order of the original breath-to-breath time series. Such a rearrangement of the data results in an uncorrelated time series. Thus, although this procedure does not alter the distribution of the amplitudes in the time series, the correlations in the individual original traces can be estimated if the value of $\alpha$ is significantly different from that after shuffling.

FINITE SIZE EFFECTS. The expected value of $\alpha$ for an infinitely long random time series (white noise) is exactly 0.5. However, for a finite realization of a random sequence, the calculated value of $\alpha$ is usually different from 0.5 and depends on several factors including the length of the record, the signal-to-noise ratio, and potentially the true value of $\alpha$. This may lead to two important problems. The first is that the estimated $\alpha$ can be in error due to the finite record length, and the second is that recognizing weak correlations (i.e., when $\alpha$ is close to 0.5) from finite data sets can be ambiguous. For example, it is possible that the original time series had a weak correlation with an $\alpha$ of 0.58 and, after shuffling, $\alpha$ became 0.56 due to the short data record. In this case, it is not simple to identify the correlations from the original data set.

To resolve the first issue, we investigated the effects of record length on the estimated $\alpha$ from simulated time series with a known $\alpha$. Time series with a record length of 4,096 data points were created as follows. The signal was generated in the frequency domain by first prescribing the squared magnitude spectrum to follow a strain line with frequency on a log-log plot. The slope of the line is the negative exponent ($\beta$) of the power law spectrum, which was specified as $\beta = 2\alpha - 1$ (24), where $\alpha$ is the desired exponent in the fluctuation function defined in Eq. 3. For example, $\alpha = 0.5$ corresponds to a white noise with $\beta = 0$, and $\alpha = 1$ corresponds to a $1/f$ noise with $\beta = 1$. The phases were randomly selected, and the time domain signal was obtained by using an inverse Fourier transform. Next, eight data segments with lengths of 128, 256, or 512 points were selected, and DFA was applied as described previously (see Theoretical background) to each segment before and after shuffling the segment. This provided estimates of the mean and SD of $\alpha$ as a function of the record length and the true value of $\alpha$. Additionally, these simulations also tested whether the effectiveness of shuffling depends on the record length and the true value of $\alpha$.

With regard to the second issue, we established the statistical properties of $\alpha$ from the shuffled $V_T$, $O_2$, and $CO_2$ data. We shuffled the original time series of each individual data set. If a particular shuffling resulted in a value of $\alpha$ that was very different from 0.5 than the average, we repeated the shuffling of that time series 10 times and estimated $\alpha$ as the average obtained from the 10 shufflings. Next, we calculated the mean, SD, and 95% confidence interval of $\alpha$ for $V_T$, $O_2$, and $CO_2$. Finally, correlations in any time series (e.g., $V_T$) were established if the $\alpha$ from that record was outside the range of the group mean $\pm 95\%$ confidence interval for that type of variable (e.g., $V_T$).

CROSSOVER PHENOMENA. In most cases, a single regression line was adequate to fit the $F(n)$ function on a log-log graph providing a single exponent $\alpha$. However, similar to the interbeat interval fluctuations in heart rate time series (24), $F(n)$ of many individual signals exhibited a crossover behavior characterized by two separate regions of linear increase of $F(n)$ on the log-log graph with two distinct slopes. In these cases, two separate exponents ($\alpha_1$ and $\alpha_2$) could be determined from the data by using two regression lines. The time scale (which is the index) at which the two regions were separated is the crossover time ($N_c$). The two regions in $F(n)$ were selected by maximizing the correlation coefficients ($r$) in the regression of both regions. In each case, $r \geq 0.95$ was required.

Statistical analysis of physiological data. In an attempt to compare the correlation properties of the different tidal breathing time series, we compared $\alpha$ (or $\alpha_1$, $\alpha_2$, and $N_c$ where a crossover was observed) from the time series of $V_T$, $O_2$, and $CO_2$ by using by using one-way ANOVA on ranks (Kruskal-Wallis one-way ANOVA on ranks). In the case of a single slope, we assumed $\alpha_1$ to be the same as $\alpha_2$. The estimation of $\alpha$ can be influenced by the number of points used in the linear regression. Thus, to exclude the possibility that the difference between the mean values of $\alpha$ of the groups ($V_T$, $O_2$, and $CO_2$) was simply a consequence of the different number of individual time series exhibiting crossover phenomena, we tested whether this number was not statistically different in the compared groups ($\chi^2$-test). To examine whether individual processes of breath-to-breath fluctuations in $V_T$, $O_2$, or $CO_2$ were governed by similar mechanisms, the exponents from $V_T$, $O_2$, and $CO_2$ were also correlated with each other by using linear regression analysis.

Additionally, to detect maturational effects, we determined the age dependence of $\alpha$ (or $\alpha_1$ and $\alpha_2$) as a function of gestation age (GA) and postnatal age (PNA). We also examined whether the crossover pattern was age related by examining the dependence of the ratio $\alpha_1/\alpha_2$ and $N_c$ on GA or PNA by using linear regression analysis. Whereas $\alpha_1$, $\alpha_2$, and $N_c$ of the ages were normally distributed, the distribution of $N_c$ of $V_T$, $O_2$, and $CO_2$ were skewed. Thus, before the linear regression analysis was performed, a log transformation was applied to data, which transformed the distribution of these variables to a normal distribution.

RESULTS
Robustness of the Methodology (Finite Size Effects)

The results of the numerical simulations are summarized in Table 1. The error in the estimated value of $\alpha$ decreases significantly from ~4 to 0.5% when the record length increases from 128 to 512 data points. The error slightly increases when the true theoretical value of $\alpha$ increases from 0.6 to 1. Thus $\alpha$ can be estimated to within 1% error if the length of the record is at least 500 points independent of actual correlation properties of the signal. The errors in $\alpha$ from the shuffled time series are generally higher, reaching 16.6%, and even for the record length of 512 points the error is between 4 and 7%. This suggests that randomization of the ordering of the time series does not in general work for short time series. However, the error for the entire original 4,096 points record length is below 1% independent of the original $\alpha$.

Measurements in infants. The anthropometric data including weight, height, and age at the measurement, average number of breaths in time series, single breath
Examples of the raw VT, O2, and CO2 signals from a group of 26 infants are given in Table 2. Mean ± SD, Error

<table>
<thead>
<tr>
<th>True α = 0.6</th>
<th>True α = 0.8</th>
<th>True α = 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>Shuffled</td>
<td>Original</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>n = 128</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>0.6205 ± 0.0893</td>
<td>0.5545 ± 0.0798</td>
<td>0.7648 ± 0.0864</td>
</tr>
<tr>
<td>Error</td>
<td>3.41</td>
<td>Error</td>
</tr>
<tr>
<td>0.6093 ± 0.0904</td>
<td>0.5352 ± 0.0757</td>
<td>0.7871 ± 0.0451</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.6017 ± 0.0817</td>
<td>0.5222 ± 0.0359</td>
</tr>
<tr>
<td>Error</td>
<td>0.3</td>
<td>Error</td>
</tr>
</tbody>
</table>

In each data set, 8 independent samples were used to estimate original slope (α) and its shuffled surrogate. Mean standard deviations (SD) of measured α and errors, which are the percent error between measured and true α, were calculated for each data set. True α, theoretical value of α in the simulation (0.6, 0.8, 1.0); n, number of data points used in data sets.

mean VT, and mean end-tidal O2 and CO2 concentrations for the group of 26 infants are given in Table 2. Examples of the raw VT, O2, and CO2 signals from a representative infant are shown in Fig. 1 as a function of time. The corresponding time series of the breath-to-breath end-tidal values of VT, O2, and CO2 from the same subject are shown in Fig. 2. It can be seen that each time series displays considerable irregularities.

**Evidence of Long-Range Correlations in Breathing**

Figure 3 shows the fluctuation functions corresponding to the data in Fig. 2 on log-log graphs before and after shuffling. The linear regression line fits are also shown in Fig. 3. For all three breathing parameters, F(n) follows a straight line over a time scale of about 1.5 decades. Exponents are above 0.8, and they decrease to 0.53 after shuffling. One example of the crossover behavior can be seen in Fig. 4. The first region has a slope of nearly 1 over a range of somewhat less than a decade, whereas the second region in this case has a slope of 0.51 covering an entire decade. F(n) of all 26 individual traces revealed a similar behavior to those seen either in Figs. 3 or 4. The individual and group means and SD for α1, α2, and N∗ for VT, O2, and CO2 (and median values for nonnormally distributed data, e.g., N∗) are summarized in Table 3.

In the case of a single slope, the group means of the scaling exponent α were 0.75 ± 0.20, 0.95 ± 0.17, and 0.83 ± 0.15 for VT, O2, and CO2, respectively. For the group with two scaling regions, the mean values of α1 were 1.00 ± 0.31, 1.19 ± 0.34, and 0.96 ± 0.27 for VT, O2, and CO2, respectively, and the mean values of α2 were 0.73 ± 0.42 for VT, 1.01 ± 0.29 for O2, and 0.92 ± 0.33 for CO2. The values of α from the shuffled time series are centered around 0.5 with a narrow 95% CI (Table 4). Thus these data provide evidence for the presence of long-range correlations in the end-tidal fluctuations of VT, O2, and CO2 in normal infants.

Considering the crossover phenomena, out of 26 time series, 11 records of VT, 9 records of O2, and 15 records of CO2 exhibited a crossover in scaling. There was no significant difference in the number of data points in the signals between one- or two-slope pattern groups (t-test, P = 0.95). In most cases where F(n) showed a two-slope pattern, both exponents were different from 0.5, indicating that although the correlation properties of the variable were different for different time scales, long-range correlations still persisted throughout the whole trace. On the other hand, in three of VT and one of CO2 time series, the second slope α2 approached 0.5, indicating that after a certain number of breaths, crossover point N∗, fluctuations in the signals became random. This phenomenon was not seen in the O2 traces. Although α2 was usually smaller than α1, which was also true for the whole group of subjects with two-slopes pattern, 2 of 11, 3 of 9, and 7 of 15 time series for VT, O2, and CO2, respectively, exhibited a reverse crossover (24) with a scaling exponent α2 bigger than α1. The median of N∗ defining the time scale at which the fluctuations in tidal breathing parameters (VT, O2, and CO2) exhibited an obvious change in their scaling behavior was 20 for VT, 10 for CO2, and 14 for O2.

**Comparisons of the Correlations in VT, O2, and CO2**

There was no statistically significant difference in the distribution of crossover phenomena in the different parameter groups (χ²-test). Considering the group

<table>
<thead>
<tr>
<th>n</th>
<th>PNA, wk</th>
<th>GA, wk</th>
<th>Length, cm</th>
<th>Weight, kg</th>
<th>VT, ml</th>
<th>CO2, kPa</th>
<th>O2, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>352</td>
<td>5.1</td>
<td>40.1</td>
<td>56.1</td>
<td>4.57</td>
<td>28.3</td>
<td>4.6</td>
</tr>
<tr>
<td>SD</td>
<td>104</td>
<td>0.9</td>
<td>1.0</td>
<td>2.1</td>
<td>0.69</td>
<td>4.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Min</td>
<td>207</td>
<td>3.6</td>
<td>38.0</td>
<td>52.3</td>
<td>3.48</td>
<td>20.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Max</td>
<td>656</td>
<td>6.7</td>
<td>42.3</td>
<td>61.5</td>
<td>0.63</td>
<td>36.4</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Group mean, SD, minimal (Min), and maximal values (Max) for anthropometric data, number of breaths in time series (n), single breath tidal volume amplitude (VT), and end-tidal O2 and CO2 concentrations are shown. PNA, postnatal age; GA, gestation age.
Means of the exponents, $\alpha_1$ for $O_2$ was significantly higher than $\alpha_1$ for $V_T$ (paired $t$-test, $P = 0.001$) and $CO_2$ ($P = 0.02$). The $\alpha_1$ of $V_T$ and the $\alpha_1$ of $CO_2$, however, were not different from each other. The same was true for $\alpha_2$; that is, $\alpha_2$ for $O_2$ was higher than $\alpha_2$ for $CO_2$ ($P = 0.02$) or $V_T$ ($P < 0.001$). In the individuals with two-slope pattern, group comparisons of $N_x$ (one-way ANOVA on ranks) of different breathing parameters ($V_T$, $O_2$, and $CO_2$) revealed no statistically significant difference in the number of breaths at which scaling behavior of the fluctuations changed.

By plotting $\alpha_1$ (or $\alpha_2$) of $O_2$ (or $CO_2$) as a function of the corresponding exponent for $V_T$, the $\alpha_1$ for $O_2$ ($P = 0.002$; linear regression; Fig. 5B) and $CO_2$ ($P = 0.04$; linear regression; Fig. 5A) was significantly correlated with the corresponding exponent for $V_T$. The same was true for the correlation between $\alpha_1$ of $CO_2$ and $O_2$ ($P = 0.02$) as well as $\alpha_2$ of $CO_2$ and $O_2$ ($P < 0.001$; Fig. 5C).

**Age Dependence of Long-Range Correlations**

Neither $\alpha_1$, $\alpha_2$, nor the $\alpha_1/\alpha_2$ ratio was significantly correlated with GA or PNA for $V_T$, $CO_2$, and $O_2$. On the other hand, log($N_x$) significantly increased with GA for $O_2$ ($P = 0.01$, linear regression) but not with PNA. The relationship between log($N_x$) for $O_2$ and GA remained statistically significant also after adjusting for a study age ($P = 0.06$, linear regression). The linear decrease of
log(Nx) vs. GA became nearly significant for VT (P = 0.058), but no statistically significant correlation was found between CO2 and GA or PNA.

DISCUSSION

The control of breathing in infants undergoes developmental changes and can be altered in disease. Searching for a noninvasive descriptor of the control of breathing seems to be crucial in an attempt to describe and understand the physiological mechanisms involved in neurorespiratory control in infants and developmental process in the regulation of breathing during postnatal life. Furthermore, such a descriptor may be useful for the early detection and monitoring of disease, and the assessment of the therapeutic interventions.

In this study, we demonstrated that breath-to-breath time series of tidal breathing parameters in infants (VT, O2, and CO2) exhibit nontrivial, scale-invariant behavior. We studied the variability of the outputs of the complex breathing control system by using DFA. We found that F(n) of all individual tidal breathing time series (VT, O2, and CO2) as a function of breath lag (n) plotted on a log-log plot revealed linear behavior with a slope \( \alpha \), which was significantly different from \( \alpha = 0.5 \), the value that signifies randomness. This implies that there are significant long-range correlations in time series of tidal breathing parameters. Thus the values of single-breath VT and end-tidal O2 or CO2 levels are not independent of those in previous breaths. In other words, breathing has a memory. Because the long-range correlations followed a power law, this behavior is consistent with fractal properties of the respiratory control system in infants.

We identified two patterns in the scaling behavior of individual VT, O2, and CO2 traces. Whereas some of the traces exhibited a single slope \( \alpha \) of the linear regression fit of \( F(n) \) vs. \( n \) on a log-log plot, denoting that the characteristics of correlations did not change on different time scales through 10-min traces, others exhibited a crossover pattern (see Crossover Phenomena). However, there was no systematic difference in the number of data points (breaths) between one- or two-slope pattern traces. In the case of a single slope, the group mean exponent \( \alpha \) for O2 approached 1, which is consistent with 1/f behavior in O2 breath-to-breath fluctuations. On the other hand, fluctuations of CO2 and VT were rougher, with values of \( \alpha \) of 0.83 and 0.75, respectively. This is consistent with persistent long-range, power-law correlations, such that a large difference in VT (O2 or CO2 concentrations) between breaths separated by a certain breath lag was more likely to be followed by a large lag and vice versa. In other words, big fluctuations (in comparison to the average) are more likely to be close in time to bigger fluctuations for
a certain time interval. Because the process is stochastic, the pattern can suddenly change so that a big fluctuation is followed first by a smaller one, which in turn is likely to be followed by even smaller fluctuations afterward. This effect is not present on a breath-to-breath basis but on a wide range of time scales.

Other complex regulatory systems, such as heart rate control (24, 25), have shown scale-invariant properties persistent with long-range correlations. Heart rate control (24, 25), have shown scale-invariant properties afterward. This effect is not present on a breath-to-breath basis but on a wide range of time scales.

Crossover Phenomena

Peng et al. (24) found two slope patterns in some of their heart rate time series in healthy subjects as well as in diseased patients. They could distinguish between the healthy and the pathological data sets on the basis of this crossover phenomena. Similarly, we found crossover phenomena in approximately half of our infant breathing time series. Although the one-slope pattern of VT, O2, and CO2 time traces showed long-range correlations through the whole recorded trace with the same exponent, the two-slope pattern traces implied that the correlated structure of the breath to breath fluctuations in VT, O2, and CO2 changed at time scales corresponding to \( N_x \), which was \( \approx 18 \) breaths. On short time scales (\( n < N_x \)), the intrinsic dynamics of VT, O2, and CO2 fluctuations approached that of an ideal 1/f behavior for all parameters, i.e., \( \alpha_1 \) was close to 1. This behavior was similar for all parameters observed (VT, O2, and CO2). The correlated structure of the time series then changed for longer time scales (\( n > N_x \)), which was characterized by a change in the correlation exponent (i.e., \( \alpha_2 \) was different from \( \alpha_1 \)). In most of the individual time series with a two-slope pattern, \( \alpha_2 \) was smaller than \( \alpha_1 \) but still different from 0.5. Nevertheless, the group means of \( \alpha_2 \) for VT, O2, and CO2 were not statistically significantly different from \( \alpha_1 \) for any of the parameters observed.

In four individual traces, \( \alpha_2 \) approached 0.5, indicating that, after a certain number of breaths (\( N_x \)), the fluctuations of the variable in question were not correlated any more. This behavior was found in VT and CO2 time series but not in O2. Thus, in these infants, the memory existed only over a short time scale, gradually became weaker, and eventually at large time scales (\( n > N_x \)) fluctuations in VT and end-tidal CO2 became independent of the previous ones. Thus, apart from

Table 3. Individual and group mean and median values for slopes \( \alpha_1 \) and \( \alpha_2 \) for different tidal breathing parameters

<table>
<thead>
<tr>
<th>Patient</th>
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<th>( \alpha_1 ) CO2</th>
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<th>( \alpha_2 ) CO2</th>
<th>( N_x ) CO2</th>
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\( N_x \), crossing point.

Table 4. Shuffled time series

<table>
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<tr>
<th></th>
<th>( \alpha_{sh} ) VT</th>
<th>( \alpha_{sh} ) O2</th>
<th>( \alpha_{sh} ) CO2</th>
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<td>95% CI</td>
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Group mean, SD, and 95% confidence interval (95% CI) for slopes \( \alpha_{sh} \) of 26 individual shuffled breath-to-breath time series (fitted through the whole trace) for VT, O2, and CO2.
four infant time series, scaling and hence memory effects existed through several hundred breaths. This behavior suggests that in a healthy infant who takes a breath in the absence of a strong external stimuli, the properties of that single breath can be influenced by those of many breaths ranging up to 400 previous breaths.

The physiological origin of the long-range correlations is not entirely clear. Theoretically, long-range correlations may serve as an organizing principle for the feedback mechanisms generating fluctuations on a wide range of scales. Alternatively, the long-range correlations may be a consequence of the combined effects of multiple nonlinear feedback loops in the control of breathing and fluctuating external stimuli. However, in a dynamic system operating far from equilibrium, significant fluctuations in the system variables can occur, even in the absence of external stimuli. The potential advantage of inherent long-range correlations in such systems may be that they allow for an improved functional responsiveness and adaptability to external perturbations (25). The lack of a characteristic scale may help prevent the system from being locked into a particular phase that would restrict the functional responsiveness of the organism (16). These arguments are supported by observations from severe diseased states where the breakdown of multiscale, long-range order is accompanied by the emergence of a dominant frequency mode characterized by a highly periodic behavior (trivial long-range correlations). The output of the system becomes nearly sinusoidal such as the low-frequency oscillations seen in heart rate pattern of infants with fetal distress syndrome (18). In other cases, the breakdown of long-range correlations may be accompanied by the emergence of uncorrelated randomness as seen in certain cardiac arrhythmias, such as ventricular fibrillation (17).

The control of breathing is a nonlinear feedback control system with various input stimuli, which themselves can fluctuate and have several feedback loops. Numerical simulations, as described in the APPENDIX, using the triphasic model of the respiratory rhythm generator (5, 28), demonstrated that long-range correlations are already present in the phrenic output fluctuations of the respiratory oscillator. A representative simulation using a model of the respiratory oscillator (14) provided power law fluctuations with values for \( \alpha \) between 0.58 and 0.65, which is consistent with long-range correlated behavior. Although this does not prove that the observed long-range correlations originate from the respiratory oscillator, it is consistent with this idea and opens the possibility for future research in this field.

Comparison of VT, O₂, and CO₂ Long-Range Correlation

The comparison of the slopes \( \alpha \) (\( \alpha_1 \) and \( \alpha_2 \)) of different tidal breathing parameters provided statistically significantly higher values for O₂ than for VT and CO₂, indicating that breath-to-breath end-tidal O₂ concentration was more strongly correlated than breath-to-breath VT or end-tidal CO₂ concentration. Stronger correlation implies a more deterministic system and hence possibly a stronger regulatory mechanism controlling the output of the system of O₂ compared with VT and CO₂.

Furthermore, we tested whether the values of \( \alpha \) for VT, O₂, and CO₂ were correlated. Such correlations are expected because, within an individual breath, VT and end-tidal O₂ and CO₂ must be related to each other on the basis of lung clearance mechanism and
feedback regulation. We found that $\alpha$ for $O_2$ and $CO_2$ were correlated both for short ($\alpha_1$) and long ($\alpha_2$) time scales, but they were correlated to $VT$ only over short time scales. For short time scales, the correlation between $\alpha_1 (O_2)$ and $\alpha_1 (VT)$ was significantly stronger than that between $\alpha_1 (CO_2)$ and $\alpha_1 (VT)$. We cannot conclude from these data whether $O_2$ or $CO_2$ is dominating $VT$ regulation; we can only say that if the breath-to-breath fluctuations in $O_2$ are strongly correlated (high $\alpha$), the same will be true for $CO_2$, independent of the time scale observed. For short time scales ($\alpha_1$), the same is true for $O_2$ and $CO_2$ compared with $VT$. However, for long time scales, we found a dissociation or uncoupling of $\alpha_2 (VT)$ and the corresponding $\alpha_2 (O_2)$ and $\alpha_2 (CO_2)$.

One possible explanation for the uncoupling of $O_2$ and $CO_2$ from $VT$ at large time scales could be as follows. Within an individual breath, there must be strong correlations between the parameters because of lung clearance effects. However, different internal or external inputs to the individual feedback loops of these variables can result in small differences in the fluctuations. These differences could become amplified by system nonlinearities for long time scales when the central regulatory feedback loops become more dominant, leading to an uncoupling of $\alpha_2$ for $VT$ compared with $O_2$ and $CO_2$. Another possibility could be that $O_2$ and $CO_2$ are simultaneously influenced by certain additional weak but long-lasting memory effects, such as those due to blood-mediated slower feedback loops. These additional factors could introduce similarities in the long time-scale fluctuations of $O_2$ and $CO_2$ but not in the fluctuations of $VT$. Theoretical investigations of how these timing effects of the various control loops have been described by Khoon (22).

Chemoregulation undergoes maturational effects in infants and is distinctively different from adults (4, 10, 30). Although we were not able to assess longitudinal data sets, in our cross-sectional data, we found that slope $\alpha$ did not change with GA or PNA in this small age range between 3.6 and 6.7 wk. However, the logarithm of $N_c$ in the two-slope fluctuation function statistically significantly decreased with GA (38.0–42.3 wk) for $O_2$ and nearly statistically significant increased with $VT$. Thus, in most infants, the transition of stronger short-range correlation for $O_2$ to weaker long-range correlation occurs after a shorter time period in the older infants. However, in some infants, $\alpha_1$ was smaller than $\alpha_2$.

Because the crossover phenomenon is sensitive to gestational age and because stronger correlation implies a more deterministic system and hence possibly a stronger regulatory mechanism, DFA could potentially be a marker of changes in the control of breathing in premature infants. Nevertheless, this should be tested in longitudinal studies.

Potential Limits of the Method

Sleep stage. Although it has been known that sleep stage influences the control of breathing in infants (29), all the measurements in this study were performed in spontaneously quiet sleeping infants. Thus the length of time for collecting tidal breathing data was significantly influenced by their natural sleep. This resulted in relatively short breathing traces of 10 min, for which stable conditions with no change in sleep states were maintained.

Nonstationary data. The nonstationary behavior of most physiological systems, including the neurorespiratory control system, could potentially influence the identification of intrinsic correlation properties of the system. In other words, correlations due to nonstationary trends have to be distinguished from more subtle system-related fluctuations. This problem was avoided by analyzing the data by using the DFA (24). The long-range correlation properties of $VT$, $O_2$, and $CO_2$ time series were further confirmed by using the statistical properties of simulated data as well as analyzing the shuffled time series. As a result, even more subtle correlation structures of the time series, such as a crossover characterized by the two-slope pattern, could reliably be detected.

Oscillations in the data sets. For higher time window length, the DFA exhibited oscillations in some of the traces. Although the oscillations may possibly emerge from nonlinearities of the respiratory system, they are not necessarily due to them. We tested this by calculating the DFA of random noise sequences of different lengths. The DFA of these time series also showed oscillations. These oscillations were different after shuffling and were significantly reduced in the longer time series. This indicates that the oscillations were related to insufficient averaging of the fluctuations for large window lengths. The oscillations in the respiratory data may contain physiological information. However, although the DFA is sensitive to correlations, it is not suitable to study system nonlinearities.

Influence of a face mask. It has to be noted that the control of breathing and, consequently, the pattern of breathing tend to become somewhat more regular after placement of a mask on the infants’ faces. Thus the possible influence of a face mask on a breathing pattern cannot be excluded (13, 33). Nevertheless, when the mask was put on the infants’ faces it was not removed until the recording was completed, thus minimizing the effect of an alteration of sleep and possibly the breath-to-breath variability of $VT$, $O_2$, and $CO_2$.

Summary and Hypothesis for Future Research

In this study, we found that breath-to-breath time series of tidal breathing parameters ($VT$, $O_2$, and $CO_2$) in infants exhibit power-law, long-range correlations, consistent with scale-invariant behavior. We quantitatively characterized this memory of the respiratory control system by using the $F(n)$, $F(n)$ of the tidal breathing parameters as a function of breath lag ($n$) plotted on log-log graphs revealed a linear behavior with the slope $\alpha$ significantly different from 0.5 (i.e., uncorrelated behavior). Thus the
time correlations present in the breath-to-breath time series of tidal breathing parameters contain information on the control of breathing in infants, and α may serve as a simple noninvasive descriptor of the control of breathing. We have shown that the long-range correlations for O₂ are stronger than those for VT and CO₂ in healthy infants. We found an uncoupling of VT, and we also found crossover phenomena as described by Peng et al. (24) and reported by Alencar et al. (2). The crossover behavior is particularly interesting because it was sensitive to gestational age and hence could be used to assess the degree of immature breathing in premature infants. For clinical applications, the effects of sleep state, intermittent hypoxia, disease (infants with chronic lung disease and neurological diseases, sudden infant death syndrome), or toxic influences (e.g., maternal smoking) on changes of the control of breathing should be investigated in future studies. DFA could potentially also be used to monitor therapeutic effects of drugs (e.g., caffeine, theophylline). The new parameters are particularly interesting because they are related to the feedback-control system properties, which is a novel approach of studying control of breathing in infants.

The long-range correlation analysis technique offers distinct advantages to probe the physiological mechanisms involved in developing the neuro-respiratory control in healthy infants and infants with disease.

**APPENDIX**

We propose a possible mechanism to explain how long-range correlations in breath-to-breath fluctuations of VT, O₂, and CO₂ could originate from the neural respiratory network. There is evidence from animal models that a three-phase model of the respiratory oscillator is similarly appropriate to describe the breathing cycle in newborns as in adults (5). There is also evidence of noise in the respiratory rhythm generator. The firing of individual neurons has been found to be a probabilistic process with intrinsic noise (3). Recently, Hoop et al. (20) demonstrated the presence of noise in respiratory-related neural activity in the brain stem of neonatal rats. In a previous study (14), our laboratory introduced noise in the neural oscillator model proposed by Botros and Bruce model (5). This model was able to quantitatively mimic the large variabilities and irregularities as well as the scaling behavior of interbreath time intervals observed in healthy and premature babies (14). In that study, scaling behavior was observed in the probability-density function of interbreath intervals, which followed a power-law form and described the likelihood of extreme values (7, 14). However, this method does not examine the ordering of amplitudes of the simulated fluctuations in the phrenic output time series.

Here, we analyzed the long-range correlations in the fluctuations of the phrenic output of the Botros and Bruce model (5) similarly as described in METHODS and calculated α from the DFA. Briefly, to reproduce the observed irregularities, we modified the neural oscillator model proposed by Botros and Bruce (5), which transforms tonic neural inputs (TNI) into a regular rhythm and hence breathing (28). The model consisted of five coupled nonlinear differential equations corresponding to the activities of five neuron groups in the respiratory center. The ramp-inspiratory neuron group provided periodic outputs to the phrenic nerve similar to the measured data. We solved the network in the time domain by using MATLAB (Mathwork, Natick, MA) and examined the amplitudes of the peaks of the output of the ramp-inspiratory neuron group. However, after a short transient period, the solution of the network was a periodic waveform without any irregularities. Thus, to mimic irregularities in phrenic output amplitudes, we added a varying amplitude noise to the TNI of the first or ramp-inspiratory neuron group (TNI₁) based on considerations of Hoop et al. (20), suggesting that neural noise is not constant but does vary within the respiratory cycle, most likely because of varying chemoreceptor responses. Hoop et al. (20) found correlations in the neural noise itself. However, to test whether the respiratory oscillator alone is able to generate long-range correlations, we added random noise to the input of the oscillator. The model parameters are summarized in Table 5. The mean value of TNI₁ was 5 with a uniformly distributed noise (SD = 4), which changed on average four times within the respiratory cycle. We simulated 300 breaths by using this model, similar to the number of breaths in our infant measurements, and obtained large variations in phrenic amplitude similar to those observed in the measured infant VT data.

![Fig. 6. F(ν) as a function of n on a log-log plot for original and shuffled time series created by using the neural network model of respiratory oscillator proposed by Botros and Bruce model (5). αoriginal, Slope of linear regression of original time series (○) and its shuffled surrogate (αshuffled; ●); r, correlation coefficient.](http://jap.physiology.org/doi/10.1152/jappl.00527.2001)

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**Table 5. Neural network modeling**

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Model parameters according to Botros and Bruce (5) are as follows. Neuronal groups: I, inspiratory; L-I, late inspiratory; p-I, post inspiratory; E, expiratory; e-I, early inspiratory. Columns 2–6 contain values for the connection weighting factors (W_i/j), where i represents the source group in the left column and j is the target group in the top row. The tonic neural inputs (TNI) are given in column 7. In the original Botros and Bruce model (5), TNI in 1st or ramp-inspiratory neuronal group (TNI₁) was 5.044. In model, we used a mean value of TNI₁ = 5.0 with a uniformly distributed noise (SD = 4) superimposed on TNI₁, which changes, on average, 4 times within one respiratory cycle.
When we calculated $F(n)$ from these simulated phrenic output series, we found a linear relationship in the log-log representation with $\alpha = 0.58$ ($r = 0.976$; Fig. 6). With the use of only the most linear range from $n = 1–200$, $\alpha$ was 0.61 ($r = 0.991$). After reshuffling this series, we found $\alpha$ to be 0.46 ($r = 0.974$; Fig. 6).

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REFERENCES