Model-based stability assessment of ventilatory control in overweight adolescents with obstructive sleep apnea during NREM sleep

L. Nava-Guerra, 1 W. H. Tran, 1 P. Chalacheva, 1 S. Loloyan, 2, 3 B. Joshi, 2, 3 T. G. Keens, 2, 3 K. S. Nayak, 1, 4 S. L. Davidson Ward, 2, 3 and M. C. K. Khoo 1

1 Department of Biomedical Engineering, University of Southern California, Los Angeles, California; 2 Division of Pediatric Pulmonology and Sleep Medicine, Children’s Hospital Los Angeles, Los Angeles, California; 3 Keck School of Medicine, University of Southern California, Los Angeles, California; and 4 Ming Hsieh Department of Electrical Engineering, University of Southern California, Los Angeles, California

Submitted 22 December 2015; accepted in final form 5 May 2016

Model-based stability assessment of ventilatory control in overweight adolescents with obstructive sleep apnea during NREM sleep. J Appl Physiol 121: 185–197, 2016. First published May 12, 2016; doi:10.1152/japplphysiol.01081.2015.—Obstructive sleep apnea (OSA) involves the interplay of several different factors such as an unfavorable upper airway anatomy, deficiencies in pharyngeal muscle responsiveness, a low arousal threshold, and ventilatory control instability. Although the stability of ventilatory control has been extensively studied in adults, little is known about its characteristics in the pediatric population. In this study, we developed a novel experimental setup that allowed us to perturb the respiratory system during normal non-rapid eye movement (NREM) sleep conditions by manipulating the inspiratory pressure, provided by a bilevel pressure ventilator, to induce sighs after upper airway stabilization. Furthermore, we present a modeling framework that utilizes the noninvasively measured ventilatory responses to the induced sighs and spontaneous breathing data to obtain representations of the processes involved in the chemical regulation of respiration and extract their stability characteristics. After validation with simulated data, the modeling technique was applied to data collected experimentally from 11 OSA and 15 non-OSA overweight adolescents. Statistical analysis of the model-derived stability parameters revealed a significantly higher plant gain and lower controller gain in the OSA group (P = 0.046 and P = 0.007, respectively); however, no differences were found in loop gain (LG) and circulatory time delay between the groups. OSA severity and LG, within the 0.03–0.04-Hz frequency band, were significantly negatively associated (r = −0.434, P = 0.026). Contrary to what has been found in adults, our results suggest that in overweight adolescents, OSA is unlikely to be initiated through ventilatory instability resulting from elevated chemical loop gain.


Obstructive sleep apnea (OSA) is one of the most common sleep-related breathing disorders (SRBD) (2, 22) and is characterized by recurrent episodes of upper airway narrowing or collapse during sleep (60). These apneic events are often accompanied by hypoxia and arousal, which might lead, in the long term, to hypertension and other cardiovascular and cerebrovascular diseases (38). In the United States, OSA is more prevalent in adults (~3%) (55) compared with the 1.6% found in children and adolescents with ages ranging between 2 and 18 yr (41). However, the prevalence of OSA in children could be increased, in large part, because of the growing prevalence of childhood overweight (51), which is a known risk factor (56).

Although there are similarities in the diverse forms of SRBD between adults and children, there are also important differences in treatment and diagnosis (46). For instance, adenoid and tonsil removal through surgical intervention is frequently used as treatment for children (58a), whereas continuous positive airway pressure (CPAP) is the most common therapy in adults (40). In terms of diagnostics, polysomnography (PSG) is the gold standard for both adults and children; nevertheless, there are differences in the way OSA is defined based on the number of obstructive respiratory events per hour of sleep. In adults, 5 events/h are considered as mild OSA (21a), while in young children, 1.5 events/h are already considered abnormal (42). Considerable research has been devoted to the study of OSA in adults; however, less attention has been paid to the pathophysiology of the disease in the pediatric population (56).

It is known that upper airway anatomy and collapsibility play an important role in the development of childhood OSA (4). However, it has been increasingly recognized that this type of breathing disorder is a rather complex phenomenon involving other nonanatomical mechanisms as well (21, 52). Other factors include a low arousal threshold, depressed genioglossus muscle responsiveness, and instability of the ventilatory control system (67). Recently, there has been growing interest in developing experimental and analytic methods that quantify the traits that predispose to OSA to help clinicians design patient-specific treatment strategies that target a particular mechanism (66).

Special attention has been focused on studying the ventilatory control system using mathematical models and employing control theory to extract the stability characteristics of the system. Loop gain (LG) has been used as an index of the propensity toward feedback instability, mediated through ventilatory disturbances that affect CO2 and/or O2. A ventilatory
system with a high LG would tend to magnify disturbances and could potentially develop self-sustained oscillations in ventilation known as periodic breathing, whereas a low LG would diminish such perturbations and exhibit a more stable ventilation. The term “loop gain,” initially employed by the engineering community, is currently being applied in the clinical environment because it provides clinicians with a concise representation of the overall performance of ventilatory control and its principal components, i.e., gas exchange, circulatory delay, chemoreception, and respiratory muscle activation. LG is a frequency-dependent parameter (34) that can be accurately estimated from data-driven dynamic mathematical models. For instance, autoregressive models have been used to estimate ventilatory stability parameters from responses to different inhaled mixtures of CO2 (26, 49). Furthermore, proportional-assist ventilation has been utilized to induce periodic breathing and quantify relative stability (69, 72). In addition, changes in ventilatory control stability in response to drug administration have also been evaluated by means of dynamic modeling (48, 50). However, these methods involve the application of strong stimuli or maneuvers that could alter LG from baseline conditions.

There are, however, other groups that have quantified stability from data collected under more “natural” sleeping conditions, in which less intrusive interventions were applied. Notable is the work developed by Asyali et al. (5), where hyperventilation due to an acoustically induced transient arousal from sleep was employed as the driving stimulus to the system, and that of Gederi et al. (25), where spontaneous variations in ventilation and end-tidal CO2 pressure (PETCO2) during non-rapid eye movement (NREM) sleep proved to be sufficient to provide accurate model estimations.

Similar to these efforts of studying the system under natural conditions, our work also exploits the spontaneous variations in ventilation and PETCO2 to identify the gas exchange process and subsequently derive the plant gain (PG). Moreover, our group designed a novel experimental technique to perturb the ventilatory control system by inducing sighs with a bilevel positive pressure ventilator and estimating LG from the ensuing responses by employing a nonparametric identification technique. This protocol emulates the spontaneous sighs that are present in natural sleep, allowing us to study ventilatory control dynamics during NREM sleep in overweight adolescents, a group at increased risk for SRBD.

**MATERIALS AND METHODS**

**Subjects**

A total of 26 adolescents (14 females and 12 males; age range, 13–21 yr) with a history of snoring and a body mass index (BMI) greater than the 85th percentile, after adjusting for age and gender, were recruited to participate in the study. Each subject underwent a standard diagnostic PSG to detect the presence of OSA; a pulmonary function test (PFT) to evaluate for pulmonary disease; and a research PSG, during which experiments were performed to obtain information about the stability of ventilatory control. The study was approved by the Institutional Review Board at Children’s Hospital Los Angeles, and all parents and participants gave written informed consent prior to their participation in the experiment.

Subjects taking medications that could affect breathing or who were using supplemental oxygen or who were on positive pressure treatments (CPAP or bilevel positive airway pressure) were excluded. Additionally, diabetes, cardiac disease, chronic lung disease, persistent asthma, syndromic conditions, mental illness, neuromuscular disorders, and craniofacial malformations were also considered exclusion criteria.

**Standard Polysomnography**

A baseline overnight PSG was carried out to classify the population into non-OSA and OSA subjects, using an obstructive apnea-hypopnea index (OAHI) of 5 events/h of sleep as the cutoff value. Surface electrodes were used to record electroencephalogram (EEG), electrocardiogram (ECG), electrooculogram (EOG), and chin and leg electromyogram (EMG). In addition, chest and abdominal displacements, pulse oximetry, and end-tidal carbon dioxide tension (PETCO2) were also monitored. Data were recorded with the SomnoStar z4 Sleep System (Carefusion, San Diego, CA), and respiratory events were scored according to the American Academy of Sleep Medicine criteria (12). Table 1 summarizes the characteristics of the subjects that participated in the study after categorizing them as non-OSA and OSA on the basis of the OAHI calculated from the baseline PSG. It should be noted that besides differences found in neck circumference, OAHI, and resting PETCO2 values, both groups are comparable in male-to-female ratio, other anthropometric measurements, and even therapeutic pressures. The surprising similarity in the latter parameter can be attributed to the persistent snoring and flow limitation episodes exhibited by the non-OSA group.

**Pulmonary Function Test**

On a different night, within 3 mo after being diagnosed (72 ± 13 days), subjects returned to the hospital for pulmonary function testing. This test was performed immediately before the experimental PSG to evaluate for pulmonary disease as a contributor to hypoxia or hypercapnia during the diagnostic PSG. The PFT consisted of the following: body plethysmography to measure various lung capacities, spirometry to assess airway obstruction, single-breath nitrogen washout to look for abnormalities in the distribution of ventilation, and a diffusing capacity test to evaluate the gas transport across the alveolar-capillary membrane (17). Table 2 summarizes the measurements collected from the aforementioned procedures.

**Experimental Polysomnography**

Subjects were asked to sleep in supine position and were fitted with a full face mask (Mirage Quattro; ResMed, San Diego, CA), which

**Table 1. Subject pool anthropometric and polysomnographic characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-OSA (n = 15)</th>
<th>OSA (n = 11)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M:F)</td>
<td>5:10</td>
<td>7:4</td>
<td>ns</td>
</tr>
<tr>
<td>Age, yr</td>
<td>14.6 ± 1.5</td>
<td>14.6 ± 1.9</td>
<td>ns</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>34.3 ± 7.9</td>
<td>37.0 ± 7.3</td>
<td>ns</td>
</tr>
<tr>
<td>Neck circumference, cm</td>
<td>36.0 ± 8.2</td>
<td>43.0 ± 5.9</td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>

**Pulmonary Function Test**

Values are means ± SD. M, male; F, female; BMI, body mass index; OAHI, obstructive apnea hypopnea index; CPAP, continuous positive airway pressure; T inspiratory time; Te, expiratory time; VT, tidal volume; PETCO2, end-tidal CO2 pressure; ns, not significant.
subject pool pulmonary function test measurements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-OSA (n = 15)</th>
<th>OSA (n = 11)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body plethysmography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC, % pred</td>
<td>115.2 ± 12.7</td>
<td>116.7 ± 23.5</td>
<td>ns</td>
</tr>
<tr>
<td>RV, % pred</td>
<td>96.8 ± 35.4</td>
<td>135.7 ± 57.1</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>VC, % pred</td>
<td>122.4 ± 16.8</td>
<td>113.6 ± 19.7</td>
<td>ns</td>
</tr>
<tr>
<td>FRC, % pred</td>
<td>101.9 ± 16.6</td>
<td>104.3 ± 22.4</td>
<td>ns</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>16.9 ± 6.1</td>
<td>23.0 ± 6.0</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>FVC, % pred</td>
<td>119.4 ± 15.4</td>
<td>110.1 ± 22.1</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Spirometry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1, % pred</td>
<td>116.2 ± 15.0</td>
<td>102.0 ± 14.9</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>81.8 ± 9.1</td>
<td>86.0 ± 5.6</td>
<td>ns</td>
</tr>
<tr>
<td>FEF 25/75, % pred</td>
<td>117.2 ± 19.5</td>
<td>93.0 ± 23.9</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td><strong>Nitrogen washout</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dN2, Delta/l</td>
<td>1.1 ± 0.6</td>
<td>1.4 ± 0.9</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Diffusing capacity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLCO/VA, ml·mmHg⁻¹·L⁻¹·min⁻¹</td>
<td>5.0 ± 0.4</td>
<td>5.5 ± 0.6</td>
<td>*ns</td>
</tr>
</tbody>
</table>

Values are means ± SD. TLC, total lung capacity; RV, residual volume; VC, vital capacity; FRC, functional residual capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; FEF 25/75, forced expiratory flow between 25 and 75% of FVC. DLCO/VA, diffusion in the lung of carbon monoxide divided by the alveolar volume; dN2, slope of phase III of the single-breath nitrogen washout test; % pred, ratio of actual results compared to predicted normal values, expressed as a percentage. *Missing data from two subjects.

was attached to a unique breathing circuit. The circuit consisted of a two-way T-shape nonrebreathing valve (Model 1400; Hans Rudolph, Kansas City, MO) with a whisper swivel valve (Respironics, Pittsburgh, PA) connected at the expiratory port to remove exhaled CO2 from the circuit. An 18-in.-long, flexible CPAP tube was appended to the swivel valve and was fed back to the inspiratory limb, to maintain pressure during inspiration and expiration constant. Positive pressure was provided via a bilevel pressure ventilator (S/T-D 30; Respironics) operating in CPAP mode. In addition to the standard polysomnography measurements, mask pressure was monitored by means of a differential pressure transducer (Validyne, Northridge, CA) referenced to atmospheric pressure. Respiratory airflow was measured by a second Validyne pressure transducer in conjunction with a pneumotachometer (Model 4813; Hans Rudolph) connected to the ventilator. Arterial blood pressure was assessed using a peripheral arterial tonometer placed on the index finger (Itamar Medical, Caesarea, Israel) and was used concomitantly with EEG signals to detect arousals (18). All physiological signals were sampled at f_s = 200 Hz and recorded with a digital acquisition system (NI USB-6218; National Instruments, Austin, TX), which was also used to send pressure command signals from the computer to the ventilator.

After sleep onset, CPAP was gradually increased starting at a baseline value of 3-cmH2O pressure and until respiratory events (snoring, hypopneas, apneas) and flow limitation, defined as a flattening in the inspiratory portion of the airflow signal (15), were eliminated. When the therapeutic level was reached, and once a stable NREM sleep stage was achieved, inspiratory pressure was abruptly increased by 5 cmH2O for two consecutive breaths, keeping the expiratory pressure at therapeutic level. The response to these "induced sighs" was recorded for 50 breaths and used for further analysis. This intervention lasted 4–5 min on average and was carried out multiple times throughout the night, discarding from our analysis those segments that resulted in arousal. In addition, segments of spontaneous breathing at therapeutic pressure during quiet NREM sleep lasting ~10 min were also recorded and utilized for analysis.

Data Processing

In the data segments selected for analysis, the airflow signal was integrated to derive breath-to-breath tidal volume (VT), inspiratory (TE) and expiratory (TD) durations, ventilation [VE = Vm(TE + TD)], and mean inspiratory flow (Vm/T). These breath-to-breath time series had the form of staircase signals sampled at the original sampling rate f_s = 200 Hz.

The PCO2 signal was low-pass filtered digitally using a finite impulse response filter with Kaiser windowing. The cutoff frequency was set to 5 Hz, and to keep the amplitude of the original measurement unaffected, the filter order was set to 30. The breath-to-breath PETCO2 was subsequently derived from the filtered PCO2 time series and had to be appropriately shifted, accounting for the instrumentation delay, to ultimately align with the rest of the breath-to-breath respiratory signals.

Breath-to-breath ventilation and PETCO2 were used in the calculations to derive PG, whereas mean inspiratory flow was used to represent ventilatory drive (VD = Vm/T) in the computations of LG. We used mean inspiratory flow instead of ventilation to represent ventilatory drive to suppress the effects on respiratory timing that frequently followed the induced sighs. The utilization of VD to analyze the respiratory response to stimulation was first proposed by Milic-Emili and Grunstein (47), as it provided more accurate results when the stimulus had effects on both tidal volume and respiratory frequency, which is what we observed during the induced sighs protocol.

Linear trends were removed from the breath-to-breath time series, and they were further downsampling to f_s = 1 Hz by averaging using a moving window of length f_s/f_s samples with no overlap to produce uniformly sampled sequences for subsequent analyses.

Mathematical Model

The convolution sum describes the linear dynamic relationship between input and output time series x(n) and y(n), respectively, for stable time-invariant systems:

\[ y(n) = \sum_{m=0}^{M-1} k(m)x(n - m) + e(n) \]  

where M is defined as the memory of the system and represents the amount of previous values of the input affecting the current output; k(m) represents the impulse response of the system, which completely characterizes its dynamic characteristics; and e(n) is an error term representing the values of the output y(n) that are not associated with the input x(n). Therefore the goal of the system identification process is to find estimates of k based solely on observable input-output data.

To make the impulse response more compact and improve model estimation, we assume that k can be expanded using a properly selected set of causal basis functions b_q(m) (see Eq. 2) defined over the dynamic range of the system [0, M] (44). We utilized the set of Meixner basis functions (MBF), which has a built-in exponential term suitable for modeling the relaxation characteristics exhibited by various physiological systems. This set of orthonormal functions represents a generalization of the widely used discrete Laguerre functions (19) and has proven to be suitable for modeling systems with sluggish dynamics such as the ones that we aim to study (6). The different slow onset can be captured by varying the order of generalization, which is an MBF parameter that controls the time at which the basis functions will start to fluctuate.

\[ k(m) = \sum_{q=0}^{Q-1} c_q b_q(m) \]  

where Q is the total number of basis functions utilized to expand the impulse response, b_q represents the qth-order MBF, and c_q are the expansion coefficients. By combining Eqs. 1 and 2 we obtain

\[ y(n) = \sum_{q=0}^{Q-1} \sum_{m=0}^{M-1} c_q b_q(m)x(n - m) + e(n) \]  

from which the expansion coefficients c_q can be estimated by least
squares minimization. The estimated coefficients $c_q$ can then be used in Eq. 2 to finally obtain the impulse response of the system. Note that by expanding the impulse response function as a weighted sum of basis functions, the amount of unknowns to be estimated from Eq. 3 has been significantly reduced from $M$ to $Q$.

This procedure was applied to the spontaneous breathing (no interventions) data to estimate the coefficients representing the gas exchange process and to the induced sighs responses to estimate the coefficients representing overall loop dynamics.

Gas exchange. The dynamic input-output relationship between the current value of end-tidal $PCO_2$ and the present and past values of ventilation was formulated by

$$
\Delta P_{ETCO_2}(n) = \sum_{m=0}^{M_p-1} k_p(m) \Delta V_p(n - m) + \varepsilon_p(n)
$$

where the operator $\Delta$ implies variations around the mean values of $P_{ETCO_2}$ and $V_p$, $k_p(m)$ is the plant impulse response, $\varepsilon_p(n)$ represents the changes in $\Delta P_{ETCO_2}$ that are not due to changes in ventilation, and $M_p$ is the memory of the gas exchange process. Given that this phenomenon has been found to exhibit fast dynamics with effects lasting for only a few breaths (48, 50), $M_p$ was assumed to be 30-s long.

Overall loop. The overall loop model characterizes the combined dynamics of several mechanisms: the gas exchange occurring in the lungs and tissues, the transport delay through circulation, the process of chemoreception by the peripheral and central chemoreceptors, and the activation of the respiratory muscles. After imposing causality by inserting the time delay $D$, the chemically mediated changes in ventilation are modeled as the output of an autoregressive linear process (3, 29):

$$
\Delta V_p(n) = \sum_{m=0}^{M_p-1} k(m) \Delta V_p(n - m - D) + \varepsilon(n)
$$

where the operator $\Delta$ indicates variations around the mean value of $V_p$; $k(m)$ is the loop impulse response (LIR) and combines the effects of all the processes that conform it; $M_p$ denotes the memory of the overall loop and it was assumed to be 100 s; $\varepsilon(n)$ represents the changes in $\Delta V_p$ that are not mediated by the chemoreflex; and $D$ is a pure time delay representing the time it takes for a change in alveolar $PCO_2$ to be transmitted through the circulatory system to the chemoreceptor loci, signal transduction, and processing within the medullary circuitry (10, 23). On the basis of previous experimentally derived models (5, 8), $D$ was assumed to lie within a range between 6 and 12 s.

Note that this model differs from the standard autoregressive model, as it is instead formulated as a weighted sum of causal basis functions with finite impulse responses just like for the gas exchange model. Also note that Eq. 5 would not hold during the application of the external perturbation (induced sighs); thus we excluded this portion of the data when fitting the model and considered only the part that immediately followed the sighs.

Model selection criterion. To avoid the problem of overfitting the data and to obtain the most parsimonious model that represented the system accurately, we employed the concept of minimum description length (MDL). This concept, first introduced by Rissanen (57), penalizes the increase in model complexity when adding parameters to be estimated (39). This penalty factor is added to the normalized mean squared error to finally yield our cost function:

$$
MDL = \ln \left( \frac{\sum_{n=1}^{N} (e(n) - \bar{e})^2}{Q \times \ln(N)} \right) + \frac{Q \times \ln(N)}{N}
$$

where $N$ denotes the length of the time series, $Q$ is the number of MBF, $e(n)$ is the difference between the model prediction and the measured output $y(n)$, and $\bar{e}$ and $\bar{y}$ are the mean values of the residuals and the output, respectively. A global search for the minimum of the MDL function was performed for different combinations of number of MBF, orders of generalization, and, in the case of the LIR estimation, time delays.

Simulations

A discrete linear feedback model of the neurochemical control of respiration implemented in Simulink (MathWorks, Natick, MA) was used to produce artificial breath-by-breath data sets that emulated our experimental interventions (see Fig. 1). The model consisted of three main components: 1) a feed-forward branch representing the gas exchange occurring in the lungs; 2) a pure time delay to account for the latency in signal transmission from the lungs to the chemoreceptor location sites; and 3) a feedback component constituting the sensing function provided by the chemoreceptors, which ultimately command a ventilatory compensation through the activation of the respiratory muscles. The gas exchanger was approximated by a single-compartment model with a negative gain so that an increase in ventilation immediately followed the sighs. Also note that $\Delta P_{ETCO_2}$ would not hold during the application of the external perturbation (induced sighs); thus we excluded this portion of the data when fitting the model and considered only the part that immediately followed the sighs.

![Simulation discrete model used to emulate the experimental interventions and generate the artificial data segments.](image)

Fig. 1. Simulation discrete model used to emulate the experimental interventions and generate the artificial data segments. Note that the dynamics are represented by single-compartmental models with specified gains and time constants. Gaussian white noise with defined statistics GWN(0,$\sigma^2$) was added to the system. The disturbance was a pulse lasting two breaths for the induced sighs protocol and was set to zero to simulate spontaneous breathing.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung sensitivity, min-mmHg$^{-1}$</td>
<td>$G_l$</td>
<td>1</td>
</tr>
<tr>
<td>Lung time constant, s</td>
<td>$T_l$</td>
<td>6.5</td>
</tr>
<tr>
<td>Peripheral chemoreflex sensitivity, l·min$^{-1}$·mmHg$^{-1}$</td>
<td>$G_p$</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral chemoreflex time constant, s</td>
<td>$T_p$</td>
<td>15</td>
</tr>
<tr>
<td>Central chemoreflex sensitivity, l·min$^{-1}$·mmHg$^{-1}$</td>
<td>$G_c$</td>
<td>2</td>
</tr>
<tr>
<td>Central chemoreflex time constant, s</td>
<td>$T_c$</td>
<td>150</td>
</tr>
<tr>
<td>Circulatory delay, s</td>
<td>$D$</td>
<td>8</td>
</tr>
<tr>
<td>Breath duration, s</td>
<td>$T_b$</td>
<td>4</td>
</tr>
<tr>
<td>Noise variance, l$^2$/min$^2$</td>
<td>$\sigma^2$</td>
<td>1.05</td>
</tr>
</tbody>
</table>

Parameters were adopted from previously proposed ventilatory control models and were ranged between 50 and 150% of their baseline values to generate the artificial data sets used for model performance evaluation.
Spontaneous breathing was simulated for 10 min by the addition of a normally distributed random signal to the system without any other external disturbance. Random variations of ventilation and PrTS\textsubscript{CO\textsubscript{2}} were then utilized as input and output, respectively, to the linear plant model to estimate the dynamics of the gas exchange process.

On the other hand, the induced sighs protocol was simulated by injecting a disturbance that took the form of a pulse with amplitude 15 l/min and a duration of two breaths, in addition to a stochastic injecting a disturbance that took the form of a pulse with amplitude 15 l/min and a duration of two breaths, in addition to a stochastic

The ventilatory response to the perturbation

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The ventilatory response to the perturbation

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The precision of our identification technique was evaluated for variations in the amount of noise incorporated in the system. In addition, a two-way sensitivity analysis was also performed to test the estimation accuracy for multiple pairwise combinations of parameter values (58) and for both of the stimuli applied to simulate the experimental protocols. A total of 100 data sets with different noise realizations was generated for each of the various scenarios and used to produce a family of estimated models. Subsequently, the estimated models and the corresponding model-extracted features were compared with the theoretical ones.

Plant, Controller, and Loop Gain Determination

Once the optimal models were determined, the impulse responses \( k_p(m) \) and \( k_i(m) \) were transformed into the frequency domain using the discrete Fourier transform. These frequency-dependent complex variables, \( K_p(f) \) and \( K_i(f) \), represent PG and LG, respectively, and were used to assess ventilatory stability. Subsequently, the average magnitude between 0.01 and 0.05 Hz was computed. This frequency range corresponds to ventilatory oscillations cycling between 20 and 100 s and has been associated with the phenomenon known as periodic breathing that could potentially lead to apnea (14, 33).

One measurement of PG was obtained per subject, since the no-intervention protocol was only performed once. On the other hand, several estimations of LG were calculated per subject from the induced sighs segments that did not result in arousal. The LG value that represented each subject was found by computing the median from the successful segments only.

Theoretically, the overall LG is the product of PG and the controller gain (CG), thus we utilized our estimated LG and PG to find representations of CG as follows:

\[
CG(f) = \frac{LG(f)}{PG(f)}
\]

Equation 5

CG estimations were found under the assumption that there were no significant changes in PG throughout the night during NREM sleep; that is, the one PG estimate was kept the same for the different LG. Similar to the LG case, the average gain over the periodic breathing frequency range was computed, and the median LG value was used to represent each subject.

Statistical Analysis

All variables were first tested for normality using the Kolmogorov-Smirnov test. Comparisons between groups were performed using independent samples Student’s \( t \)-test for those variables that passed the normality test, whereas, for the variables that failed normality, the comparisons between the groups were performed via the Mann-Whitney rank sum test. Linear correlations between the model-derived parameters and various measurements, obtained during the pulmonary function testing and the diagnostic PSG, were evaluated with the Pearson linear correlation coefficient. All tests used \( P \leq 0.05 \) to determine statistical significance.

RESULTS

Simulations

A simulation study with artificially generated data emulating our experimental interventions was executed to test the performance of the proposed models. First, we evaluated the accuracy in the estimations for different noise present in the data but keeping the theoretical model parameters at nominal values. Figure 2 shows examples of the simulated induced sighs data (panels at left) for diverse noise amplitudes ranging from low (50%) to high (150%) around a nominal value obtained from the experimental data, as well as a comparison between the mean of the estimated overall loop models and the ground truth, in the time (panels in middle) and frequency domains (panels at right). The estimation algorithm was able to capture the negative onset of the impulse response fairly accurately for the different noise magnitudes; however, the latter part was underestimated in all cases, becoming more prominent as noise increased. Despite the inaccuracies found in the time domain, the estimated dynamic gain resembled the true gain in the frequency range of interest (0.01–0.05 Hz) as noise varied.

Second, we examined the performance of the estimation algorithm using data generated with different combinations of the model parameters. Parameter values were varied two at a time ranging between 50 and 150% around the mean values shown in Table 3, while fixing the remaining parameters and the variance of the added noise to their nominal values. Both of our protocols were simulated to generate data sets with all the possible pairwise parameter combinations, which were subsequently used for modeling purposes and to extract their stability characteristics. Performance was evaluated by means of the percent error between the model-derived stability parameters and the theoretical ones. Figure 3 depicts, in the form of a heat map, the resulting two-way sensitivity analysis of the estimation percent error in LG within the periodic breathing region from the simulated induced sighs. It can be seen from the color gradient that the accuracy of our estimations is mainly sensitive to changes in lung and peripheral chemoreceptor gains (elements inside the box). The estimation error mostly lies below 20%, increasing for combinations of long circulatory delays, high time constants, and low gains. The percent error exhibits a maximum of over 40% for low gain values in both the lung and peripheral chemoreceptor compartments.

The no-intervention protocol was simulated as well, and comparison of the estimated parameters with the “true” model revealed some discrepancies in the plant impulse response, but comparable results in the frequency response. We also found from the two-way sensitivity analysis that the accuracy in plant gain estimation is very high and independent of the parameter values (results not shown here).

Experiments

Figure 4 shows representative data recorded from the induced sighs protocol. As can be seen, this particular subject was initially provided with a therapeutic pressure of 8 cmH\textsubscript{2}O for 10 baseline breaths. Inspiratory pressure was then abruptly increased by 5 cmH\textsubscript{2}O for two consecutive breaths and brought back to the therapeutic level. The increase in inspiratory pressure roughly doubled tidal volume and consequently ven-
Ventilatory drive, which led to a corresponding drop in PETCO2 levels. This fall in PETCO2 then caused ventilatory drive to decrease. Diminished ventilation then allows PETCO2 to increase thus stimulating the chemoreceptors, causing an activation of the respiratory muscles resulting in a rise in ventilation. The effects of the perturbation continued to propagate around the chemoreflex loop until PETCO2 was restored back at its homeostatic state.

Sample recordings of ventilatory drive (panels at left) and the corresponding estimated models in the time (panels in middle) and frequency domains (panels at right) of a subject from each category are presented in Fig. 5. It can be noted that the non-OSA subject (Fig. 5A) exhibited larger and longer fluctuations of ventilatory drive following the induced sighs, compared with the OSA subject (Fig. 5B). The long-lasting ventilatory fluctuations exhibited by the non-OSA subject were captured by a model that has an impulse response that oscillates before reaching steady state, whereas the short-duration ventilatory response observed in the OSA subject was better characterized by a less oscillatory model with a shorter settling time. Furthermore, while the dynamic loop gain of the non-OSA subject revealed the presence of two resonant peaks within the frequency band of interest around 0.015 and 0.045 Hz, the OSA subject appeared to only have one peak around 0.015 Hz.

Figure 6 displays and compares the average estimated dynamic plant (Fig. 6A) and loop gains (Fig. 6B) from the two cohorts of subjects. It can be noted that the average plant gain in both groups follows a similar profile; however, the non-OSA group exhibits a lower gain within the entire 0.01–0.05-Hz frequency band compared with OSA. LG shows a resonant peak at ~0.015 Hz that is common in the two groups. Nonetheless, the estimated dynamic loop gain in the periodic breathing region appeared to be higher in the non-OSA group, because of the presence of a second resonant peak around 0.04 Hz that is not particularly dominant in the OSA group.

Four model-derived stability features were defined to facilitate statistical comparisons between the two phenotypes: average magnitudes of the dynamic PG and LG within the periodic breathing region (0.01–0.05 Hz; Fig. 7, A and B); estimates of CG in the same frequency band derived by simply dividing LG by PG (Fig. 7C), and median circulatory time delay extracted from the various LIR estimations obtained from the responses to the induced sighs protocol (Fig. 7D). Figure 7 illustrates the comparison of the stability markers between the two phenotypes. Statistical analyses revealed a significantly higher plant gain and a significantly lower controller gain in OSA compared with its non-OSA counterpart (P = 0.046 and P = 0.007, respectively). Although, loop gain was higher in non-OSA because of the presence of an addi-
were not significantly associated with OAHI.

Negative correlation between LG and the severity of the disease in the non-OSA group (see Fig. 6B). Contrary to what has been found previously, two phenotypes due to the presence of a resonant peak in the specific frequency bin within the periodic breathing region was selected because of the apparent difference in LG between the groups. The loop gain within the 0.03–0.04-Hz frequency band. This spectral resonant peak, it failed to reach statistical significance ($P = 0.106$). Similarly, circulatory time delay was found not to be statistically significantly different in the two groups ($P = 0.653$). All variables were compared via independent samples $t$-tests, except for the controller gain, which was found not to be normally distributed and thus required testing with the Mann-Whitney rank sum test.

The main purpose of this study was to develop the methodology that would enable us to accurately quantify ventilatory control stability under natural NREM sleep circumstances (quiet sleep and sighing) after bypassing the mechanical properties of the upper airway with the application of CPAP. This work involved the design and implementation of the experimental setup that allowed us to replicate quiet sleep and sighing episodes during NREM sleep and collect data completely noninvasively. Furthermore, it also involved the development of the model estimation techniques that facilitated stability feature extraction. This study was carried out in a group of obese adolescents with and without OSA to help us better understand the contributions of instabilities in the ventilatory control system to the development of OSA.

Simulated Data

Our simulation study revealed that the proposed models adequately recovered the dynamics of the systems under study; nonetheless, it also helped us recognize some of their potential limitations. First, there are inaccuracies in the estimates of the circulatory time delay since they were obtained from breath-by-breath data, which have a coarser temporal resolution compared with events occurring on a beat-by-beat scale. Second, the LIR long-lasting effects and, in the frequency domain, the very low frequency components, which are attributed to the central chemoreflex, were underestimated (see Fig. 2). This systematic error occurred mainly because of two factors: 1) fixing the memory $M_1$ of the autoregressive model to 100 s neglected the effects of the central chemoreceptor, which has a more sluggish response; however, experimental results have demonstrated that the contributions to LG from the peripheral chemoreceptors are more substantial than the ones from the medullary chemoreceptor (37, 71); 2) keeping the length of the response to the induced sighs used for the estimations short enough (~50 breaths) so that the stationarity property would hold (32).

The application of this methodology to the simulated spontaneous breathing data exhibited a better estimate of the long-lasting effects of the impulse response and a very accurate representation in the frequency domain, even at the very low

![Fig. 3. Heat map representing the two-way sensitivity analysis of the percent error between the estimated and the theoretical loop gain within the periodic breathing frequency band. Each data point represents the ensemble average over 100 trials with different noise realizations.](image-url)
frequencies. This accuracy was achieved by the analysis of considerably longer (approximately threefold) data segments, compared with the induced sighs. As discussed previously, the presence of nonstationarity is evident in long data sets (54) even when there is no transition from NREM to REM sleep or wakefulness. There are likely to be subtle time-varying changes in ventilatory control even within the same NREM sleep stage (11) that we are not accounting for. Gederi et al. (25) proposed an adaptive autoregressive algorithm that circumvents this problem and could potentially be used to track changes in ventilatory control within the various NREM sleep stages.

**Physiological Interpretation of Experimental Models**

The application of our estimation technique to experimental spontaneous breathing and induced sighs data yielded interesting results. For the plant branch, the optimal number of basis functions required for accurate model representations ranged between 1 and 4 across subjects (mode = 2), while the overall loop model required a range of 4–7 basis functions (mode = 4). These differences relate to the complexity of the systems under study. While the overall loop model includes the processes of chemoreception, circulatory transport delay, and gas exchange in the lungs, the plant branch only involves the latter. When transforming the estimated models into the frequency domain, the dynamic plant and loop gains obtained from the cohort of subjects with and without OSA (see Fig. 6) revealed features that can be related to physiology. On the one hand, the plant exhibited a frequency response similar to that of a low-pass filter in the periodic breathing region with no resonant peaks in both groups. This characteristic might indicate that the gas exchange process occurring in the lungs under normoxic conditions can be approximated by a first-order differential equation related to the mass balance of CO₂ as has been previously proposed (14, 34). On the other hand, the chemoreflex loop as a whole exhibited impulse responses that were oscillatory in both groups, which appeared in the form of resonant peaks in the frequency domain. The presence of resonant peaks in ventilatory control has been reported previously from experimental studies based on other nonparametric techniques such as spectral analysis (62) and dynamic modeling (48) and has been attributed mainly to the feedback action of the peripheral chemoreceptors. The absence of a resonant peak within the 0.03–0.04-Hz frequency region in the OSA group suggests decreased gain of the peripheral chemoreceptor, which could possibly be attributable to OSA.

**Stability Markers**

The model-extracted stability parameters (see Fig. 7) revealed a significantly elevated PG in the OSA group compared with its non-OSA counterpart. The increase in PG in the OSA group might be due to multiple factors including a lower cardiac output, a decreased lung storage volume for CO₂, or the inability of the gas exchanger to eliminate CO₂ adequately due to a ventilation/perfusion mismatch (13, 35). Cardiac output was not measured during the experiment, but it is unlikely that there was a systematic difference between the two subject groups given their young age. Any change in cardiac output resulting from CPAP was likely to be comparable in both groups, considering that therapeutic CPAP was similar in both groups (see Table 1) (20, 31). Pulmonary function tests revealed that there was no significant differ-
ence in vital capacity (VC) or in functional residual capacity (FRC) between the groups (see Table 2), discarding the possibility that increased PG was associated with low lung volumes. However, forced expired volume after 1 s (FEV$_1$) and forced expired volume between 25 and 75% of forced vital capacity (FEF 25/75) were found to be significantly lower in the OSA group, although these measurements were not sufficiently low to imply clinically abnormal lung mechanics as mean values were still within the normal range. These reductions in forced expiratory flows may be attributed to inflammation and/or constriction in the small airways (53, 73) and has been previously reported in children and adolescents with OSA (64, 65). Hence we speculate that the differences found in PG are mainly due to a reduced effective volume for pulmonary CO$_2$ exchange. This reduction is likely due to changes in the ventilation/perfusion matching relationship, as a result of obstruction in the small airways.

Overall, LG was found to be low in both groups, implying highly stable neurochemical control of ventilation. This could be in part due to an increase in lung volumes produced by the

![Image of graphs showing ventilatory drive, loop impulse response, and dynamic loop gain](image-url)

**Fig. 5.** Sample results obtained from the induced sighs protocol in a non-OSA subject (A) and an OSA patient (B). The panels at left show the measured responses to the sighs along with the prediction produced by the estimated models. The panels in middle show the corresponding estimated impulse responses. The panels at right describe the associated frequency responses.

![Image of graphs showing group average dynamic plant gain and loop gain](image-url)

**Fig. 6.** Group average dynamic plant gain (A) and loop gain (B). Individual representative plant gain was estimated from the single spontaneous breathing recording performed in each subject. The median loop gain obtained from the multiple induced sighs was selected to represent each individual. The average and variability of both dynamic gains were computed at each frequency to obtain the group frequency responses. Group results are displayed as means ± SE.
high therapeutic CPAP levels required by the subjects to maintain upper airway patency. Given that there was no significant difference in therapeutic values between the groups, we believe that the effect that CPAP produced in lung volume was comparable. Figure 7 shows a tendency for LG to be lower in the OSA group compared with non-OSA. Even though these results did not reach statistical significance, the observed trend contradicts what has been proposed by some recent studies in adults, which have suggested that one phenotype of OSA may be associated with increased loop gain that leads to chemical control instabilities (30, 72). Furthermore, CG was found to be significantly lower in the OSA group, indicating a lower sensitivity in the chemoreceptors to changes in CO2 levels. Our results suggest that OSA in pediatric overweight is unlikely to be the consequence of ventilatory instability via a hyperresponsive chemoreflex to external perturbations. Further research is required to investigate the importance of other factors such as the interaction between the arousal mechanism, upper airway collapsibility, and elevated plant gain.

**Correlation Analysis**

We found a moderate negative correlation between the severity of OSA and the LG in the frequency band that we assumed to reflect the effect of the chemoreceptors (0.03–0.04 Hz) (see Fig. 8). Associations between LG and OAHI have been reported in recent studies. Wellman et al. (68) found a significant and strongly positive correlation between LG and OAHI in subjects with a moderately collapsible upper airway. Interestingly, a negative correlation between these variables was found in subjects with a less collapsible airway; however, this result was not found to be significant, primarily because of the lack of statistical power. Although Wellman et al.’s study was conducted on adults, their results could well be applicable to the pediatric population, since children tend to have an increased upper airway caliber (45) and augmented upper airway muscle function (70), making it less collapsible compared with adults. Terrill et al. (61) found a strong positive correlation between NREM OAHI and LG and, conversely, a moderate though significant negative correlation between LG and the relative predominance of NREM over REM OSA. In Fig. 8 the reported OAHI encompassed those events occurring during both NREM and REM sleep; thus our correlation might have been confounded by those subjects with REM-predomi-

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**Fig. 7. Model-derived stability marker comparison between the non-OSA and OSA groups. Dynamic plant (A), overall loop (B), and controller (C) gains represent the average magnitude of the transfer functions within the periodic breathing frequency band; Fig. 7D represents the circulatory time delay. Variables are presented as means ± SE. †Results are statistically significantly different between the groups.**

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**Fig. 8. Correlation between the loop gain and OSA severity represented by the OAHI. Note that the OAHI was log-transformed prior to the correlation analysis and is plotted in logarithmic scale.**
nant OSA, which has been reported to be common among the pediatric population (27). To discern whether our correlation analysis was being severely affected by REM predominant OSA, we determined the correlation between NREM OAHI and LG within the 0.03- and 0.04-Hz frequency band. We found the correlation to be negative, as in the case between overall OAHI and LG, although this fell short of statistical significance ($r = -0.361; P = 0.070$).

Methodological Considerations

Among the advantages of our modeling technique is the lack of required a priori assumptions in the model structure; that is, the model is entirely data driven (43). Furthermore, the number of free parameters was considerably reduced by expanding the impulse response in a set of basis functions. This approach allowed us to obtain more accurate model parameter estimates from short data recordings (44). Moreover, the utilization of MBF for impulse response estimation helped improve the estimation of slow systems dynamics. Despite the aforementioned advantages of the kernel expansion technique, it has not yet been widely exploited in the context of respiratory control to quantify stability. Previous efforts that utilized this technique with the Laguerre set of basis functions include the study by Asyali et al. (5), where a linear autoregressive model was implemented to measure LG. In this case, esophageal pressure was assumed to represent ventilatory drive, making their model extendable to the case where an airway obstruction occurs. However, this necessitated a slightly more invasive regimen of instrumentation. In contrast, both of our models were estimated with variables derived from tidal volume, which was measured completely noninvasively. Mitsis et al. (48) also employed Laguerre-based Volterra models to find estimations of the feed-forward and feedback pathways of the ventilatory control loop and subsequently multiplied their frequency responses to finally obtain estimations of LG. Our autoregressive model, on the other hand, combined the feed-forward and feedback effects in one single model, which simplified the manner for estimating LG.

There are, however, some constraints in our model formulations that must be considered. First, we performed direct estimation of the plant impulse response, disregarding the effects of the feedback branch. This procedure could lead to biased estimations because of the correlations existing between the input and the disturbance signals that are inevitable in systems operating under closed loop conditions (7, 63). To reduce the effects of the disturbance, we excluded from the analysis those data segments containing large breaths that were unlikely to be generated by changes in $\text{PETCO}_2$ as proposed by Mitsis et al. (48). Second, our autoregressive model could be formulated given the existence of a sufficiently strong driving stimulus (sighs) and the imposition of a time delay in the time series to assure causality (3). This model structure yielded estimations that were accurate in a limited frequency range.

One limitation to our approach is the fact that PG and LG were estimated from data recorded at different points of the night, under the assumption that the plant remained unchanged within the various NREM sleep stages. Ideally, both PG and LG should have been estimated from the induced sighs segments; however, we detected that $\text{PCO}_2$ measurements (sampled noninvasively by a nasal cannula) were not sufficiently reliable to approximate $\text{PETCO}_2$ during and after the sighs. These inaccuracies could be attributed to the flushing effect on expired $\text{PCO}_2$ caused by the changes in air pressure used to provoke the sighs. This led us to analyze more stable segments for PG computations where $\text{PETCO}_2$ estimations were more trustworthy.

Finally, it should also be noted that the results presented herein are based on the underlying assumption that the ventilatory control system behaves as a linear system under the conditions of a stable upper airway. Although it is known that the rest of the system components are nonlinear (28, 35), a linear approximation was used here, as in previous ventilatory control models (36). In this case, the assumption of linearity is valid because, aside from the perturbation, there were no large fluctuations present in the signals. In addition, by assuming the feedback system to be linear, the problem of stability quantification was greatly simplified by the application of classical control theory.

Conclusion

In summary, we have developed a novel experimental setup and the computational methodology for quantifying stability of the chemoreflex control of respiration during sleep. Our findings in this study suggest that OSA in pediatric overweight subjects is unlikely to result primarily from increased chemical loop gain. To better understand the pathophysiology of OSA in this cohort of subjects and potentially personalize treatment, future studies should explore alternative mechanisms of ventilatory instability that involve the complex interactions among other factors such as upper airway dynamics, arousal threshold, wakefulness drive, and increased plant gain.

ACKNOWLEDGMENTS

The authors would like to thank Wanwara Thuptimdang for her contribution to the software development for physiological signal processing. We would also like to thank Emilily Gillet for the help provided with clinical data analysis and valuable discussions during the preparation of this manuscript.

GRANTS

This work was supported in part by National Institutes of Health Grants P41-EB001978 and R01-HL105210. L. Nava-Guerra was supported by the Mexican National Council of Science and Technology (CONACyT).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


