ERJ Express. Published on January 7, 2009 as doi: 10.1183/09031936.00063008

Inspiratory Duty Cycle Responses to Flow Limitation Predict Nocturnal Hypoventilation

Schneider H, Krishnan V, Pichard LE, Patil SP, Smith PL, Schwartz AR.

Johns Hopkins Sleep Disorders Center,

Division of Pulmonary and Critical Care Medicine

Short Title:

Duty Cycle Responses to Flow Limitation

Address correspondence to: Hartmut Schneider, M.D., Ph.D.
Division of Pulmonary and Critical Care Medicine
The Johns Hopkins Asthma and Allergy Center
5501 Hopkins Bayview Circle
Telephone: (410) 550-4706
FAX: (410) 550-2612
email: hschneid@jhmi.jhu.edu

Funded by: HL 72126, HL 50381, HL 37379, HL077137, P50 HL084945-01

"This publication was also made possible by Grant Number UL1 RR 025005 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Information on NCRR is available at http://www.ncrr.nih.gov/. Information on Re-engineering the Clinical Research Enterprise can be obtained from http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp."

I. ABSTRACT

Upper airway obstruction can elicit neuromuscular responses that mitigate and/or compensate for the obstruction. We hypothesize that flow-limited breathing elicits specific timing responses that can preserve ventilation due to increases in inspiratory duty cycle rather than respiratory rate.

By altering nasal pressure during NREM sleep, similar degrees of upper airway obstruction were induced in healthy men and women (N=10 each). Inspiratory duty cycle, respiratory rate and minute ventilation were determined for each degree of upper airway obstruction during NREM sleep and compared to the baseline non-flow limited condition.

A dose dependent increase in the inspiratory duty cycle and respiratory rate was observed in response to increasing severity of upper airway obstruction. Increases in the inspiratory duty cycle, but not respiratory rate, helped to maintain ventilation acutely. Heterogeneity in these responses was associated with variable degrees of ventilatory compensation, allowing us to segregate individuals at risk for hypoventilation during periods of inspiratory airflow limitation.

Upper airway obstruction constitutes a unique load on the respiratory system. The inspiratory duty cycle but not the respiratory rate determine the individual's ability to compensate for inspiratory airflow limitation during sleep, and may represent a quantitative phenotype for obstructive sleep apnea susceptibility.

Word Count 196

II. INTRODUCTION

Obstructive sleep apnea comprises a spectrum of patients with varying degrees of upper airway obstruction as manifested by snoring with intermittent arousals (UARS, RERA's), obstructive hypopneas and apneas (1-3). While male sex and obesity constitute strong risk factors for the varied manifestation of obstructive sleep apnea (4-6), heritable factors can also play a significant role to the risk of this disorder(7-13), contributing to the heterogeneity in the expression of this disorder. Nevertheless, physiologic mechanisms that explain the heterogeneity of sleep disordered breathing severity are not known.

Upper airway obstruction during sleep plays a pivotal role in the pathogenesis of obstructive sleep apnea (14) and is caused by structural defects and disturbances in neuromuscular control (14;15). Upper airway obstruction can elicit neuromuscular responses that mitigate and/or compensate for the obstruction. Under conditions of upper airway obstruction (inspiratory airflow limitation), immediate responses in respiratory timing indices can help restore ventilation (16-19) and blunt disturbances in gas exchange (20) . Nevertheless the impact of respiratory pattern responses on ventilation during periods of upper airway obstruction remains unclear.

The purpose of the current study is to examine ventilatory responses to upper airway obstruction during sleep in normal men and women. We hypothesize that flow-limited breathing elicits specific timing responses that can preserve ventilation with increases in inspiratory duty cycle rather than respiratory rate. To test this hypothesis, we examined responses to defined levels of upper airway obstruction that were experimentally imposed in NREM sleep. Responses in inspiratory duty cycle, respiratory rate, and minute ventilation were evaluated in BMI and age matched normal men and women, and have been partially reported in abstract form (21;22).

Word Count: 270

III. MATERIAL AND METHODS

Conceptual Approach

Although the mechanisms involved in stabilizing ventilation in the presence of upper airway obstruction (UAO) have not been well defined, UAO is known to increase respiratory drive (19), which normally should increase mean inspiratory flow. As the upper airway collapses, however, such increases in drive could not produce further increase in the mean inspiratory airflow because inspiratory flow is limited to a maximal level despite increased effort (23;24). Therefore, during periods of inspiratory flow limitation, increases in inspiratory effort (drive) cannot maintain ventilation during sleep. Instead, ventilation can only be preserved by prolonging the inspiratory duty cycle (17;18), which will maintain and stabilize ventilation during periods of inspiratory flow limitation (see Figure 1, middle panel). In contrast, for a given inspiratory duty cycle, increases in respiratory rate (Figure 1, right panel) would decrease the tidal volume. As the tidal volume falls, the dead space fraction will increase, and alveolar ventilation will decrease accordingly. Thus, inspiratory duty cycle and respiratory rate responses to a given level of UAO may determine the degree of hypoventilation during sleep. Specifically, as the inspiratory duty cycle increases, compensate for upper airway obstruction and decrease obstructive sleep apnea susceptibility, whereas increases in respiratory rate may compromise alveolar ventilation and increase the susceptibility to obstructive sleep apnea.

Study Subjects

26 healthy volunteers (10 men, 16 women) were initially recruited from the community for a baseline sleep study with no history of snoring or concurrent illness, no evidence of sleep disordered breathing (apnea and hypopnea index < 5 events per hour) or flow limitation (less than 50% NREM time). From the group, 10 women were matched to the men based on BMI (± 3 kg/m^2) and age (± 5 years). The study protocol was approved by the Johns Hopkins Bayview Medical Center Institutional Review Board and all subjects provided written informed consent.

Study Methods

Polysomnography: Standard polysomnography included monitoring of electroencephalograms (C_3-A_2, C_3-O_1), left and right electrooculograms (EOG), submental electromyogram, electrocardiogram (ECG modified V2 lead), oxygen saturation (SaO_2), body position via infrared video cameras, tidal airflow with a pneumotachometer (model 3700A, Hans Rudolph Inc., MO) affixed to a tight fitting nasal mask and nasal pressure through a side hole in the nasal mask.

Nasal Pressure Generator: Nasal pressure was controlled by a "Pcrit-machine", which is a modified CPAP device (Resmed/MAP, Germany), specifically designed to apply both negative and positive pressure over a range of –20 to 20 cmH_2O, as previously described (25;26).

Study Design

Altering Nasal Pressure (P_N): During wakefulness, individuals were acclimatized to breathing through a nasal mask at a pressure of 6 cmH_2O (holding pressure). When stable NREM stage 2 sleep was observed for at least 3 minutes, P_N was abruptly lowered by 2 cmH_2O for 5 breaths or until an arousal occurred. P_N was then returned to holding pressure for approximately 120 seconds, and was then repeatedly lowered by additional steps of ~2 cmH_2O decrements until airflow ceased**.** Note: the nasal pressure at baseline was lowered from 6 cmH_2O to either 5 (n=2) or 4 (n=3) cmH_2O in selected subjects in order to facilitate sleep onset.

Determination of Ventilatory: Responses to Upper Airway Obstruction: Breaths during NREM sleep were selected from the holding pressure and each pressure drop as follows: During stable breathing at the holding pressure, the last three breaths prior to the first pressure drop were selected for determining ventilatory parameters for non-flow-limited breathing during sleep. Each step decrease in nasal pressure was first assessed for the presence of inspiratory flow limitation. Breaths 2 to 4 of each pressure drop with stable flow limited breathing pattern were then tabulated, and the degree of upper airway obstruction was categorized as mild, moderate, or severe flow limitation based on the mean inspiratory airflow (V_T/T_I) of 200 ± 25 ml/s, 150 ± 25 ml/s, 100 ± 25 ml/s, respectively. For each category, inspiratory duty cycle (T_I/T_T),

respiratory rate (f), tidal volume (V_T), and minute ventilation ($Vdot_I$) were calculated. In addition, we calculated dead space volume (V_{DS}) by using dead space volume norms in men and women, as given by height^2/189 in ml (27). Alveolar ventilation ($Vdot_A$) was assessed by subtracting dead space ventilation (V_{DS} x RR) from minute ventilation.

Statistical Analysis

Two-way analysis of variance (ANOVA) for repeated measures and Taguchi's method of post-hoc analysis of significance was used for comparing ventilatory responses for each degree of UAO within and between sex groups (Stata V9.0,Stata Corp, TX). Linear regression was utilized to examine the relationship between respiratory timing indices in the moderate UAO condition against BMI and sex. A p-value <0.05 was considered statistically significant.

Word Count: 761

IV. RESULTS

Anthropometric data, sleep study results, lung function tests, and smoking history are shown in Table 1 for the entire group matched by BMI and age (left two columns) and a subset matched by minute ventilation (+/- 0.5 L/min) at baseline (right two columns).

A total of 141 nasal pressure drops with induced upper airway obstruction were available for analysis of which 464 flow limited breaths (6-7 breaths per upper airway obstruction category) were analyzed and compared to 60 normal non-flow limited breaths (3 breaths per subject). While the nasal pressure was similar between sexes for the baseline non flow-limited condition (females: 5.2±1.6 vs. males: 5.8±1.8 cmH_2O), it was minimally lower ($P<0.05$) during all flow limited categories in women (mild: -1.5±3.6 vs. 0.2±4.3; moderate -2.1±4.0 vs. 1.0±2.6; severe -2.8±4.9 vs. -0.1±2.6 cmH2O, females vs. males, mean and SD respectively).

Baseline Ventilatory Parameters during Non-Flow-Limited Breathing

The baseline respiratory parameters of the subjects are presented in Table 1. Respiratory timing indices (T_I, T_T, T_I/T_T) were similar in both sexes in the non-flow limited state. In contrast, mean inspiratory airflow (V_T/T_I) and minute ventilation ($Vdot_I$) during NREM sleep were approximately 40% lower in women compared to men, indicating a lower ventilatory demand in BMI and age matched women compared to men during stable NREM sleep. It should be noted: the anatomic dead space volume was also lower in women compared to men in both groups.

Inter-individual Variability of Ventilatory Responses of Upper Airway Obstruction

Figure 2 illustrates the minute ventilation and timing responses to experimentally induced upper airway obstruction in one individual. While minute ventilation declined with increasing degrees of upper airway obstruction, both the inspiratory duty cycle and the respiratory rate increased progressively. Pooled data of all individuals in Figure 3 demonstrate that increasing levels of upper airway obstruction led to a dose dependent response of the inspiratory duty cycle (left panel)

and the respiratory rate (right panel). Figure 4 shows that individual responses of the duty cycle (left panel) and respiratory rate (right panel) responses to moderate upper airway obstruction varied markedly from 97 to 140% and 95 to 135%, respectively.

As outlined in the Conceptual Approach, we hypothesized that an increase in duty cycle, rather than respiratory rate, will improve minute ventilation. We therefore determined quartiles of duty cycle and respiratory rate responses to moderate upper airway obstruction of individuals shown in Figure 4. Individuals of all quartiles of the duty cycle and the respiratory rate did not differ by age, gender, or BMI at baseline. In each quartile, we calculated minute ventilation and compared it to the mean minute ventilation of the entire group. In Figure 5, minute ventilation is illustrated for individuals in each quartile of the duty cycle (left panel) and respiratory rate response (right panel). Compared to the mean minute ventilation of 4279 ml/min for the entire group, individuals with a low duty cycle response (0.44) had approximately 400 ml lower minute ventilation compared to those with a high duty cycle response (0.51) who had a 500 ml higher ventilation ($P<0.01$). In contrast, respiratory rate responses did not contribute to an increase in minute ventilation.

Sex Differences in Ventilatory Responses to Upper Airway Obstruction

Several post hoc analyses were conducted to determine the influence of sex on ventilatory responses to upper airway obstruction. In the first analysis, all men and women were included and timing indices and minute ventilation were determined in response to decreasing absolute levels of mean inspiratory airflow. As can be seen in Figure 6, while inspiratory duty cycle (T_I/T_T) responses were similar between men and women (left upper panel), the respiratory rate (f) (middle upper panel) had a greater increase in women compared to men. Nevertheless, minute ventilation ($Vdot_I$) (right upper panel) during upper airway obstruction was similar between sexes, despite marked differences in minute ventilation at baseline.

As noted above (Table 1), the mean inspiratory airflow at baseline was 80 ml lower in women. Thus, categories of flow limitation based on absolute levels of inspiratory airflow represented a smaller % reduction in mean inspiratory airflow in

women compared to men. We therefore conducted two additional post hoc analyses to account for absolute differences in mean inspiratory airflow at baseline between men and women. First, the mean inspiratory airflow and minute ventilation was matched in a subgroup of women (n=6) and men (n=6, see Table 1) which produced similar % reductions in inspiratory airflow from baseline to mild (89/84%), moderate (67/63%) and severe (45/42%) levels of upper airway obstruction. As can be seen in the lower panels of Figure 6, this approach produced similar responses in inspiratory duty cycle (T_I/T_T), respiratory rate (RR) and minute ventilation ($\dot{V}_I$) between women and men.

Second, the severity of upper airway obstruction was defined by a % reduction in mean inspiratory airflow from baseline for all subjects. Comparing women and men(see Online Repository), we demonstrated that responses in inspiratory duty cycle and respiratory rate similar to the above approaches, indicating that sex differences in ventilatory responses persist, regardless of the method used for defining the exposure to upper airway obstruction (flow limitation).

Alveolar Ventilation: As outlined in Conceptual Approach, a high respiratory rate under conditions of a fixed inspiratory airflow and unchanged inspiratory duty cycle should increase dead space ventilation and thereby lower alveolar ventilation. Since women had a higher respiratory rate at all categories of upper airway obstruction and inspiratory duty cycle was similar between sexes, one would expect lower alveolar ventilation in women. Men and women, however, had comparable levels of alveolar ventilation at all degrees of upper airway obstruction (see Figure 7), indicating that a lower dead space volume (see Table 1) offset the higher respiratory rate in women.

Women also had markedly lower alveolar ventilation at baseline, indicating a lower ventilatory demand during NREM sleep. In contrast, women had similar alveolar ventilation at al categories of upper airway obstruction than men (Figure 7, left panel). Relative to baseline (Figure 7, right panel), women preserved alveolar ventilation better than men during the mild and moderate flow limited condition.

BMI Effect on Ventilatory Responses

To explore the influence of BMI on ventilatory responses to UAO in men and women, we analyzed timing responses during conditions of moderate UAO (V_T/T_I= 150 ± 25 mL/s) using linear regression analysis with BMI and sex as independent variables. Marked differences in respiratory timing responses in both men and women were observed across the spectrum of BMI. In men, neither the respiratory rate nor duty cycle responses varied significantly by BMI. In contrast, women increased the absolute difference and percent change in respiratory rate with increasing BMI. Specifically, an increase 10 kg/m^2 was associated with increases of 5 breaths/min and 30% from baseline, respectively; $p<0.01$ for both).

Word Count: 1117

V. DISCUSSION

We examined the acute effects of upper airway obstruction on respiratory patterns during sleep. We found that during periods of inspiratory airflow limitation, there was a dose dependent increase in the inspiratory duty cycle and respiratory rate in response to increasing levels of upper airway obstruction. Heterogeneity in these responses led to variable degrees of ventilatory compensation to upper airway obstruction. In particular, we found that increases in the inspiratory duty cycle, not the respiratory rate, helped to maintain ventilation and stabilize breathing acutely. Moreover, responses in the inspiratory duty cycle were independent of sex and weight, but female sex and obesity were associated with a greater response in the respiratory rate. Thus, upper airway obstruction constitutes a unique load on the

respiratory system, and the respiratory timing responses determine the ability to stabilize ventilation and compensate for upper airway obstruction during sleep.

Timing Responses to Upper Airway Obstruction;

In the current study, we demonstrated that brief periods of upper airway obstruction elicited compensatory increases in the inspiratory duty cycle and the respiratory rate. This prolongation of duty cycle and respiratory rate was dose dependent and instantaneous, suggesting that upper airway and pulmonary mechano-receptors (28-33), rather than chemo-receptors, mediated these immediate responses to upper airway obstruction. This increase in inspiratory duty cycle should help to stabilize minute ventilation ($Vdot_I$) at any given level of upper airway obstruction, as described by the relationship: $Vdot_I = T_I/T_T * V_T/T_I$, where T_I/T_T represents the inspiratory duty cycle, and V_T/T_I the mean inspiratory flow rate (17;18;20), which was imposed experimentally. Under conditions of upper airway obstruction, the mean inspiratory airflow (V_T/T_I) approximates the peak inspiratory airflow rate ($Vdot_Imax$) during inspiratory airflow limitation. In the current study, we found that compensatory increases in the inspiratory duty cycle were associated with greater degrees of ventilatory compensation, as reflected by greater increases in minute ventilation (Fig. 5). In contrast, increases in the respiratory rate would be expected to decrease T_{TOT} and T_I proportionally (see Figure 1), thereby leaving the inspiratory duty cycle and minute ventilation unchanged. Thus, upper airway obstruction is a unique load for which minute ventilation is independent of the respiratory rate at any given level of inspiratory duty cycle and mean inspiratory airflow.

It is intriguing that inspiratory duty cycle and respiratory rate responses to upper airway obstruction varied markedly among subjects. This variability in timing responses may be related to differences in metabolic rate, which is known to vary markedly between individuals. (34;35). As shown in Figure 4, at the moderate flow limited condition, the increases in the inspiratory duty cycle varied markedly among individuals, ranging from 7% (0.39 to 0.42) to 48% (0.39 to 0.57). Similarly, respiratory rate responses varied substantially at moderate levels of upper airway obstruction. We have previously demonstrated that the inspiratory duty cycle response

to hypercapnia is an intermediate physiological phenotype linked to mouse chromosome 5 (17). Thus, inspiratory duty cycle and respiratory rate responses to upper airway obstruction may represent constitutive traits that determine the individual's ability to compensate for a given degree of upper airway obstruction during sleep.

Sex Differences in Ventilatory Responses to Upper Airway Obstruction

Timing Responses: While inspiratory duty cycle responses to upper airway obstruction was similar between sexes, the respiratory rate increased more in women than men. As outlined in Methods (Conceptual Approach, Figure 1), under conditions of unchanged inspiratory duty cycle (T_I/T_T), dead space ventilation ($Vdot_{DS}$) will increase as the respiratory rate (f) rises, and the magnitude of this increase will be determined by the subject's dead space volume (V_{DS}). An increase in the respiratory rate would have little impact on dead space ventilation if the dead space volume is negligible, but will increase the dead space ventilation markedly if the dead space volume comprises a large proportion of the tidal volume. The dead space volume was considerably lower in women than men (132±11 vs. 179±24 mL, mean±SD), thereby minimizing the impact of elevations in respiratory rate on dead space ventilation in women. Thus, a lower dead space volume makes women relatively tolerant to a rise in respiratory rate during periods of upper airway obstruction.

V*entilation:* Upper airway obstruction produced similar reductions in minute and alveolar ventilation in men and women. Nevertheless, the relative change alveolar ventilation from baseline was less in women than men (Figure 7). Alveolar ventilation tracks metabolic rate during sleep (35), which is approximately 30% lower in women than men due to body composition and stature (34-39). At comparable levels of upper airway obstruction, women are less likely to hypoventilate than men. Thus, both a lower ventilatory demand and lower dead space volume in women are likely to make women less susceptible to ventilatory instability during periods of upper airway obstruction.

Limitations

There are several limitations to be considered. First, our analyses of timing responses were limited to acute periods of upper airway obstruction. Responses to sustained periods of upper airway obstruction might differ from acute conditions due to differences in chemical and upper airway control (15;40;41). Second, we estimated dead space volume rather than directly measuring it. Our attempts to directly measure dead space volume with the Fowler technique ((42;43)) demonstrated a high inter- and intra-rater variability. We therefore used estimates of dead space volume based on anthropometric data, which appears to be more reliable in subjects without underlying lung diseases. Finally, we did not consider controlling the impact of oral contraceptives or menstrual phase on timing responses. Hormonal differences may explain some of the variability in timing responses in women. Nevertheless, men had a similar variability in timing responses, making us suspect that hormones did not account for variations in timing responses within women, but may explain the greater respiratory rate response in women compared to men.

Implications.

We have shown that timing responses to upper airway obstruction allowed us to segregate individuals based on their propensity to preserve ventilation or to hypoventilate in face of upper airway obstruction. Crisp intermediate phenotypes such as these are required to probe for the genetic basis of obstructive sleep apnea susceptibility. Moreover, the respiratory pattern may predict the susceptibility and expression of sleep disordered breathing independent of the upper airway properties. First, diseases of the lungs and chest wall produce resistive and elastic loads to the respiratory system, which impact inspiratory duty cycle and the respiratory rate (44;45). Because mean inspiratory airflow responses during upper airway obstruction are limited (fixed), compensation to defend ventilation are dependent primarily on responses of the inspiratory duty cycle and the baseline respiratory rate. Further work is required to examine the role of elastic and restrictive loads on the degree of hypoventilation during periods of upper airway obstruction compared to normal. Second, individuals who have an increased metabolic rate (pregnancy) or dead space

volume (lung diseases) may be susceptible to hypoventilation if compensatory increases in inspiratory duty cycle are limited and fail to increase alveolar ventilation. Thus, variations in inspiratory duty cycle and respiratory rate may explain disturbances in gas exchange across a spectrum of sleep disordered breathing etiologies.

Summary

In summary, our findings indicate that upper airway obstruction elicits specific respiratory responses that may serve as quantitative intermediate traits for OSA and suggest that these factors may play a role in sex differences in the expression of sleep disordered breathing.

Word Count: 1207

Word Count Entire Manuscript: 3378

Acknowledgements: The authors thank Mrs. Sarah L. Kamsheh, Leigh A. Frame and Mr. Samuel B. Squier for contributions to this manuscript, which included technical support and help in the preparations of tables and figures.

List of abbreviations

T_I:	Inspiratory time
T_E:	Expiratory time
T_T:	Total respiratory cycle duration
T_I / T_T:	Inspiratory duty cycle
$Vdot_I$:	Inspiratory minute ventilation
$Vdot_A$:	Alveolar ventilation per minute
$Vdot_{DS}$:	Dead space ventilation per minute
$Vdot_I max$:	Peak inspiratory airflow
V_T/T_I:	Mean inspiratory airflow
V_{DS}:	Dead Space Volume
$Vdot_A$:	Alveolar Ventilation
f:	Respiratory Rate
P_N:	Nasal Pressure

Table 1:

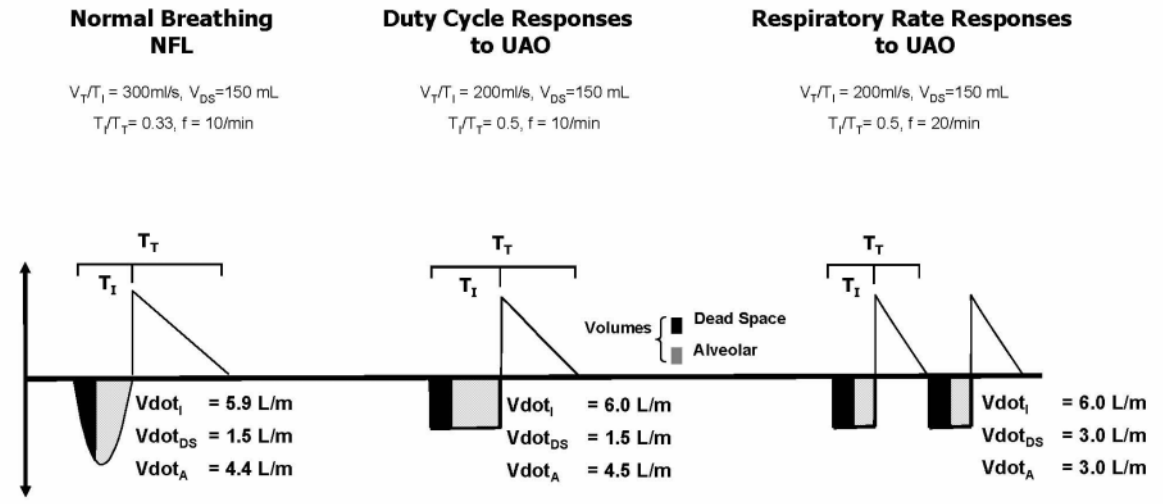
Variable	Matched by BMI and Age		Matched by Ventilation at Baseline	
	Normal Men (n=10)	Normal Women (n=10)	Normal Men (n=6)	Normal Women (n=6)
Anthropometry				
Age, yrs	33.5 (9.6)	33.4 (10.8)	35.2 (11.0)	34.0 (8.5)
Height, cm	184.4 (8.4)	157.7 (8.6) *	180.84 (8.1)	156.5 (6.6) *
Weight, kg	91 (11.5)	71.1 (7.8)	86.9 (19.3)	78.7 (15.8)
Body Mass Index, kg/m^2	26.6 (3.0)	28.4 (3.4)	26.6 (3.0)	30.1 (2.1) *
Etnicity: Cau/AAm/As	1/9/0	0/9/1	5/1/0	5/0/1
Lung function				
FVC, l	5.7 (1.0)	3.7 (0.8)	5.0 (1.0)	3.5 (0.8)
FEV_1/FVC, %	84.1 (7.0)	84.6 (7.0)	82.5 (13.8)	84.7 (6.6)
pH	7.4 (0.0)	7.4 (0.0)	7.4 (0.0)	7.4 (0.0)
PaO_2, mmHg	83.4 (11.6)	83.9 (7.9)	76.0 (8.7)	81.6 (8.2)
$PaCO_2$, mmHg	39.3 (3.5)	36.4 (4.5)	40.7 (1.2)	36.0 (4.6)
Sleep				
Total sleep time, min	396.7 (44.3)	338.6 (51.3)	373.6 (44.9)	332.8 (63.9)
Sleep efficiency, %	88.1 (6.0)	76.2 (30.2)	87.0 (8.9)	86.2 (11.4)
Sleep stages, % of total sleep time				
NREM	78.0 (7.5)	85.1 (6.2)	81.7 (16.3)	75.0 (27.5)
REM	22.0 (9.0)	14.9 (6.6)	18.3 (4.9)	15.0 (2.8)
Sleep Disordered Breathing				
Apnea Hypopnea Index (AHI), events/h	3.5 (1.3)	3.1(1.5)	3.1 (1.5)	2.8.(1.7)
NREM AHI, events/h	2.4 (1.7)	2.7 (1.4)	2.3 (1.8)	2.3 (1.8)
REM AHI, events/h	6.0 (4.3)	5.2 (5.1)	6.0 (7.5)	6.9 (8.5)
Proportion of obstructed events, (%)	73.2 (31.7)	92.8 (9.1)	62.5 (47.0)	73.3 (39.9)
Baseline SaO_2, %	97.1 (1.5)	97.1 (1.8)	96.8 (2.1)	97.2 (1.7)
Average Low SaO_2, %	94.4 (2.5)	94.6 (2.0)	95.1 (2.7)	94.5 (2.9)
Respiratory Parameters – Non flow limited condition				
Timing Parameters				
Respiratory rate (f), breaths/min	13.6 (1.4)	15.1 (2.5)	13.4 (1.6)	15.5 (1.6)
Inspiratory Time (T_I), sec	1.8 (0.3)	1.6 (0.2)	1.8 (0.3)	1.6 (0.2)
Respiratory cycle length (T_T), sec	4.4 (0.5)	4.1 (0.8)	4.6 (0.6)	3.9 (0.4)
Inspiratory Duty Cycle (T_I/T_T)	0.40 (0.05)	0.40 (0.03)	0.40 (0.04)	0.40 (0.02)
Ventilation				
Mean Inspiratory Airflow (Vt/T_I), ml/s	288 (118)	205 (48) *	224 (27)	237 (27)
Inspiratory Tidal Volume (V_t), ml	501 (168)	330 (71) *	400 (46)	374 (56)
Inspiratory Minute Ventilation ($Vdot_I$), l/min	6903 (2696)	4971 (1268) *	5336 (903)	5747 (634)
Anatomic dead space volume (V_{DS}), ml	179 (24)	132 (11) *	173 (21)	131 (12) *
History				
Smoking (Yes/No/missing data)	4/4/2	2/4/4	4/4/2	4/4/2
Medication (Yes/No)	1/8	2/8	1/8	1/8

Legends:

Table 1: Anthropometric data for the entire group matched by BMI and age (left two columns) and a subset matched by minute ventilation (+/- 0.5 L/min) at baseline (right two columns). Abbreviations: Cau: Caucasian; AAM: African American;As: Asian: FVC: forced vital capacity; FEV1/ FVC, %: forced expiratory volume in 1 sec as % FVC; PaO2: partial pressure of oxygen in arterial blood, PaCO2: arterial partial pressure of carbon dioxide in arterial blood, 1) Current medication included use of Ibuprofen, Levoxyl 75mg, and Claritin.

Figure 1: Ventilatory responses to upper airway obstruction (UAO) (middle and right panel) compared to normal non flow-limited (NFL) breathing (left panel). For illustrative purposes, we assumed a reduction in mean inspiratory airflow (V_T/T_I) from 300 mL/s at baseline to 200 ml/s during UAO. Prolongation of the inspiratory duty cycle (T_I/T_T, middle panel) may help maintain alveolar ventilation ($Vdot_A$) during periods of UAO. In contrast, increases in respiratory rate (right panel) would increase the portion of dead space ventilation ($Vdot_{DS}$) to minute ventilation ($Vdot_I$), thereby lowering alveolar ventilation, if inspiratory duty cycle maintains unchanged. Alveolar ventilation was calculated by assuming a dead space volume of V_{DS} of 150 ml and the equation given in the lower panel. Abbreviations: T_I: Inspiratory time, T_T: Total respiratory cycle duration.

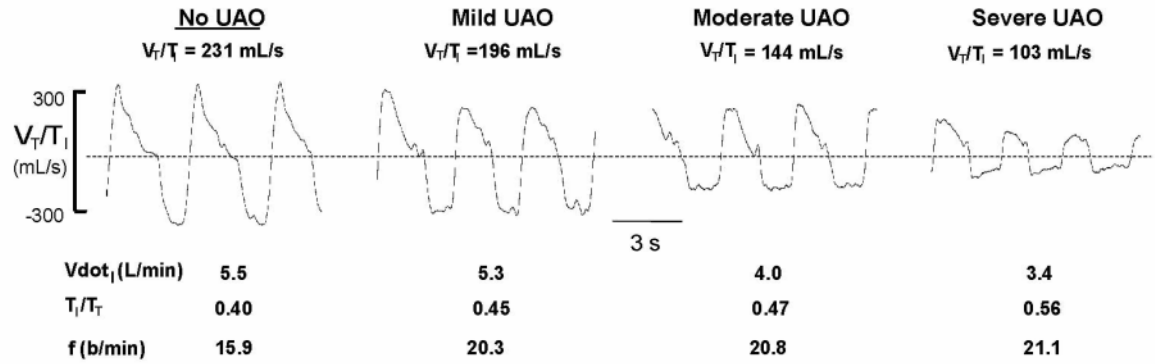
Figure 1



$$Vdot_A = Vdot_I - Vdot_{DS}$$
$$= V_T/T_I \times T_I/T_T - V_{DS} \times RR$$

Figure 2: Recording example from a male illustrating flow signals and ventilatory parameters at baseline (left panel) and specific levels of upper airway obstruction (UAO, right three panels). It should be noted that airflow (V_T/T_I) deflection represents inhaled flow downward. With decreasing levels of mean inspiratory airflow (V_T/T_I) duty cycle (T_I/T_T) and respiratory rate (f) increased while minute ventilation ($Vdot_I$) decreased, progressively.

Figure 2



$Vdot_I$ (L/min)	5.5	5.3	4.0	3.4
T_I/T_T	0.40	0.45	0.47	0.56
f (b/min)	15.9	20.3	20.8	21.1

Figure 3: The mean ± s.e. duty cycle (T_I/T_T) and respiratory rate (RR) in response to increasing severity (mild=200 ml/s, mod: 150 ml/s, sev: 100 ml/s) of upper airway obstruction in normal individuals. * $P < 0.05$ compared to baseline (NFL), NFL: Non-flow-limited.

Figure 3

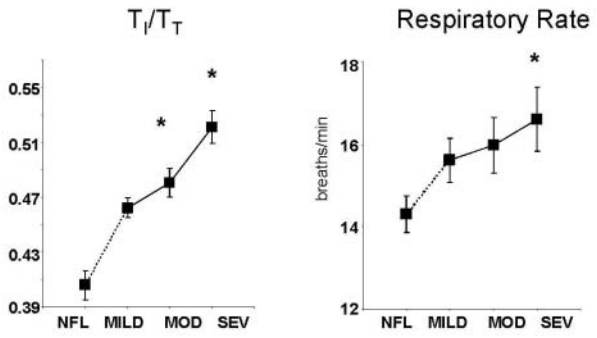


Figure 4: The % change in inspiratory duty cycle (left panel) and respiratory rate (right panel) from baseline (100% to moderate upper airway obstruction (UAO)) are shown for each men (open squares) and women (open circles) and presented as the mean (± s.e.) for each sex.

Figure 4

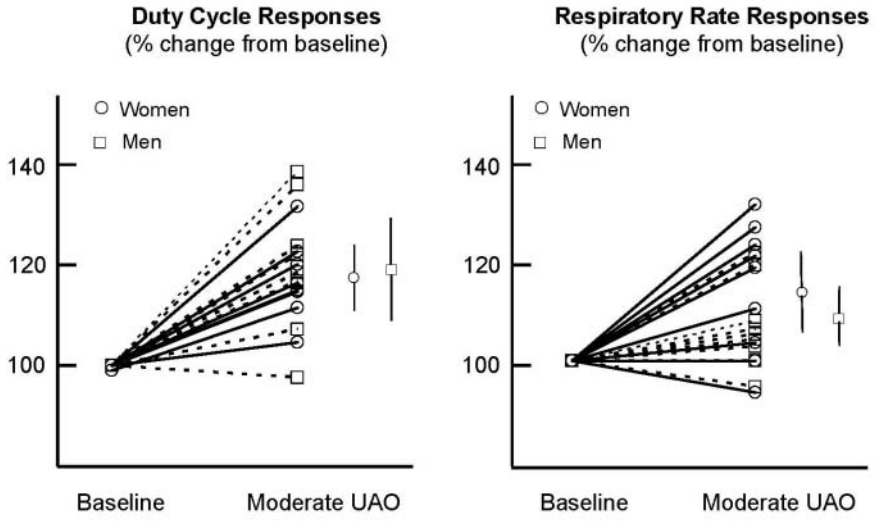


Figure 5: The effect of increasing levels of duty cycle (left panel) and respiratory rate (right panel) responses on minute ventilation compared to the mean minute ventilation, which was 4279 ml/minute of the entire group during moderate upper airway obstruction (UAO).

Figure 5

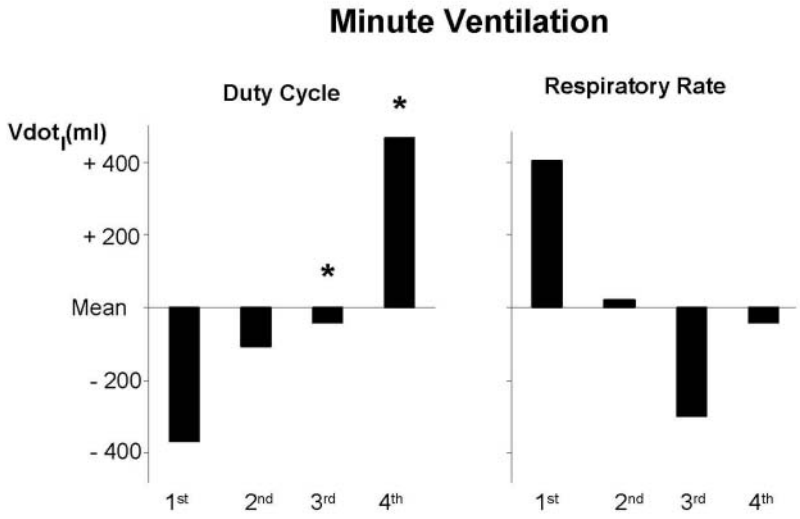


Figure 6: The mean ± s.e. inspiratory duty cycle (T_I/T_T), respiratory rate (f) and minute ventilation (V_I), for men (black squares) and women (open circles) matched by BMI and age (upper panel) and matched by baseline minute ventilation (lower panel). Differences were determined by two-way ANOVA (* $P< 0.05$).

Figure 6

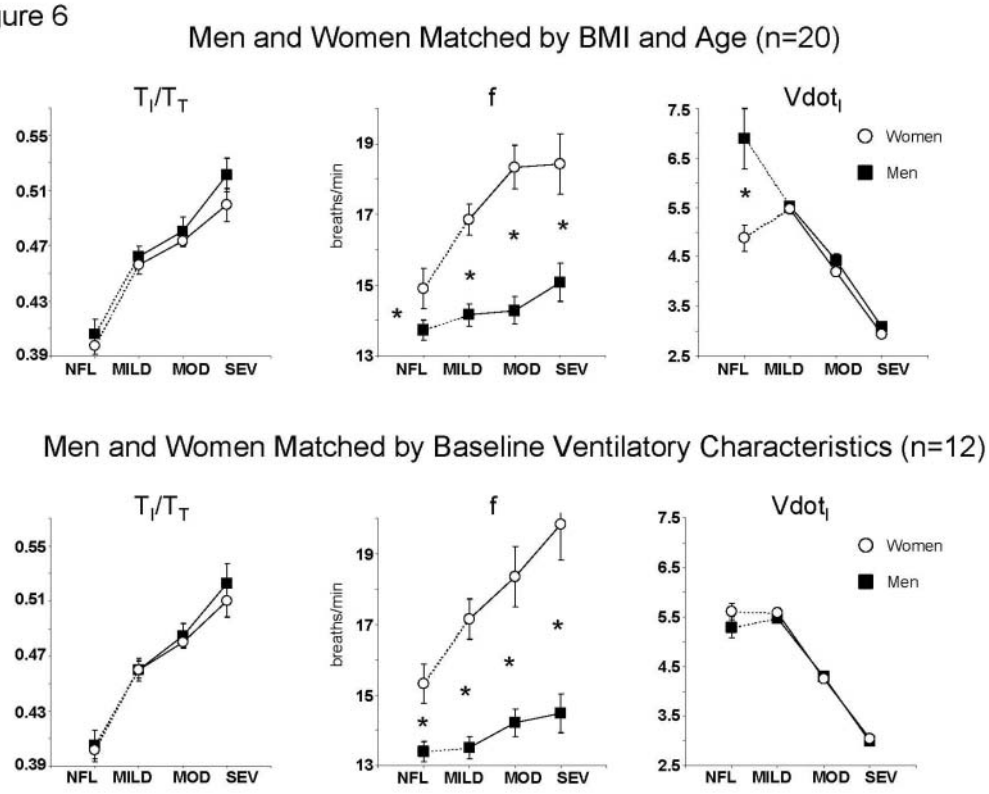
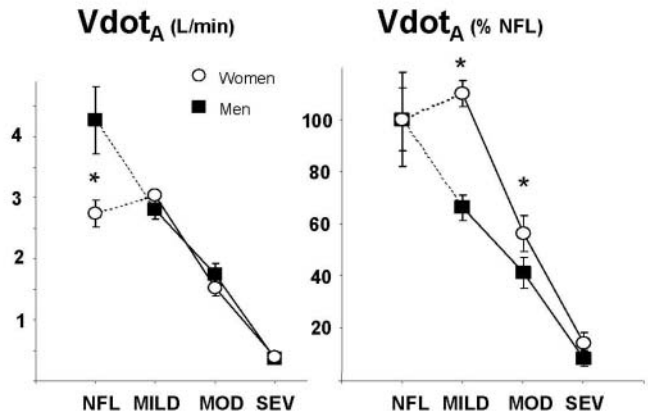


Figure 7: Left panel: The alveolar ventilation (mean ± s.e) for men (black squares) and women (open circles). Right panel: relative changes in alveolar ventilation compared to baseline (100%). Differences were determined by paired t-test (* P< 0.05).

Figure 7


Vdot$_A$ (L/min)
Vdot$_A$ (% NFL)
Women
Men
4
3
2
1
100
80
60
40
20
*
*
*
NFL MILD MOD SEV
NFL MILD MOD SEV

Reference List

(1) Gleadhill IC, Schwartz AR, Schubert N, Wise RA, Permutt S, Smith PL. Upper airway collapsibility in snorers and in patients with obstructive hypopnea and apnea. Am Rev Respir Dis 1991 June;143(6):1300-3.

(2) Gold AR, Marcus CL, Dipalo F, Gold MS. Upper airway collapsibility during sleep in upper airway resistance syndrome. Chest 2002 May;121(5):1531-40.

(3) Schwartz AR, Smith PL, Wise RA, Bankman I, Permutt S. Effect of positive nasal pressure on upper airway pressure-flow relationships. J Appl Physiol 1989 April;66(4):1626-34.

(4) Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002 May 1;165(9):1217-39.

(5) Jordan AS, McEvoy RD. Gender differences in sleep apnea: epidemiology, clinical presentation and pathogenic mechanisms. Sleep Med Rev 2003 October;7(5):377-89.

(6) Redline S, Kump K, Tishler PV, Browner I, Ferrette V. Gender differences in sleep disordered breathing in a community-based sample. Am J Respir Crit Care Med 1994 March;149(3 Pt 1):722-6.

(7) Guilleminault C, Partinen M, Hollman K, Powell N, Stoohs R. Familial aggregates in obstructive sleep apnea syndrome. Chest 1995 June;107(6):1545-51.

(8) Schwab RJ. Genetic determinants of upper airway structure that predispose to obstructive sleep apnea. Respir Physiol Neurobiol 2005 July 22;147((2-3)):289-98.

(9) Schwab RJ, Pasirstein M, Kaplan L, Pierson R, Mackley A, Hachadoorian R, Arens R, Maislin G, Pack AI. Family aggregation of upper airway soft tissue structures in normal subjects and patients with sleep apnea. Am J Respir Crit Care Med 2006 February 15;173(4):453-63.

(10) Redline S, Tishler PV. Familial influences on sleep apnea. In: Saunders NA, Sullivan CE, editors. Sleep and Breathing. 2 ed. New York: Marcel Dekker, Inc.; 1994. p. 363-77.

(11) Patel SR. Shared genetic risk factors for obstructive sleep apnea and obesity. J Appl Physiol 2005 October;99(4):1600-6.

(12) Palmer LJ, Buxbaum SG, Larkin EK, Patel SR, Elston RC, Tishler PV, Redline S. Whole genome scan for obstructive sleep apnea and obesity in

African-American families. Am J Respir Crit Care Med 2004 June 15;169(12):1314-21.

(13) Redline S, Tishler PV, Tosteson TD, Williamson J, Kump K, Browner I, Ferrette V, Krejci P. The familial aggregation of obstructive sleep apnea. Am J Respir Crit Care Med 1995 March;151(3 Pt 1):682-7.

(14) King ED, O'Donnell CP, Smith PL, Schwartz AR. A model of obstructive sleep apnea in normal humans. Role of the upper airway. Am J Respir Crit Care Med 2000 June;161(6):1979-84.

(15) Patil SP, Schneider H, Marx JJ, Gladmon E, Schwartz AR, Smith PL. Neuromechanical control of upper airway patency during sleep. J Appl Physiol 2007 February;102(2):547-56.

(16) Jordan AS, Wellman A, Heinzer RC, Lo YL, Schory K, Dover L, Gautam S, Malhotra A, White DP. Mechanisms used to restore ventilation after partial upper airway collapse during sleep In humans. Thorax 2007 April 5.

(17) Schneider H, Patil SP, Canisius S, Gladmon EA, Schwartz AR, O'Donnell CP, Smith PL, Tankersley CG. Hypercapnic duty cycle is an intermediate physiological phenotype linked to mouse chromosome 5. J Appl Physiol 2003 July;95(1):11-9.

(18) Younes M. Contributions of upper airway mechanics and control mechanisms to severity of obstructive apnea. Am J Respir Crit Care Med 2003 September 15;168(6):645-58.

(19) Stoohs R, Guilleminault C. Snoring during NREM sleep: respiratory timing, esophageal pressure and EEG arousal. Respir Physiol 1991 August;85(2):151-67.

(20) Tagaito Y, Schneider H, O'Donnell CP, Smith PL, Schwartz AR. Ventilating with tracheal gas insufflation and periodic tracheal occlusion during sleep and wakefulness. Chest 2002 November;122(5):1742-50.

(21) Pichard LE, Patil SP, Gladmon E, Smith PL, Schwartz AR, Schneider H. Women have a greater ventilatory responses to upper airway obstruction than men. Conf Proc IEEE Eng Med Biol Soc 2004;5:3878-80.

(22) Krishnan V, Pichard LE, Patil S, Schwartz A.R., Smith PL, Schneider H. Gender Differences in Ventilatory Response to Inspiratory Flow Limitation during Non Rapid Eye Movement (NREM) Sleep. 3, A197. 2007. The American Thoracic Society.
Ref Type: Generic

(23) Smith PL, Wise RA, Gold AR, Schwartz AR, Permutt S. Upper airway pressure-flow relationships in obstructive sleep apnea. J Appl Physiol 1988 February;64(2):789-95.

(24) Smith PL, Schwartz AR, Gauda E, Wise R, Brower R, Permutt S. The modulation of upper airway critical pressures during sleep. In: Issa FG, Surratt PM, Remmers JE, editors. Sleep and Respiration.New York: Wiley-Liss; 1990. p. 253-60.

(25) Eastwood PR, Szollosi I, Platt PR, Hillman DR. Collapsibility of the upper airway during anesthesia with isoflurane. Anesthesiology 2002 October;97(4):786-93.

(26) Patil SP, Punjabi NM, Schneider H, O'Donnell CP, Smith PL, Schwartz AR. A simplified method for measuring critical pressures during sleep in the clinical setting. Am J Respir Crit Care Med 2004 July 1;170(1):86-93.

(27) Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. General considerations for lung function testing. Eur Respir J 2005 July;26(1):153-61.

(28) Chow CM, Xi L, Smith CA, Saupe KW, Dempsey JA. A volume-dependent apneic threshold during NREM sleep in the dog. J Appl Physiol 1994 June;76(6):2315-25.

(29) Coleridge HM, Coleridge JCG. Reflexes evoked from tracheobronchial tree and lungs. In: Fishman AP, Cherniack NS, Widdicombe JG, Geiger SR, editors. Handbook of Physiology. Section 3: The Respiratory System. Volume II, Control of Breathing, Part 1.Baltimore, Maryland: Waverly Press, Inc.; 1986. p. 395-429.

(30) Iber C, Simon P, Skatrud JB, Mahowald MW, Dempsey JA. The Breuer-Hering reflex in humans. Effects of pulmonary denervation and hypocapnia. Am J Respir Crit Care Med 1995 July;152(1):217-24.

(31) Kimoff RJ, Sforza E, Champagne V, Ofiara L, Gendron D. Upper airway sensation in snoring and obstructive sleep apnea. Am J Respir Crit Care Med 2001 July 15;164(2):250-5.

(32) Leevers AM, Simon PM, Xi L, Dempsey JA. Apnoea following normocapnic mechanical ventilation in awake mammals: a demonstration of control system inertia. J Physiol (Lond) 1993 December;472:749-68:749-68.

(33) Manchanda S, Leevers AM, Wilson CR, Simon PM, Skatrud JB, Dempsey JA. Frequency and volume thresholds for inhibition of inspiratory motor output during mechanical ventilation. Respir Physiol 1996 August;105(1-2):1-16.

(34) Aitken ML, Franklin JL, Pierson DJ, Schoene RB. Influence of body size and gender on control of ventilation. J Appl Physiol 1986 June;60(6):1894-9.

(35) White DP, Weil JV, Zwillich CW. Metabolic rate and breathing during sleep. J Appl Physiol 1985 August;59(2):384-91.

(36) Fontvieille AM, Rising R, Spraul M, Larson DE, Ravussin E. Relationship between sleep stages and metabolic rate in humans. Am J Physiol 1994 November;267(5 Pt 1):E732-E737.

(37) Webb P, Hiestand M. Sleep metabolism and age. J Appl Physiol 1975 February;38(2):257-62.

(38) Ferraro R, Lillioja S, Fontvieille AM, Rising R, Bogardus C, Ravussin E. Lower sedentary metabolic rate in women compared with men. J Clin Invest 1992 September;90(3):780-4.

(39) Kreider MB, Biskirk ER, Bass DE. Oxygen consumption and body temperatures during the night. J Appl Physiol 1958 May;12(3):361-6.

(40) Schneider H, Boudewyns A, Smith PL, O'Donnell CP, Canisius S, Stammnitz A, Allan L, Schwartz AR. Modulation of upper airway collapsibility during sleep: influence of respiratory phase and flow regimen. J Appl Physiol 2002 October;93(4):1365-76.

(41) Schwartz AR, O'Donnell CP, Baron J, Schubert N, Alam D, Samadi SD, Smith PL. The hypotonic upper airway in obstructive sleep apnea: role of structures and neuromuscular activity. Am J Respir Crit Care Med 1998 April;157(4 Pt 1):1051-7.

(42) Kars AH, Bogaard JM, Stijnen T, de VJ, Verbraak AF, Hilvering C. Dead space and slope indices from the expiratory carbon dioxide tension-volume curve. Eur Respir J 1997 August;10(8):1829-36.

(43) Fowler WS, Comroe JH. Lung Function Studies. I. The Rate ofIncrease of Arterial oxygen saturation during the inhalation of 100% O2. J Clin Invest 1948 May;27(3 Pt 1):327-34.

(44) Milic-Emili J, Zin WA. Breathing responses to imposed mechanical loads. In: Fishman AP, Cherniack NS, Widdicombe JG, Geiger SR, editors. Handbook of Physiology. Sec. 3 - The Respiratory System, Vol. II.Bethesda, MD: American Physiological Society; 1986. p. 751-69.

(45) Iber C, Berssenbrugge A, Skatrud JB, Dempsey JA. Ventilatory adaptations to resistive loading during wakefulness and non- REM sleep. J Appl Physiol 1982 March;52(3):607-14.