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Measuring Upper and Lower Airway Resistance During Sleep with the Forced Oscillation Technique

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Abstract

The forced oscillation technique (FOT) is a non-invasive technique to monitor airway obstruction in those with asthma. The aim of this study was to design and validate a system to use FOT during sleep, both with and without bi-level positive airway pressure (BPAP), and to separate upper airway resistance from lower. 8 Hz pressure oscillations were supplied, over which the subject breathed, pressure and flow measurements were then used to calculate impedance. A phase-shift induced by the pressure transducer tubing was characterized, and FOT resistance was compared to steady flow resistance both with and without BPAP. A Millar catheter was used to measure pressure at the epiglottis, allowing the separation of upper from lower airway resistance. A phase shift of -0.010 s was calculated for the pressure transducer tubing, and the average error between FOT and steady flow resistance was -0.2 ± 0.2 cmH₂O/L/s without BPAP and 0.4 ± 0.2 cmH₂O/L/s with BPAP. The system was tested on three subjects, one healthy, one with obstructive sleep apnea, and one with asthma. The FOT was well tolerated and resistance was separated into upper and lower airway components. This setup is suitable for monitoring both upper and lower airway obstruction during sleep in those with and without asthma.

Keywords

Asthma; Lung; Apnea; Airway mechanics; Impedance

INTRODUCTION

Many people with asthma experience nighttime wheezing and awakenings due to lower airway constriction. One study found that 64% of those with asthma experience nocturnal symptoms at least three times a week.²⁶ Nocturnal symptoms are well known to be predictive of poor asthma control and thus poor outcome in these patients.²⁴ However, the typical metrics of asthma control [such as the peak expiratory flow and the forced expiratory volume expelled in 1 s (FEV₁)] require cooperation during wakefulness to assess. As such, changes in respiratory function are difficult to monitor while the subject is asleep. In theory, medical therapy could be intensified in those patients who are poorly controlled, prior to the development of overt symptoms or exacerbations. On the other hand, the situation is complicated during sleep since both upper and lower airway resistance can be considerably impacted by the transition from wakefulness to sleep. One potential method to monitor airway caliber during sleep is the forced oscillation technique (FOT).

The FOT was introduced in 1956 by Dubois *et al.* as a non-invasive measure of respiratory mechanical properties.⁷ FOT uses small pressure oscillations superimposed on top of the subject's normal breathing, with the resulting pressure and flow signals being used to calculate impedance of the respiratory system. Although multiple parameters can be assessed, by selecting a single 8 Hz pressure input one can track airway resistance changes on a breath to breath basis.¹² FOT has primarily been used to assess airway obstruction and disease state in asthma subjects during the day; however, FOT can also be used to measure respiratory system resistance and reactance (R_{rs} , X_{rs}) during sleep since the need for patient cooperation is minimal.¹⁸ To date, previous studies using FOT during sleep have only used it to monitor *upper* airway obstruction in conjunction with continuous positive airway pressure (CPAP) in obstructive sleep apnea subjects.^{8–10,18,23} These studies have not employed bi-level positive airway pressure (BPAP) since CPAP is the standard therapy for obstructive apnea. One study has examined airway resistance in a small cohort of subjects with chronic obstructive pulmonary disease without PAP, with CPAP, and with BPAP, but has not assessed sleep.¹ The technique may be useful in monitoring asthma subjects during the night to obtain information on both upper and lower airway obstruction.

Previous studies have successfully used pressure tipped catheters, placed below the base of the tongue, in order to measure airway pressure at the level of the epiglottis.¹³ Using these catheters in conjunction with FOT could provide the information necessary to separate the relative contributions of upper airway and lower airways to total resistance and reactance measured at the airway opening.

The aim of this study was to develop and validate a forced oscillation system which could be used during sleep to distinguish between upper airway and lower airway mechanical properties. Furthermore, we sought to design a system that could be used both with and without positive airway pressure so that we could study both those with obstructive sleep apnea and those without. To this end, we developed and validated such an FOT system as well as performed a feasibility study in human subjects with two different diseases and a healthy control.

MATERIALS AND METHODS

System Design and Validation

A forced oscillation system was designed to supply 8 Hz pressure oscillations with ~1 cmH₂O peak to peak pressure swings to a subject. The system consists of a 12 in subwoofer speaker (Image Dynamics D4 V.3) housed in a Plexiglas box. The voltage signal to the speaker is controlled by data acquisition software (Spike V6) which outputs an 8 Hz sinusoidal signal to a power amplifier (JBL CS200.1). The amplifier is powered by a 12 V power supply and is wired to the four coils of the subwoofer in a parallel fashion.

Three different setups were used in the system design (Fig. 1). Setup A was used to test the phase response of the transducers as well as the accuracy of the resistance calculations without any positive airway pressure. Setup B was used to test the validity of the resistance calculations when BPAP was on and setup C was used when attached to a subject. In each setup a disposable bio-filter (nSpire KoKo Moe Filter) is placed at the outlet of the speaker box. A parallel dead space tube is in place, as well as a one-way exhalation valve, which allows exhaled gas to exit the system. Two pressure transducers (Validyne Corp.) measure the pressure oscillations, while flow is measured through a heated pneumotachometer (model 3700A, Hans Rudolf Inc) and a differential pressure transducer (Validyne Corp). All the setups were based on previously validated models for FOT application.^{18,19}

In setup A, two transducers were used to measure pressure simultaneously, one with long thin tubing connecting it to the system (P_{far}) and the other connected directly to the system (P_{short}). In a separate trial we used the Millar catheter (P_{millar}) (model MPC-500, Millar, Houston, TX, USA) to confirm that magnitude and phase angle of the 8 Hz oscillations were preserved as compared to P_{short} . Impedance was calculated using both P_{short} and P_{far} as compared to flow ($\dot{V}$) using the method described below. We tested the system with linear resistors made in house with mesh screens. The steady flow resistance was determined by measuring mean pressure over a range of flows and calculating resistance (Fig. 2).

$$R = P_{\text{short}} / \dot{V} \quad (1)$$

The root mean square of flow was found when the 8 Hz oscillations were on for each resistor and this signal was used to predict the theoretical value of resistance through linear regression. We then compared the response of the transducers when attached closely to the measurement point as opposed to the one attached far away and the response of the Millar catheter. Since the transducer must be placed at some distance away from the patient due to the logistics of the sleep study, any phase shift (θ) induced by extra tubing would be correctable by time shifting the resulting pressure signal. To calculate the time equivalent of this phase shift we simply divide the calculated phase shift by $2\pi f$ where f is the frequency of oscillations (8 Hz) (Eq. 2).

$$P_{\text{far}} = \sin(2\pi f \times t + \theta) \quad (2)$$

After determining the correct phase shift of the transducer and tubing system, the system was configured to setup B (Fig. 1) in order to check the accuracy of resistance measurements when BPAP was on. The BPAP device could not reach the target pressures when the system was open to atmosphere, so a 3 L chamber was added to the setup to simulate a lung. Inspiratory pressure was set to 8 cmH₂O while expiratory pressure was set to 4 cmH₂O. Flow ($\dot{V}$), and pressures before and after the resistor were measured. By subtracting the two pressure recordings the magnitude of the resistors was calculated when BPAP was on and compared it to the known steady flow resistance values (Fig. 2).

During the feasibility study, the system was attached to a research subject (setup C) while room air was bled into the system to prevent rebreathing. Pressure (P_m) and flow ($\dot{V}$) were measured through a nasal mask (Philips-Respironics Inc.). A pressure tipped catheter (model MCP-500, Millar, 1.67 mm diameter) was placed through the nostril to 1 cm below the base of the tongue in order to measure airway pressure at the level of the epiglottis (P_{epi}). Due to the setup of a sleep study, the transducer for the mask pressure had to be placed at some distance away from the patient. Data were sampled at 128 Hz (1401 plus, Cambridge Electronic Design Limited) and outputted to Matlab. Setup C was based on a previously published design,¹⁸ however with our system we have replaced the CPAP device with a BPAP device and have added a epiglottic catheter to allow portioning of resistance in the upper and lower airways.

Patient Testing

We tested the performance of the system on one healthy subject, one subject with asthma, and one subject with obstructive sleep apnea. All studies were conducted at Brigham and Women's Hospital in Boston, MA, and all study procedures were approved by the hospital's institutional review board. All subjects gave informed consent before participation in the study. A nasal decongestant (Oxymetazoline) and topical lidocaine were used to decongest and numb the nose, respectively, before placing the Millar catheter. A nasal mask was

placed over the nose and attached to the FOT system. Pressure and flow were measured at the airway opening as described above P_{mask} ; ($\dot{V}$). Subjects were monitored with electroencephalography (EEG), electrooculography (EOG), and chin electromyography (EMG), for accurate sleep staging.¹¹ Exhaled carbon dioxide and oxygen saturation were also measured using the established techniques of our laboratory.²⁷

Data Analysis

Flow and all pressure signals were sampled at 128 Hz. To calculate impedance at 8 Hz, pressure and flow signals were first filtered using a fourth order Butterworth high pass filter with a cutoff frequency of 4 Hz and then with a low pass fourth order Butterworth filter with a cutoff frequency of 12 Hz. To calculate the 8 Hz component of resistance we used the cross-power spectrum method.^{5,15} In this method the fast Fourier transforms of the pressure signals (P) and the flow through the nose ($\dot{V}$) were computed over 16 data points (one 8 Hz cycle) and recalculated with a sliding window of step size 2. Next, the cross power spectra of P and the complex conjugate of flow ($\dot{V}^*$) ($G_{P\dot{V}}$) and the auto-power spectra of $\dot{V}$ ($G_{\dot{V}\dot{V}}$) were calculated using Eqs. (3)–(4).

$$G_{P\dot{V}} = P \times \dot{V}^* \quad (3)$$

$$G_{\dot{V}\dot{V}} = \dot{V} \times \dot{V}^* \quad (4)$$

The cross power spectra were ensemble averaged over every eight overlapping spectra (two 8 Hz cycles). Impedance (Z) was then calculated using the average cross power spectra (Eq. 5), resulting in a resistance measurement every 0.25 s (4 Hz). The resistance is the real (R), or in phase, component of Z , while reactance (X) is the imaginary or out of phase component of Z (Eq. 6).

$$Z = \frac{\langle G_{P\dot{V}} \rangle}{\langle G_{\dot{V}\dot{V}} \rangle} \quad (5)$$

$$\begin{aligned} R &= \text{real}(Z) \\ X &= \text{imag}(Z) \end{aligned} \quad (6)$$

The coherence function can be calculated to confirm that noise and non-linearities are only a small portion of the transfer characteristics of the system. Coherence (γ) is calculated using Eq. (7).

$$\gamma = \frac{|\langle G_{P\dot{V}}^2 \rangle|}{\langle G_{\dot{V}\dot{V}} \rangle \langle G_{PP} \rangle} \quad (7)$$

To calculate total respiratory system impedance (R_{TS} , X_{TS}) in human subjects, the pressure signal used is P_{m} (pressure measured at the nasal mask). To calculate upper airway impedance (R_{up} , X_{up}), the pressure signal used was $P_{\text{m}} - P_{\text{epi}}$. Lower airway mechanics (R_{low} , X_{low}) were found by subtracting upper airway impedance from total respiratory system impedance. Resistance and reactance were also quantified over points in the entire breathing cycle, including end inspiration and expiration, and mid inspiration and expiration points.

RESULTS

The forced oscillation system was first tested against four well characterized resistors, ranging from 1.6 to 12.1 cmH₂O/L/s when no positive airway pressure was applied (Fig. 2). The average difference between calculated and measured resistance was -0.2 ± 0.2 cmH₂O/L/s ($-2.4 \pm 2.7\%$ of the steady flow resistance) (Fig. 3). The magnitude and phase of impedance calculated with P_{far} was compared to that of P_{short} (Table 1). The magnitude of impedance was similar between the two pressure recordings with an average difference of 0.09 ± 0.07 cmH₂O/L/s. However, there was a measurable phase difference between P_{far} and P_{short} that was similar over the range of impedances tested (-0.51 ± 0.02 rad). The time shift needed to be imposed on the P_{far} signal to correct for this phase shift, was calculated to be -0.010 s. The difference in magnitude and phase between P_{short} and P_{far} was calculated after time shifting the P_{far} signal by -0.010 s ($P_{\text{far-shifted}}$) (Table 1). When testing the Millar catheter, the magnitude of impedances was similar and a small phase difference of 0.10 ± 0.05 radians was found (Table 2). Coherence values were >0.99 for all resistors.

Knowing the characteristics of the tubing of the P_{far} transducer, this signal was used for the rest of the analysis after time shifting by -0.010 s. When BPAP was on, good agreement was found again between the predicted resistance value and what was measured with FOT (Fig. 3). The average error between calculated and measured resistance was 0.4 ± 0.2 cmH₂O/L/s ($9.3 \pm 9.5\%$). The average coherence value was >0.99 , the minimum coherence was 0.96. To eliminate artifacts, only resistances that corresponded to coherence values greater than 0.95 were used when analyzing data from the overnight studies.

For the patient testing, the system was applied to a healthy 31-year-old female subject with no asthma or obstructive sleep apnea (Body Mass Index = 27.7 kg/m²) (Fig. 4). The average R_{rs} across the entire respiratory cycle over this 30-s period of NREM sleep is 5.1 ± 1.2 cmH₂O/L/s. When split into upper and lower airway components, the mean R_{up} is found to be 1.5 ± 1.3 cmH₂O/L/s and R_{low} is 3.6 ± 1.1 cmH₂O/L/s.

The FOT/BPAP system was next applied to a 46-year-old female subject with obstructive sleep apnea (OSA) (apnea-hypopnea index = 26.1 events/h, BMI = 45.8 kg/m²). During periods of flow limitation (Fig. 5), flow decreased despite increasingly negative downstream pressure, indicating increasing resistance. During these periods of flow limitation, R_{rs} approaches 20 cmH₂O/L/s, with the upper airway resistance the dominant factor during inspiration. The highest resistances occurred during inspiration, which is consistent with other studies in OSA subjects.¹⁸

Next the system was applied to a male subject with asthma and no OSA (age = 30 years, BMI = 26.4 kg/m²) (Fig. 6). Two and a half hours of resistance data are plotted with periods of wakefulness indicated by arrows. To smooth the data, a moving average filter of 10 breaths is applied before plotting. Total R_{rs} averaged over this time period was 9.3 ± 4.4 cmH₂O/L/s, approximately double the value seen in the healthy subject. Somewhat surprisingly, both the upper and lower airway components were increased compared to the healthy control subject (R_{up} : 5.1 ± 4.7 cmH₂O/L/s and R_{low} : 4.2 ± 2.8 cmH₂O/L/s).

When quantifying resistance and reactance over the entire breathing cycle (Fig. 7) in the subject with asthma, it was found that local minima of resistances occurred at end inspiration and end expiration. R_{rs} and R_{up} were found to be the largest at mid-inspiration, while R_{low} did not vary as much across the breath cycle.

DISCUSSION

The goal of this study was to develop, validate, and test, the feasibility of an FOT system capable of measuring respiratory resistance in patients during sleep with and without BPAP, as well as partition the resistance into its upper and lower airway components. This system applied pressure oscillations and calculated resistance accurately both with and without the addition of positive airway pressure. As shown by the Bland–Altman plot the differences between the steady flow and FOT resistance measurements were negligible (Fig. 3). However, a digital time shift had to be applied in order to measure accurately the relative phases between pressure and flow when the pressure transducer was located at a distance from the patient. The epiglottic catheter was capable of recording 8 Hz oscillations with the correct magnitude and phase and can be used to measure resistance of the upper airway.

Resistance was measured accurately, with only a small deviation from the steady flow resistance, both with and without positive airway pressure. Coherence values were high both with and without airway pressure, although the minimum coherence was slightly lower with BPAP on. The minima in coherence corresponded to time periods when BPAP was transitioning from one pressure setting to the other. Our system is similar to previous system designs which have employed forced oscillations over CPAP during sleep. However, with our device we can use FOT with either CPAP or BPAP and have added an epiglottic pressure catheter enabling us to separate upper airway from lower airway resistance. With this setup we can characterize lower airway resistance in those with asthma, which has not been studied during sleep.

The FOT was well tolerated by the subjects making it feasible to calculate impedance over the course of the entire night during stable sleep. By placing the epiglottic pressure transducer, upper airway resistance can be separated from the total resistance. Resistance measurements during sleep at frequencies of 6–8 Hz have not been done in large populations. The asthma subject had an average lower airway resistance of 4.2 cmH₂O/L/s during sleep, which is in the range of resistances reported by other FOT studies during wakefulness.^{2,20} Upper airway resistance through the nose has also not been characterized using 6–8 Hz frequencies. Young men and women with no obstructive disease have upper airway resistances of 6.6 cmH₂O/L/s and 10.2 cmH₂O/L/s respectively at the onset of NREM sleep.²⁵ However, these were not measured with FOT, but with pressure differentials at low flow and high flow conditions. Using this method, resistances cannot be measured over the entire breathing cycle and are not completely analogous to what one measures at high frequencies.

As shown in a previous study, total airway resistance measured with FOT during sleep is larger during mid inspiration as compared to mid expiration, even when the airway is open and not flow limited.¹⁸ Our data confirm this finding, but also show that this effect is driven by the upper airway. This leads one to conclude that the upper airway is narrowing slightly during inspiration even when no flow limitation is occurring. Given that some authors have suggested that airway collapse occurs in sleep apnea at end-exhalation,¹⁶ our data and technique suggest alternative hypotheses should be pursued.

We propose that FOT can be used to monitor changes in airway resistance over the breathing cycle, and over the course of the entire night, in asthma and healthy subjects. FOT can also be used to detect changes in the caliber of the upper airway in those with compromised anatomy leading to OSA, and determine at what point in the breathing cycle the upper airway collapses. Furthermore, this system would be ideal to study the variability of resistance over time, which has received considerable attention recently.^{6,17,22} The system was also validated for use with a BPAP device. Several previous studies have sought

to study the effect of CPAP during sleep in those with both asthma and obstructive sleep apnea. Results have been mixed with one study finding improvements in peak expiratory flow rates³ and other studies finding no change in pulmonary function tests^{4,14} after CPAP usage in those with asthma. With this FOT system we will be able to investigate how positive airway pressure affects both upper and lower airway obstruction during sleep in a population of asthma patients with and without obstructive sleep apnea.

One limitation of this technique is that upper airway resistance makes up a large portion of the total resistance. Therefore, it would be difficult to draw conclusions about changes in lower airway resistance during sleep without an epiglottic pressure catheter in place to rule out changes in upper airway caliber. Furthermore, during periods of flow limitation, any changes in lower airway resistance will be masked by large increases in upper airway resistance. CPAP or BPAP application would stabilize the upper airway and possibly allow for a more accurate measurement of lower airway resistance. However, in those without OSA the upper airway may narrow slightly but will not collapse. The magnitude of the 8 Hz oscillations measured on the epiglottic catheter can be used to assess the patency of the upper airway. We only separate upper airway from lower airway resistance when we are confident that the pressure oscillations are reaching the epiglottis. We recognize that resistance estimation in the setting of flow limitation is complicated. Another limitation is that respiratory system resistance contains both chest wall resistance as well as airway resistance. However, it has been shown that chest wall resistance does not change significantly on a breath to breath basis, except during deep inspirations to TLC,² which are rare during sleep.²¹

In summary, we have developed, validated and tested an FOT system that can partition respiratory resistance to upper and lower components during sleep while subjects were on BPAP. The system can be used in the future to test various mechanistic hypotheses regarding asthma and OSA. One such hypothesis is that obesity may increase asthma incidence or severity through decreased mechanical stretch on airway smooth muscle, which may be reversible with BPAP. Resting lung volumes are low in the obese and tidal volumes during sleep are limited; this lack of stretch of the airway smooth muscle could lead to airway hyper-reactivity in response to provocation. BPAP may be able to reverse these effects through increasing resting lung volumes and through increasing tidal volumes dynamically during sleep, possibly leading to decreases in airway smooth muscle reactivity. While our system could be used to monitor changes in upper and lower airway resistance throughout the night both on and off BPAP to measure its effect on airway mechanics, a larger prospective study is needed to test the above hypothesis.

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ABBREVIATIONS

FOT	Forced oscillation technique
BPAP	Bi-level positive airway pressure
P_{far}	Pressure measured at a distance from the FOT system
P_{short}	Pressure measured near the FOT system
P_{millar}	Pressure measured from Millar catheter

P_m	Pressure measured at a nasal mask
$\dot{V}$	Flow
R_{rs}	Respiratory system resistance
R_{up}	Upper airway resistance
R_{low}	Lower airway resistance

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FIGURE 1.

System to generate forced oscillations in a sleeping patient. (A) Setup used to test phase-shift of pressure transducer tubing and validate resistance measurements without positive airway pressure. (B) Setup used to validate resistance measurements with bi-level positive airway pressure (BPAP). (C) Setup used for overnight studies with patient volunteers.

FIGURE 2.

Resistance of house made resistors calculated over a range of flows. Resistance was calculated during no positive airway pressure (black circles) and during BPAP (gray circles) calculated at the root-mean-square of flow when FOT is on.

FIGURE 3.

Bland–Altman plot of the difference between resistances measured with steady flow and FOT as a function of the average of the two resistances. Resistance when no positive airway pressure is applied (squares) and the mean (dashed line), and resistance when BPAP is on (triangles) and the respective mean (dotted line).

FIGURE 4. Example data collected for a healthy subject during Stage 2 sleep. Flow, tidal volume (V_t), pressure at the nasal mask (P_m), pressure at the epiglottis (P_{epi}), and resistance of the respiratory system (R_{rs}) separated into upper airway (R_{up}) and lower airway (R_{low}) resistances.

FIGURE 5.

Example of a hypopnea in an OSA subject during Stage 2 sleep. Flow, tidal volume (V_t), pressure at the nasal mask (P_m), pressure at the epiglottis (P_{epi}), and resistance of the respiratory system (R_{rs}) separated into upper airway (R_{up}) and lower airway (R_{low}) resistances.

FIGURE 6.

Example of resistance data from asthma subject over a 2–3 h period. Respiratory system resistance (R_{rs}) is averaged over a moving 10 breath window (top). R_{up} (gray) and R_{low} (black) are plotted below. Arrows indicate drops in resistance that occur with arousals from sleep.

FIGURE 7.

Average of resistance at different points in the breathing cycle during NREM sleep (~1700 breaths) in the asthma subject (mean $\pm$ SE).

TABLE 1

Measured impedance of P_{short} , P_{far} , and $P_{\text{far-shifted}}$.

	Z magnitude (cmH ₂ O/L/s)	Z phase (rad)	Magnitude difference ($P_{\text{far}} - P_{\text{short}}$) (cmH ₂ O/L/s)	Phase difference ($P_{\text{far}} - P_{\text{short}}$) (rad)	Time shift (s)
Resistor 1					
P_{short}	11.84	0.17	0.19	-0.54	-0.0107
P_{far}	12.03	-0.37			
$P_{\text{far-shifted}}$	12.03	0.14			
Resistor 2					
P_{short}	4.90	0.20	0.09	-0.53	-0.0105
P_{far}	4.98	-0.33			
$P_{\text{far-shifted}}$	4.98	0.17			
Resistor 3					
P_{short}	2.67	0.24	0.05	-0.50	-0.0100
P_{far}	2.72	-0.27			
$P_{\text{far-shifted}}$	2.72	0.23			
Resistor 4					
P_{short}	1.65	0.29	0.05	-0.48	-0.0096
P_{far}	1.70	-0.20			
$P_{\text{far-shifted}}$	1.70	0.31			
Average			0.09	-0.51	-0.0102
SD			0.07	0.02	0.0005

TABLE 2

Measured impedance of P_{short} and P_{millar} .

	Magnitude (cmH ₂ O/L/s)	Phase (rad)	Magnitude difference (cmH ₂ O/L/s)	Phase difference (rad)	Time shift (s)
Resistor 1					
P_{short}	11.61	0.14	0.28	0.05	0.0009
P_{millar}	11.89	0.19			
Resistor 2					
P_{short}	5.01	0.18	0.25	0.07	0.0013
P_{millar}	5.26	0.25			
Resistor 3					
P_{short}	3.08	0.21	0.08	0.12	0.0023
P_{millar}	3.16	0.33			
Resistor 4					
P_{short}	1.82	0.25	0.13	0.16	0.0031
P_{millar}	1.94	0.41			
Average			0.18	0.10	0.0019
SD			0.10	0.05	0.0010