Effect of sighs on breathing memory and dynamics in healthy infants

D. N. Baldwin,1,3 B. Suki,2 J. J. Pillow,3 H. L. Roiha,1 S. Minocchieri,1 and U. Frey4

1Pediatric Respiratory Medicine, University Children’s Hospital, Bern 3010, Switzerland; 2Department of Biomedical Engineering, Boston University, Boston, Massachusetts 02215; and 3Clinical Sciences Division, Institute for Child Health and Centre for Child Health Research, University of Western Australia, Perth 6008, Australia

Submitted 18 March 2004; accepted in final form 16 June 2004

Baldwin, D. N., B. Suki, J. J. Pillow, H. L. Roiha, S. Minocchieri, and U. Frey. Effect of sighs on breathing memory and dynamics in healthy infants. J Appl Physiol 97: 1830–1839, 2004.—Deep inspirations (sighs) play a significant role in altering lung mechanical and airway wall function; however, their role in respiratory control remains unclear. We examined whether sighs act via a resetting mechanism to improve control of the respiratory regulatory system. Effects of sighs on system variability, short- and long-range memory, and stability were assessed in 25 healthy full-term infants at 1 mo of age [mean 36 (range 28–57) days] during quiet sleep. Variability was examined using moving-window coefficient of variation, short-range memory using autocorrelation function, and long-range memory using detrended fluctuation analysis. Stability was examined by studying the behavior of the attractor with use of phase-space plots. Variability of tidal volume (VT) and minute ventilation (Ve) increased during the initial 15 breaths after a sigh. Short-range memory of VT decreased during the 50 breaths preceding a sigh, becoming uncorrelated (random) during the 10-breath presigh window. Short-range memory increased after a sigh for the entire 50 breaths compared with the randomized data set and for 20 breaths compared with the presigh window. Similar, but shorter duration, changes were noted in Ve. No change in long-range memory was seen after a sigh. Coefficient of variation and range of points located within a defined attractor segment increased after a sigh. Thus control of breathing in healthy infants shows long-range stability and improvement in short-range memory and variability after a sigh. These results add new evidence that the role of sighs is not purely mechanical.

INFANTS DEMONSTRATE DYNAMIC regulation of lung function over time. Lung volume is actively elevated above that determined by tissue elastic properties and a compliant chest wall (26). Recent studies suggested that dynamic regulation of airway tone is particularly important in infants (16). It is likely that this dynamic regulatory process represents a tightly controlled negative-feedback system, whereby information from peripheral and central chemoreceptors, as well as pulmonary stretch receptors, is provided to respiratory regulatory neurons in the brain stem, with continuously variable output to the respiratory system musculature (43, 44).

Biological feedback systems such as those utilized in, e.g., respiratory control, are reflective of engineering control systems and may be modeled using similar mathematical concepts (9, 35). From an engineering point of view, a control system requires an appropriate balance between system stability and sensitivity, permitting responsiveness to fluctuations while maintaining function within tightly regulated limits. Excess sensitivity of such a system may lead to dramatic “overshoot”-type responses, instability, and positive feedback (24). Reduction in sensitivity and excessive stability may result in diminished capacity for response to environmental change and poor feedback control. On the other hand, a certain amount of stability is required in order for the biological system to return to a steady state after a perturbation. Variability observed in the output parameters of a system is often the result of these two competing mechanisms. Long- and short-range memory within such a dynamical system are responsible for maintaining this delicate equilibrium by incorporating information from previous events into the current system state. An ideal error-tolerant system returns quickly to a steady state, whereby long-range memory is not altered. Long-range memory may therefore be considered a feature of stability.

From engineering systems, it is known that many control loop feedback systems incorporate a resetting mechanism. There is evidence that spontaneous deep inspirations (sighs) play an important role in resetting the mechanical properties of the lung tissue (10, 12) and airway walls (7); however, there is little information in the literature as to whether sighs also act as a “resetting” mechanism for the control loop system. In adults, sighs during sleep are associated with increased inspiratory and expiratory flows and increased inspiratory time (Ti) as a fraction of respiratory cycle time (Tc/Ti), indicating that they may play an important role in the control process (31). Sighs are a more frequently observed phenomenon in infant than in adult breathing (19, 31) and, given the increased contribution of dynamic processes to respiratory control in this age group, may make a major contribution to homeokinesis. Fleming et al. (13) used a linear approach to investigate the developmental changes in oscillatory responses of breath-to-breath minute ventilation (VN) after a sigh in 7-mo-old infants. Newborn infants had a stable system with delayed responses to the sigh stimulus that evolved with age to exhibit a stable, but more responsive system suggestive of improvement in feedback control. Animal studies demonstrate no difference in respiratory pattern after a sigh between rapid eye movement (REM) and non-REM (NREM) sleep; however, a smaller tidal volume (VT) and longer expiratory time (TE) are evident, resolving on most occasions by the third postsigh breath (20). The factors responsible for inducing a sigh and the effects of this event on the stability of the system remain unclear.

We hypothesized that sighs may play a crucial role not only for lung mechanics but also as a resetting mechanism for the negative-feedback control system. To examine whether full-term healthy infants demonstrate alterations in regulation of...
breathing after sighs during quiet natural sleep, we analyzed the effect of sighs on tidal breathing indexes in terms of respiratory variability, short- and long-range memory, and stability.

METHODS

Study Design

This cross-sectional observational study examined regulation of breathing in relation to sighs in healthy infants during quiet natural sleep. Breath-by-breath VT, VE, and minimum exhaled O2 and end-tidal CO2, as well as the classical parameters of respiratory drive [Ti/Tt, Vt/Ti, time to peak tidal expiratory flow (tPTEF)/TE, Ti, TE, and maximal inspiratory flow (VImax)], were examined for 50 breaths before and after a spontaneous sigh. Data were analyzed in terms of variability, short- and long-range memory, and stability of VT and VE. Variability was examined using moving-window coefficient of variation (CV). Short-range memory was assessed for data sets of 50 breaths using an autocorrelation function (c) (23). Detrended fluctuation analysis (28) examined long-range memory over 100 breaths. Stability of the system was assessed using phase-space plots (23).

Subjects

Data were obtained from a subgroup of 25 infants from a total cohort of 80 healthy full-term infants recruited antenatally to a separate large epidemiological study. Data from each infant were visually examined for the presence of a sigh. A sigh was defined as a tidal breath at least double the mean VT of the preceding 10 breaths (10, 40). A sigh breath was identified in 40 infants; however, 15 were excluded because of the absence of NREM sleep state, insufficient data adjacent to the sigh (<50 breaths), significant data artifact or when a change in sleep state, movement, or arousal occurred during the study. This left data from 25 infants that were suitable for analysis. Demographic data are provided in Table 1. All infants were born after unremarkable pregnancies, and delivery was normal. None of the infants had respiratory infections between birth and date of the study. The study was approved by the Ethics Committee of the University Hospital of Berne. Written informed parental consent was obtained before study, and parents were most often present at the time of measurement.

Measurements

The technique for measurement of tidal breathing parameters in spontaneously sleeping infants has been published in detail previously (8). Briefly, infants were studied in the supine position in a cot or in the mother’s arms during quiet natural sleep. Sleep state was defined clinically using the criteria of Prechtl (33), with closed eyes, absence of gross body or limb movements, and regular respiratory pattern. Heart rate and O2 saturation were monitored continuously for the duration of study (Biox 3700, Datex-Ohmeda, Helsinki, Finland). Measurements were made over periods of up to 10 min using methodology and equipment compliant with recently published international standards for measurement of lung function in infancy (5, 17, 18).

Tidal breathing was measured by application of a compliant silicone face mask to the infant’s mouth and nose (size 1, Homedica, Cham, Switzerland) after the face mask was warmed to skin temperature (17). The mask was connected in series with a CO2 analyzer, combined nitric oxide and O2 sensor (Exhalyzer, Ecodymedics, Duernten, Switzerland), and prototype ultrasonic flowmeter (Spiroson model MS0.8001, Ecodymedics) containing a bacterial filter (Spirette) surrounding a dead space (Vd) reduction apparatus (size 1). The measurement setup was connected to a bias flow of 14 l/min.

Table 1. Demographic data

<table>
<thead>
<tr>
<th>Infant No.</th>
<th>Birth wt, g</th>
<th>Gestational, wk</th>
<th>Postnatal, days</th>
<th>Study wt, g</th>
<th>VT, ml</th>
<th>VE, ml/min</th>
<th>VT, ml</th>
<th>VE, ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.43</td>
<td>40.7</td>
<td>38</td>
<td>4.60</td>
<td>33.4</td>
<td>1.055</td>
<td>33.9</td>
<td>1.028</td>
</tr>
<tr>
<td>2</td>
<td>3.57</td>
<td>39.4</td>
<td>37</td>
<td>5.45</td>
<td>28.2</td>
<td>1.755</td>
<td>24.4</td>
<td>1.444</td>
</tr>
<tr>
<td>3</td>
<td>3.61</td>
<td>40.9</td>
<td>31</td>
<td>4.19</td>
<td>36.7</td>
<td>1.308</td>
<td>32.4</td>
<td>1.208</td>
</tr>
<tr>
<td>4</td>
<td>4.15</td>
<td>42.3</td>
<td>30</td>
<td>5.51</td>
<td>37.8</td>
<td>1.349</td>
<td>35.2</td>
<td>1.318</td>
</tr>
<tr>
<td>5</td>
<td>3.58</td>
<td>40.6</td>
<td>32</td>
<td>4.32</td>
<td>33.4</td>
<td>1.402</td>
<td>29.8</td>
<td>1.314</td>
</tr>
<tr>
<td>6</td>
<td>4.82</td>
<td>40.6</td>
<td>37</td>
<td>6.30</td>
<td>38.9</td>
<td>1.304</td>
<td>41.1</td>
<td>1.299</td>
</tr>
<tr>
<td>7</td>
<td>2.53</td>
<td>36.1</td>
<td>37</td>
<td>3.60</td>
<td>24.8</td>
<td>1.258</td>
<td>25.1</td>
<td>1.344</td>
</tr>
<tr>
<td>8</td>
<td>2.83</td>
<td>40.6</td>
<td>33</td>
<td>3.52</td>
<td>29.0</td>
<td>1.610</td>
<td>26.6</td>
<td>1.472</td>
</tr>
<tr>
<td>9</td>
<td>3.84</td>
<td>40.6</td>
<td>38</td>
<td>4.70</td>
<td>39.1</td>
<td>1.267</td>
<td>38.4</td>
<td>1.269</td>
</tr>
<tr>
<td>10</td>
<td>2.75</td>
<td>35.3</td>
<td>57</td>
<td>4.70</td>
<td>34.5</td>
<td>1.182</td>
<td>29.3</td>
<td>1.262</td>
</tr>
<tr>
<td>11</td>
<td>3.48</td>
<td>39.3</td>
<td>43</td>
<td>5.07</td>
<td>29.4</td>
<td>0.876</td>
<td>25.9</td>
<td>0.858</td>
</tr>
<tr>
<td>12</td>
<td>2.97</td>
<td>40.7</td>
<td>41</td>
<td>3.76</td>
<td>29.7</td>
<td>1.148</td>
<td>26.5</td>
<td>1.176</td>
</tr>
<tr>
<td>13</td>
<td>3.03</td>
<td>37.7</td>
<td>36</td>
<td>4.06</td>
<td>35.9</td>
<td>2.558</td>
<td>30.9</td>
<td>1.923</td>
</tr>
<tr>
<td>14</td>
<td>3.92</td>
<td>41.1</td>
<td>32</td>
<td>5.10</td>
<td>33.2</td>
<td>1.835</td>
<td>28.3</td>
<td>1.827</td>
</tr>
<tr>
<td>15</td>
<td>2.66</td>
<td>38.9</td>
<td>36</td>
<td>3.48</td>
<td>23.6</td>
<td>0.762</td>
<td>21.5</td>
<td>0.800</td>
</tr>
<tr>
<td>16</td>
<td>3.67</td>
<td>40.0</td>
<td>37</td>
<td>4.76</td>
<td>31.3</td>
<td>1.208</td>
<td>28.5</td>
<td>1.320</td>
</tr>
<tr>
<td>17</td>
<td>4.60</td>
<td>37.1</td>
<td>37</td>
<td>5.20</td>
<td>28.6</td>
<td>1.434</td>
<td>27.9</td>
<td>1.317</td>
</tr>
<tr>
<td>18</td>
<td>3.39</td>
<td>38.1</td>
<td>28</td>
<td>4.43</td>
<td>31.6</td>
<td>1.077</td>
<td>28.4</td>
<td>1.050</td>
</tr>
<tr>
<td>19</td>
<td>4.25</td>
<td>41.9</td>
<td>29</td>
<td>5.65</td>
<td>27.7</td>
<td>2.173</td>
<td>28.3</td>
<td>1.837</td>
</tr>
<tr>
<td>20</td>
<td>3.30</td>
<td>41.0</td>
<td>39</td>
<td>3.84</td>
<td>40.1</td>
<td>1.149</td>
<td>38.1</td>
<td>1.132</td>
</tr>
<tr>
<td>21</td>
<td>3.06</td>
<td>41.4</td>
<td>33</td>
<td>3.95</td>
<td>31.7</td>
<td>1.256</td>
<td>33.1</td>
<td>1.385</td>
</tr>
<tr>
<td>22</td>
<td>3.97</td>
<td>41.1</td>
<td>38</td>
<td>5.72</td>
<td>37.3</td>
<td>1.179</td>
<td>37.9</td>
<td>1.223</td>
</tr>
<tr>
<td>23</td>
<td>2.80</td>
<td>39.6</td>
<td>37</td>
<td>4.35</td>
<td>33.5</td>
<td>1.280</td>
<td>34.3</td>
<td>1.228</td>
</tr>
<tr>
<td>24</td>
<td>3.55</td>
<td>39.3</td>
<td>37</td>
<td>4.16</td>
<td>36.2</td>
<td>1.196</td>
<td>34.8</td>
<td>1.161</td>
</tr>
<tr>
<td>25</td>
<td>3.02</td>
<td>39.1</td>
<td>36</td>
<td>3.87</td>
<td>22.7</td>
<td>0.979</td>
<td>22.5</td>
<td>1.045</td>
</tr>
<tr>
<td>Maximum</td>
<td>4.82</td>
<td>42.3</td>
<td>57</td>
<td>6.30</td>
<td>40.1</td>
<td>2.558</td>
<td>41.1</td>
<td>1.923</td>
</tr>
<tr>
<td>Mean</td>
<td>3.47</td>
<td>39.7</td>
<td>36</td>
<td>4.57</td>
<td>32.3</td>
<td>1.342</td>
<td>30.5</td>
<td>1.290</td>
</tr>
<tr>
<td>Minimum</td>
<td>2.53</td>
<td>35.3</td>
<td>28</td>
<td>3.48</td>
<td>22.6</td>
<td>0.726</td>
<td>21.5</td>
<td>0.800</td>
</tr>
</tbody>
</table>

Data from infants 2, 4, 9, 12, 15, 17, 19–22, and 25 were used for 100-breath analysis. VT, tidal volume; VE, ventilation.
Combined instrumental \( \dot{V}_d \) without the face mask was 3 ml. Total \( \dot{V}_d \) of the silicone mask was 15 ml. The effective total measurement \( \dot{V}_d \) was 10.5 ml, with 50% of the mask space assumed to be occupied by the infant's face. This gives a mean \( \dot{V}_d \) of \( \sim 2.2 \) ml/kg body wt, which is at the upper limit of current recommendations (17) for short-range measurements. End-tidal \( \dot{CO}_2 \) was monitored for the entire test procedure and did not increase during the measurements. Signals were 12-bit analog-to-digital converted and sampled at 200 Hz using a custom-designed data acquisition and analysis package (WBreath version 3.7.6.0, Firmware v3.06, EcoMedics). The sampling time delay was corrected for each signal.

**Data Analysis**

Data were analyzed using custom software written in Matlab (Matlab 6, version 12, Mathworks). \( \dot{V}_T \) was integrated from the flow signal after correction for any technical signal drift. \( \dot{V}_E \) was calculated by multiplying \( \dot{V}_T \) by the respiratory frequency (f) on a breath-by-breath basis. A representative example of \( \dot{V}_T \) and associated sigh used for analysis is shown as a function of time in Fig. 1A. Breath-to-breath \( \dot{V}_T \) was plotted as a function of breath number for a 10-min time series (Fig. 1B). The sigh breath itself was excluded from the analysis.

**Classical tidal breathing parameters associated with respiratory drive.** We analyzed the mean, along with 95% confidence interval (CI), of \( T_d/T_i \), \( T_d/T_e \), \( \dot{I}_{TEE}/T_e \), \( T_i \), \( T_e \), and \( \dot{V}_{max} \) (31, 41) for 50 breaths before and after the sigh and compared them using paired t-tests. Moving-window CV analysis was used to determine whether these parameters were predictive for the sigh or changed after the sigh (see below).

**Change in minimum exhaled \( \dot{O}_2 \) and end-tidal \( \dot{CO}_2 \) in response to a sigh.** To examine the possible influence of alterations in \( \dot{O}_2 \) and \( \dot{CO}_2 \) on sigh and postsigh control of breathing, breath-to-breath changes in minimum exhaled \( \dot{O}_2 \) and end-tidal \( \dot{CO}_2 \) were investigated in 18 of 25 and 25 of 25 infants, respectively. In seven cases, \( \dot{O}_2 \) was not measured, inasmuch as an analyzer was not present within our equipment setup. Mean, along with 95% CI, minimum exhaled \( \dot{O}_2 \) and end-tidal \( \dot{CO}_2 \) values were calculated for the 10-breath period immediately before the sigh and compared with values for each breath after the sigh for a period of 20 breaths.

**Variability of \( \dot{V}_T \) and \( \dot{V}_E \).** Variability was examined using an established moving-window algorithm whereby CV was obtained by dividing the SD by the mean for repeated windows of 10 breaths (23, 29). A 50% window overlap was used for each subsequent measurement until the end of the 50-breath series. This technique provided 8 windows of 10 breath periods for each of the 50-breath pre- and postsigh data series. Comparisons were made between changes of CV in the period leading to the sigh, alteration of CV in response to the sigh, and the period required for return to the baseline level of CV after the sigh. Results for all 25 infants were pooled and mean (95% CI) for each window was displayed as a function of window number before and after the sigh.

**Short-range memory.** Within each analysis window containing 10 breaths as described above, the breath-to-breath \( c \) (Matlab 6, version 12, Mathworks) was also calculated with a lag of 1 breath \([c(1)]\), which represents the correlation coefficient between 2 consecutive breaths; \( c(1) = 1 \) indicates a 100% correlation between adjacent breaths, whereas \( c(1) = 0 \) indicates that they are totally uncorrelated or random. Statistical analysis was performed for the entire group (\( n = 25 \)).

To test whether correlations represented the presence of true memory, data within an individual window were shuffled 10 times (i.e., the order of data points within the window was randomized), with the autocorrelation calculation repeated on each occasion. The average \( c(1) \) for the 10 shuffles was then obtained for each window. By definition, a randomized data set such as this is uncorrelated, and \( c(1) \) should approximate 0. The existence of a significant difference in \( c(1) \) for the whole group of infants before and after shuffling indicated the presence of true short-range memory.

**Long-range memory.** In a subgroup of 12 infants, 100 tidal breaths were available on either side of the sigh, such that long-range correlations could be examined using a modified form of detrended fluctuation analysis (28). Calculation of the correlation exponent (\( \alpha \)) with this algorithm uses a modified root-mean-square analysis, a detailed description of which has been reported previously (8, 28, 30). Briefly, the breath-by-breath \( \dot{V}_T \) and \( \dot{V}_E \) time series before and after the sigh were analyzed as follows. The breath-to-breath series \( (x_i = x_1, x_2, \ldots, x_N) \) was first integrated \([y(k)]\)

\[
y(k) = \frac{1}{N} \sum_{i=1}^{N} [x_i - x_{avg}]
\]

The series was then divided into equally sized nonoverlapping windows of length \( n \), and a linear regression line was fit through the data in each window, giving the local trend of the data \( y(k) \). The fluctuation function \( F(n) \) of the time series corresponding to each window length \( n \) was calculated after detrending of data within each window by subtraction of the local trend \([y_k(k)]\)

\[
F(n) = \frac{1}{N} \sum_{k=1}^{N} [y(k) - y_k(k)]^2
\]

If the functional form of \( F(n) \) follows a power law, \( F(n) \sim n^\alpha \), the process is said to exhibit long-range correlation. The exponent \( \alpha \) can be obtained as the slope of a straight-line fit to \( F(n) \) vs. \( n \) on a log-log plot (Fig. 2). A random process with uncorrelated data is represented by \( \alpha = 0.5 \). A positively correlated signal occurs when \( \alpha > 0.5 \).

![Fig. 1. Sigh data from a representative infant. A: raw tidal flow data. B: breath-by-breath tidal volume (\( \dot{V}_T \)).](image-url)
measurements sampled at a point of interest $f_i$ of other points located at specified embedding (39). For a given time series $s_i = (s_1, s_2, ..., s_N)$ of $N$ measurements sampled at a fixed rate, a data point $s_i$ within the scalar time series is plotted against a point $s_{i-	au}$ that is “delayed” in time within the series by a given value $\tau$, called the embedding delay. The appropriate embedding of the vector time series $(S_i)$ is given by the relation $S_i = m\tau$, where $m$ represents the number of dimensions in which the data are to be embedded and $\tau$ is the time lag. The dimension is therefore represented by the number of delayed points used in the reconstruction of the attractor. Each time a point within the scalar series is related to another point located a given delayed time distant, a dimension is added to the reconstruction. Hence, a reconstruction in three dimensions relates a given reference point with two or three-dimensional embedded phase space. Each pre- and postsigh plot therefore comprised 15,000–18,000 data points. Different embedding time delays were systematically examined to obtain the best unfolding of the attractor dynamics in phase space. In most instances, the embedding delay was similar between infants, and in each infant the same embedding delay was used to examine pre- and postsigh data. As would be expected from a periodic or quasi-periodic signal, the embedding delay was related to the breathing frequency, in most cases on the order of 400 ms. This delay is similar in magnitude to that reported previously for respiratory data embedding (37) and is representative of the dominant period relation observable in low-dimensional attractor systems in which a self-excited or forced periodic behavior is present. Within such systems, a useful starting point for identification of the time delay is around one-quarter of the dominant period (1). We have selected an embedding delay of ~0.25 of normal respiratory cycle period to provide an acceptable unfolding of the attractor dynamics. To quantify the dynamics before and after a sigh, we examined the variability of cycles of the attractor within phase space plotted in two dimensions. A small region of one limb of the attractor cycles was selected to obtain at least one point from each embedded cycle. Data from the selected region were normally distributed in each infant, and variability of the cycles around the mean was assessed in terms of CV and range.

**Statistical Analysis**

Comparisons of indexes of variability, autocorrelation, and detrended fluctuation analysis, as well as pre- and postsigh attractor dynamics, were made for the grouped data using paired $t$-test. Values are means and 95% CI unless otherwise stated. Results were considered statistically significant when $P < 0.05$.

**RESULTS**

**Classical Tidal Breathing Parameters Associated With Respiratory Drive**

When examined over the 50-breath period, mean $V_t$, $T_i$, and $T_o/T_i$ decreased after a sigh (Table 2). Other parameters of respiratory drive ($\dot{V_i}$, $V_{T_i}$, $T_{PEF}/T_e$, and $V_{max}$) were unchanged. More detailed analysis using a moving-window CV algorithm showed that most of the observed alteration in $T_i$ and $T_o/T_i$ occurred during the first one to two windows (10–15 breaths) after a sigh.

**Change in Minimum Exhaled O2 and End-Tidal CO2 in Response to a Sigh**

The minimum exhaled O2 and end-tidal CO2 concentration data demonstrated a high level of stability during the 50-breath period leading to a sigh. Consequently, the mean, along with 95% CI, value for the 10 breaths immediately before a sigh were used to compare data after a sigh (Fig. 3). A significant

**Table 2. Classical indexes of respiratory drive**

<table>
<thead>
<tr>
<th></th>
<th>Presigh</th>
<th>Postsigh</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f$, breaths/min</td>
<td>42.4 (36.8, 48.0)</td>
<td>44.1 (39.3, 48.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>$V_t$, ml/min</td>
<td>32.3 (30.3, 34.3)</td>
<td>30.5 (28.3, 32.7)</td>
<td>0.0001*</td>
</tr>
<tr>
<td>$T_i$, s</td>
<td>0.64 (0.59, 0.74)</td>
<td>0.59 (0.55, 0.63)</td>
<td>0.0005*</td>
</tr>
<tr>
<td>$T_e$, s</td>
<td>0.90 (0.79, 1.01)</td>
<td>0.88 (0.77, 0.99)</td>
<td>0.27</td>
</tr>
<tr>
<td>$T_o/T_i$, %</td>
<td>42.5 (40.3, 44.7)</td>
<td>41.1 (39.2, 43.0)</td>
<td>0.001*</td>
</tr>
<tr>
<td>$V_{T_i}$, ml/s</td>
<td>52.5 (47.6, 57.4)</td>
<td>52.2 (49.1, 55.3)</td>
<td>0.83</td>
</tr>
<tr>
<td>$T_{PEF}/T_e$, %</td>
<td>39.3 (33.1, 45.5)</td>
<td>35.0 (29.7, 40.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>$V_{max}$, ml/s</td>
<td>72.8 (66.4, 79.2)</td>
<td>73.3 (69.0, 77.6)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Values are grouped means [means – 95% confidence interval (CI), means + 95% CI] of all 25 infants for mean of 50 breaths before and after a sigh in each infant. $f$, respiratory frequency; $T_i$, inspiratory time; $T_e$, expiratory time; $T_o$, total respiratory cycle time; $t_{PEF}$, time to peak inspiratory flow; $V_{max}$, maximal inspiratory flow; $P$ values were determined by $t$-test, * $P < 0.05$.
increase in minimum exhaled O₂ was evident for the first two breaths after a sigh compared with the presigh values when examined for the entire group. Changes in end-tidal CO₂ lasted slightly longer, with a significant reduction to the fifth postsigh breath.

Variability of Vₜ and V̇ₑ

CV of Vₜ increased in 23 of 25 infants after a sigh when examined over the entire 50-breath period. For the moving-window analysis, cross-sectional data were normally distributed, allowing the use of mean and 95% CI for presentation of data. Individual Vₜ variability data for each analysis window were grouped for all 25 infants and are presented in Fig. 4A. Baseline Vₜ variability was not significantly different between measurement windows during the presigh period (P = 0.22), implying that no indication of the approaching sigh was evident in the presigh variability. Compared with the 10-breath window immediately before the sigh, there was a significant increase in variability during the first two analysis windows after the sigh, representing a period of 15 breaths. Similar changes in variability were observed in Vₑ (Fig. 4B).

Short-Range Memory

Autocorrelation data for windows located at an increasing distance after the sigh and for the window immediately before the sigh are compared in Fig. 5A. Grouped mean CV of c(1) for Vₜ was significantly increased during the first three postsigh windows, representing a period of 20 breaths (Fig. 5A). In contrast, c(1) of Vₑ was significantly higher for the first postsigh window only; the second window had a borderline significance of P = 0.05 (Fig. 5B).

Linear regression analysis through the group means for each analysis window before the sigh showed a significant decrease of correlation of Vₜ (r² = 0.59, P = 0.02) and Vₑ (r² = 0.53, P = 0.04) compared with a randomized series during the period leading to the sigh (Fig. 6). The Vₜ and Vₑ series demonstrated a weak breath-to-breath correlation that was significantly different from a randomized series but became less significant as the sigh approached. In the case of the Vₜ series, the original and randomized data were not significantly different for the presigh window (P = 0.08), indicating a loss of deterministic correlation. After the sigh, Vₜ and Vₑ showed a significant increase in correlation compared with their respective randomized series, which persisted for the duration of eight postsigh analysis windows (i.e., the full 50 breaths).

Long-Range Memory

The exponent α, characterizing the long-range correlation of Vₜ and Vₑ, was unchanged in response to the sigh (Table 3). The observed trend (P = 0.06) toward change in long-range correlation (over 100 breaths) of Vₜ is consistent with a
contribution from short-range correlations observed over 50 breaths.

**Stability**

An example of a typical phase-space embedding in two and three dimensions from a single infant is shown in Fig. 7. The significant alteration in attractor dynamics after a sigh is clearly evident. Similar visual changes were observed in all infants. CV of data points within the analyzed attractor region increased significantly after the sigh in 18 of 25 infants (0.18 (95% CI = 0.09–0.27) and 0.37 (95% CI = 0.22–0.52) before and after the sigh, respectively, P < 0.001). The range increased in 22 of 25 infants (0.03 (95% CI = 0.02–0.04) and 0.05 (95% CI = 0.04–0.06) before and after the sigh, respectively, P < 0.02). Importantly, on each occasion, the respiratory behavior returned to the same position within the phase space after the sigh, indicating overall stability of the system.

**DISCUSSION**

Sighs play an important role in altering the mechanical properties of the lungs and airway walls. In bronchoconstricted adults, sighs lead to an increase in specific airway conductance and bronchodilatation secondary to an increase in transpulmonary pressure that is not related to change in lung volume (11). In preterm infants, mechanical effects of sighs include maintenance of lung volume (32), increased dynamic lung compliance, and reduced lung resistance (10), confirming their role in altering lung mechanics.

The exact origin of spontaneous sighs remains controversial. They may result from activation of lung and chest wall recep-

---

**Table 3. Long-range regulation of V_t and V_e, before and after a sigh**

<table>
<thead>
<tr>
<th></th>
<th>Presigh</th>
<th>Post sigh</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>V_t</td>
<td>0.72 (0.63,0.81)</td>
<td>0.83 (0.71,0.95)</td>
<td>0.06</td>
</tr>
<tr>
<td>V_e</td>
<td>0.88 (0.78,0.98)</td>
<td>0.85 (0.72,0.98)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Values are means (means ± 95% CI; means ± 95% CI); n = 12. α, Correlation coefficient: P values were determined by paired t-test.
tors in response to reduced pulmonary compliance associated with alveolar atelectasis (6). Animal studies have demonstrated increasing sigh frequency in response to hypoxia (3) and hypercapnia (34), whereas interruption of vagal pathways leads to loss of these feedback responses (3). Vagal neural feedback to the brain stem respiratory center plays a significant role within the reflex pathway responsible for mediating sigh activity (25). For example, the increase in neurally mediated end-expiratory volume and respiratory frequency after sighs in cats is not observed after passive inflation maneuvers (38). The shorter time required for end-expiratory volume than for lung compliance to return to baseline in these cats is further evidence of dissociation between neural and mechanical effects of sighs. The increased sigh frequency reported in infants with an immature breathing control system (e.g., preterm infants) (2, 19) highlights the likely importance of sighs within the neuroregulatory feedback loop.

Recently, regulatory properties of the respiratory negative-feedback loop have been analyzed using mathematical techniques derived from engineering systems control theory (24, 35). The behavior of the control loop after a sigh may be reflective of the maturity and functional integrity of neurorespiratory feedback control. Using these techniques, we investigated whether sighs are important for the regulation and resetting of the neurorespiratory controller. Our data showed that a highly regulated and stable negative-feedback loop system exists in healthy infants and that sighs represent a mechanism for improving the memory associated with neurorespiratory control of breathing within this system.
Classical Tidal Breathing Parameters Associated With Respiratory Drive

This study suggests that established indexes of respiratory drive and control, such as $T_i/T_T$, $V_T/T_i$, $I_{PEF}/T_E$, $T_i$, $T_e$, and $V_{max}$, are not predictive of an impending sigh. Most of these parameters remained unchanged during the 50-breath post sigh period, although a small, but statistically significant, decrease in $T_i$ and $T_i/T_T$ occurred during the two window periods immediately after the sigh compared with the presigh window. Ueda et al. (41) showed that $I_{PEF}$ was one factor that identified reduced respiratory drive in infants of smoking mothers, suggesting its potential usefulness for the examination of control. The reason for the insensitivity of most of the classical drive parameters to changes in respiratory control induced by a sigh in this study is unclear. Although $T_i/T_T$ and $T_i$ are higher in adults during presigh breaths than immediately after a sigh (31), physiological differences make comparisons between infants and adults particularly difficult. Techniques permitting analysis of the dynamic characteristics of respiratory drive, such as those derived from system control theory, may reveal more information about the continually changing behavior of this control system than is provided by standard linear methods.

Change in Minimum Exhaled $O_2$ and End-Tidal $CO_2$ in Response to a Sigh

The correlation between arterial $O_2$ and $CO_2$ values and exhaled gas concentrations is known to be limited (42); however, because of the noninvasive nature of this study, we were unable to analyze blood gases. We did, however, monitor $O_2$ and $CO_2$ in exhaled gas continuously. Breath-to-breath minimum exhaled $O_2$ and end-tidal $CO_2$ revealed highly stable values over 50 breaths before and after a sigh, with exhaled concentrations of both gases returning to presigh values within six breaths (Fig. 3). These changes were of a shorter duration than those observed in variability or short-range memory of $V_T$ and $V_E$ after a sigh. Changes in flow and volume during the first few breaths after a sigh may impact on the concentrations of exhaled gases. When examined over a longer period, the mean minimum $O_2$ and end-tidal $CO_2$ were not different from presigh values.

Variability of $V_T$ and $V_E$

A typical feature of an adaptive control system operating in a noisy environment is variability. A system locked into a steady state is likely to be insensitive to small perturbations within its external environment. Reduction of physiological variability has been associated with morbidity and mortality, e.g., in the reduced heart rate variability observed with age (22, 30) and heart disease (29) and in extreme cases preceding sudden infant death syndrome. Together, these two studies show that sighs may play an important role in resetting autonomic tone in NREM sleep.

Stability of the Control System

To characterize the clear increase in fluctuations of the attractor after a sigh, we analyzed a segment of the attractor path within a predetermined region of two-dimensional phase space (Fig. 7). Compared with the locked-in and unresponsive behavior of the presigh attractor (Fig. 7A), there was a clear increase in fluctuations of the attractor after a sigh (Fig. 7B). The comparatively low variability indexes observed before a sigh occurred alongside a gradual reduction in short-range memory of the system, and we speculate that this reduced memory and apparent reduction in system responsiveness are intimately related. The significant increase in path fluctuation suggests that the attractor was less “locked-in” and more responsive to perturbations (Fig. 7B). This marked increase in cycle fluctuation within phase space is confirmed by the significant increases in the range and variability of data points obtained from the attractor segments. Importantly, the breathing control system returned to the same basin of attraction during the period after the sigh in all infants, as indicated by

Memory in Respiratory Control

The existence of memory within a feedback system allows the recent history (or state) to play a role in the response to a transient perturbation, thus assisting with return to steady-state behavior. Many biological systems exhibit long-range memory characterized by a power law in which decay of correlations slowly fades with time. These systems may be said to demonstrate scale-invariant or fractal characteristics. Although this has been shown for heart rate (29) and breathing (30) in adults, we recently demonstrated such long-range memory in infant breathing (8). Detrended fluctuation analysis (28) performed on $V_E$ during this study identified no change of long-range correlation after a sigh in healthy infants. A trend toward an increase in $\alpha$ of $V_T$ after sigh might be related to the observed changes in short-range memory described below. The presence of a power law memory is likely to be beneficial for the long-range stability of the control system. However, such analysis does not reveal the rapid dynamics after a perturbation of the system.

The analysis techniques used in this study allowed us to follow rapid changes in system dynamics. In the context of an engineering control system, the presence of short-range memory may act like a low-pass filter for a sudden perturbation, allowing a smoother response to the stimulus. The loss of short-range memory [decrease in $c(1)$] as the sigh approached and apparent random behavior of $V_T$ immediately before the sigh suggest that the complete loss of correlations in $V_T$ may predict the next sigh. After the sigh, $c(1)$ was significantly increased compared with the randomized series for the 50 breaths after the sigh but steadily decreased probably toward the onset of the next sigh. These data are compatible with a recovery of short-range memory of the respiratory control system after the sigh, which is consistent with the hypothesis that sighs may act as a resetting mechanism for the control loop. Our findings are supported by the data of Franco et al. (15), who recently demonstrated differences in the response to a sigh between healthy infants and those who later succumbed to sudden infant death syndrome. Together, these two studies show that sighs may play an important role in resetting autonomic tone in NREM sleep.
the unchanged position of the attractor within the phase-space plot. Thus, although the system is more variable and, perhaps, better regulated, it remains stable. It is worth noting that stability and variability represent different phenomena in system behavior and often coexist. Furthermore, an increase in variability (e.g., CV) does not necessarily imply an alteration of correlation properties. Consequently, a system may be intrinsically stable while demonstrating significant variability in response to, e.g., extrinsic fluctuations (24).

**Technical Issues and Limitations of the Study**

Because the aim of this study was to assess the alterations in neuroregulatory control after a sigh, we examined the output parameters of this complex system in terms of tidal breathing indexes. The techniques employed during this study allowed us to investigate the global properties of this feedback system. A limitation of these methods was the inability to separate and define the contributions of the various input parameters to this regulatory system, e.g., those from chemoreceptors and pulmonary stretch receptors.

From a physiological point of view, the conditions under which measurements are made are important. Measurement conditions were standardized as far as possible, while the noninvasive nature of this study was maintained. Nevertheless, even the pressure and temperature of the face mask can influence control of breathing (14). The mask was warmed to skin temperature before application, and infants were given time to adapt to the new face-mask conditions before measurements were begun. Although infants were studied in a cot or in the mother’s arms, in all cases, position of the body and head were standardized. A major strength of this study lies in the homogeneous population of healthy infants, all of whom were measured under conditions of quiet undisturbed sleep. Such studies must be performed carefully, because sigh behavior of infants during different sleep stages may vary (19). In this study, we undertook careful prospective evaluation of behaviorally defined sleep patterns (33) to avoid the possibility of observing alterations in sleep state after a sigh.

Sighing occurs about every 50–100 breaths in healthy infants. Thus the information on long-range correlations is limited to a maximum of ~100 breaths. Detrended fluctuation analysis was designed for much longer data sets, and a limited number of data points can introduce bias. Using a correlated noise signal with a known $\alpha$ of 1.0, we have tested the effect of reducing the number of data points from 1,000 to 100. Using a data set size 100, we found that the difference in $\alpha$ was ±15% compared with the larger series. To partly overcome this limitation of data set size, we always compared the same number of data points before and after a sigh. Phase-space plot analysis is dependent on the correct choice of raw data, the embedding dimension, and the time delay. We used raw tidal flow time series data, which represent the most basic form of information obtained from the respiratory system with use of our equipment. Consequently, the attractor may be visualized in phase space in its “original” form, before data manipulations such as integration. In addition, the accuracy of the reconstruction of the attractor is dependent on the amount of data included. Attractor reconstructions normally incorporate at least several thousand points (1, 21, 23, 37); hence, short data series of 50–100 breaths (e.g., Vr) are insufficient. For our purposes, a time series of 50 breaths consisted of ~15,000–18,000 data points, providing much clearer information regarding the attractor behavior and, therefore, about the global system dynamics.

Reconstruction of the attractor in phase space is dependent on the nature of the individual signal under study. Numerous techniques have been developed to assist with accurate representation of the intrinsic dynamics of the system graphically. It is possible to obtain a suitable value of the embedding delay ($\tau$) in several ways (1, 23). In this study, the embedding delay was increased systematically, and the attractor trajectories were viewed for consistency of appearance at different delays. That is, the unfolding of the attractor trajectories was examined at many delays, with an appropriate delay being one that provided the best visual representation of the system dynamics.

**Summary**

We found an increased variability of tidal breathing after a sigh in healthy infants during quiet sleep. Short-range breath-to-breath memory of the neurorespiratory control system decreased toward the sigh. After the sigh, this memory was recovered before steadily returning to presigh conditions. Long-range memory and the location of the system attractor within phase space were unchanged after the sigh, consistent with the presence of long-range stability. Attractor dynamics were markedly different, with a relatively fixed, locked-in behavior before the sigh changing to a more adaptive pattern with increased fluctuation after the sigh. These findings support the hypothesis that sighs in infants not only act to reset mechanics but also to change the properties of the neurorespiratory control system. Finally, an intriguing finding was the observation that loss of short-range memory appeared to be a predictor of a sigh.

The ability to sigh may be an important mechanism of control of breathing. The response to a sigh may be different in various groups of infants at risk for inadequate control of breathing, such as premature infants, those with neurological impairment, or those at risk for sudden infant death syndrome. Further studies should investigate sigh behavior during maturation and in disease to develop a new sensitive marker of control of breathing in these infants at risk.

**ACKNOWLEDGMENTS**

We thank the parents of the infants who participated in the study and G. Wirz, M. Graf, C. Becher, and H. Gehr for help with enrollment of infants and assistance in performing measurements.

**GRANTS**

This study was supported in part by Swiss National Fund Grant 32-68025.02. Partial support was provided to D. N. Baldwin by Swiss Government Grant 2002-0041 and European Respiratory Society Long-Term Research Fellowship 2002-032.

**REFERENCES**


