BODY POSITION EFFECTS ON PHYSIOLOGICAL FACTORS THAT CONTRIBUTE TO OSA

The Effect of Body Position on Physiological Factors that Contribute to Obstructive Sleep Apnea

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Study objectives: Obstructive sleep apnea (OSA) resolves in lateral sleep in 20% of patients. However, the effect of lateral positioning on factors contributing to OSA has not been studied. We aimed to measure the effect of lateral positioning on the key pathophysiological contributors to OSA including lung volume, passive airway anatomy/collapsibility, the ability of the airway to stiffen and dilate, ventilatory control instability (loop gain), and arousal threshold.

Design: Non-randomized single arm observational study.

Setting: Sleep laboratory.

Patients/participants: 20 (15M, 5F) continuous positive airway pressure (CPAP)-treated severe OSA patients.

Interventions: Supine vs. lateral position.

Measurements: CPAP dial-downs performed during sleep to measure: (i) V_{eupnea}: asleep ventilatory requirement, (ii) passive V_0: ventilation off CPAP when airway dilator muscles are quiescent, (iii) $V_{arousal}$: ventilation at which respiratory arousals occur, (iv) active V_0: ventilation off CPAP when airway dilator muscles are activated during sleep, (v) loop gain: the ratio of the ventilatory drive response to a disturbance in ventilation, (vi) arousal threshold: level of ventilatory drive which leads to arousal, (vii) upper airway gain (UAG): ability of airway muscles to restore ventilation in response to increases in ventilatory drive, and (viii) pharyngeal critical closing pressure (Pcrit). Awake functional residual capacity (FRC) was also recorded.

Results: Lateral positioning significantly increased passive V_0 (0.33 ± 0.76L/min vs. 3.56 ± 2.94L/min, P < 0.001), active V_0 (1.10 ± 1.97L/min vs. 4.71 ± 3.08L/min, P < 0.001), and FRC (1.31 ± 0.56 L vs. 1.42 ± 0.62 L, P = 0.046), and significantly decreased Pcrit (2.02 ± 2.55 cm H_2O vs. −1.92 ± 3.87 cm H_2O, P < 0.001). Loop gain, arousal threshold, $V_{arousal}$, and UAG were not significantly altered.

Conclusions: Lateral positioning significantly improves passive airway anatomy/collapsibility (passive V_0, pharyngeal critical closing pressure), the ability of the airway to stiffen and dilate (active V_0), and the awake functional residual capacity without improving loop gain or arousal threshold.

Keywords: sleep apnea, obstructive; supine position; airway obstruction; lung volume measurements; functional residual capacity.

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INTRODUCTION

Obstructive sleep apnea (OSA), a medical condition that affects up to 24% of men and 9% of women, is characterized by repetitive upper airway obstruction, oxygen desaturation, and sleep fragmentation. In the long term, OSA predisposes to poor cardiovascular outcome, neurocognitive dysfunction, metabolic dysfunction, and increased risk of motor vehicle accidents.[1–6] Current evidence demonstrates that patients with OSA experience varying severities of obstruction depending upon body position. Of all patients who have OSA, up to 60% have a preponderance of respiratory events when sleeping supine[7,8]; for approximately 20% of patients, upper airway obstruction occurs exclusively in the supine position.[8,9] An obvious inference from the existence of positional dependence of OSA is that the pathophysiological causes of upper airway obstruction manifest themselves variably with body position.

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Recent evidence has suggested that OSA is not simply due to poor upper airway anatomy,[10,11] but has other pathophysiological causes including (1) inability of the pharyngeal muscles to hold open or stiffen the airway during sleep (i.e., impaired upper airway gain),[12,13] (2) oversensitive ventilatory control system (i.e., high loop gain),[14,15] (3) low respiratory arousal threshold,[16,17] and (4) low lung volume.[18,19] Surprisingly, the only studies to have investigated the impact of body position on OSA have focused on just one trait—passive upper airway anatomy/collapsibility. These studies, which measured the pharyngeal critical closing pressure (Pcrit), demonstrated a 2.2–2.9 cm H_2O increase in Pcrit (i.e., airway more collapsible) when adopting the supine sleeping position.[20–22]

The current literature fails to assess why 20% of OSA patients have resolution of obstructive events in lateral sleep. Consequently, the aim of the current study was two-fold. Firstly, in patients with severe OSA, we aimed to measure how sleeping position (i.e. lateral versus supine) affects: (i) V_{eupnea}: eupneic ventilatory demand, (ii) passive V_0: ventilation off CPAP (pressure = 0 cm H_2O) when the upper airway dilator muscles are quiescent, (iii) $V_{arousal}$: the ventilation at which respiratory arousals begin to occur, (iv) active V_0: ventilation off CPAP (pressure = 0 cm H_2O) when the upper airway dilator muscles are activated during sleep, (v) loop gain: assessed by the ratio of the ventilatory drive response to a disturbance

in ventilation, (vi) arousal threshold: the level of ventilatory drive at which a patient will arouse from sleep, (vii) upper airway gain (UAG) the ability of the upper airway muscles to activate and restore ventilation in response to increases in ventilatory drive, and (vii) functional residual capacity (FRC). Secondly, we aimed to assess the physiological characteristics that differentiate OSA patients who have a reduced apnea and hypopnea index (AHI) in the lateral sleeping position compared to other OSA patients with severe OSA regardless of sleep position. We prespecified the definition of supine OSA based on previously published data from our group.[23] Preliminary results of this analysis have been published in abstract form.[24]

METHODS

Institutional ethics approval was obtained from the Monash Health Human Research Ethics Committee. Patients with severe OSA (AHI > 30 events/h) were identified from a hospital database. To be included, patients were required to have recorded > 30 min supine and > 30 min non-supine NREM sleep on their diagnostic study. Patients were required to be using CPAP for > 2 months and to be adherent for > 4h/night in the 30 days prior to enrolment. Patients were randomly selected from the included list, given written informed consent to participate, and attended the Monash Sleep Centre for 2 overnight studies one week apart in order to measure the OSA traits (detailed below). Anthropomorphic and lung volume measurements were made prior to each overnight study. One overnight study was conducted with the subject in the supine position (with the head also supine). The other study was performed with the patient lying in the right lateral position with the head in the neutral position as comfort allowed. Patients were under continuous video monitoring and were repositioned if they moved from the prescribed position. The order of the position studied was randomized. We defined 2 groups of OSA patients for the purpose of this study based on our previously published work[23]: patients with a supine AHI to non-supine AHI ratio of > 4:1 on their diagnostic polysomnogram (PSG), whom we refer to as the supine OSA group, and patients with a supine AHI to non-supine AHI ratio of < 4:1, whom we refer to as the position-independent OSA group.

Anthropomorphic Measurements

Weight was measured with electronic scales (Seca 703, Hamburg, Germany) and height with a stadiometer (Seca 264, Hamburg, Germany) in order to determine body mass index (BMI). Circumferential measurements were carried out upright with the tape measure in a plane parallel to the ground, completely surrounding the body without compressing the subcutaneous tissues; the neck was measured just inferior to the cricoid cartilage, the chest at the level of the third intercostal space, the waist at the smallest girth between the iliac crest and the costal margin, and the hips at the level of the largest dimension over the buttocks.

Lung Volume

Awake measurements of FRC were performed 4 times in each of the seated, supine, and lateral positions (with the order of measurement randomized in each patient) using a nitrogen gas washout method,[25] with the average of the 4 measurements used subsequently. The full description of the method used can be found in section 1 of the supplemental material.

Overnight Phenotyping

On the study night, patients were instrumented for a standard clinical PSG montage with electroencephalogram, submental and leg electromyogram, electrocardiogram, arterial oxygen saturation, and CPAP mask pressure. Additional respiratory measurements were made using a pneumotachograph, capnograph, and an oxygen analyzer. Exhaled CO_2 (NICO Cardiopulmonary Management System, Respironics Novametrix, Wallingford, CT) and exhaled O_2 (Ametek S-3A/I, Ametek Process Instruments, Pittsburgh, PA) were sampled via a cannula inserted through a port into the CPAP mask and under constant 0.1 L/min suction. The CPAP mask was sealed and connected to a pneumotachograph (model 3700A, Hans Rudolph, Kansas City, MO) with a vent inserted in the circuit distal to the pneumotachograph (i.e., with the pneumotachograph closer to the CPAP mask and the vent closer to the pressure source). The circuit was connected to a positive/negative pressure source (Resmed, New South Wales, Australia) that was used to control the level of CPAP delivered and was capable of delivering +20 cm H_2O to −20 cm H_2O pressure. Sleep state and arousals were scored by an experienced sleep scientist in accordance with standard criteria.[26] The scientist was blinded to the respiratory measurements and the position state of the patient. All signals were recorded and displayed overnight using Compumedics Profusion PSG 3 (Compumedics, Abbotsford, Australia). Data were exported from Profusion PSG3 in the European Data Format (EDF) and analyzed in Spike2 (Cambridge Electronic Design, Cambridge, UK) and MatLab (Mathworks, Natick, MA).

The method for measuring the contributory mechanisms for OSA has been described in detail previously[27] and is summarized in Figure 1 (with subsequent numbering corresponding to the numbering in Figure 1). In brief, CPAP was altered during sleep to measure 4 different ventilations and loop gain. Ventilation was determined from flow on a breath-by-breath basis. Subsequent analysis involved averaging of these breaths as described below. The ventilation measurements included (i) V_{eupnea}: the eupneic ventilatory demand or the subject's asleep ventilatory requirement (which is determined by dead space ventilation and ventilatory requirement), (ii) passive V_0: ventilation off CPAP (pressure = 0 cm H_2O) when the upper airway dilator muscles are quiescent, (iii) $V_{arousal}$: the ventilation at which respiratory arousals begin to occur, and (iv) active V_0: ventilation off CPAP (pressure = 0 cm H_2O) when the upper airway dilator muscles are activated during sleep, (v) loop gain: assessed by the ratio of the ventilatory drive response to a disturbance in ventilation.

Initially, the CPAP pressure was increased to eliminate snoring and flow limited breathing to obtain the measurement of V_{eupnea} (i). Then the mask pressure was rapidly dialled down to 0 cm H_2O for 5 breaths to obtain a measurement for passive V_0 (ii). The CPAP was then returned to optimal pressure and subsequently decreased slowly according to the algorithm presented in section 2 of the supplemental material. The pressure was decreased to achieve flow-limited breathing and then to determine the level of ventilation at which arousals begin

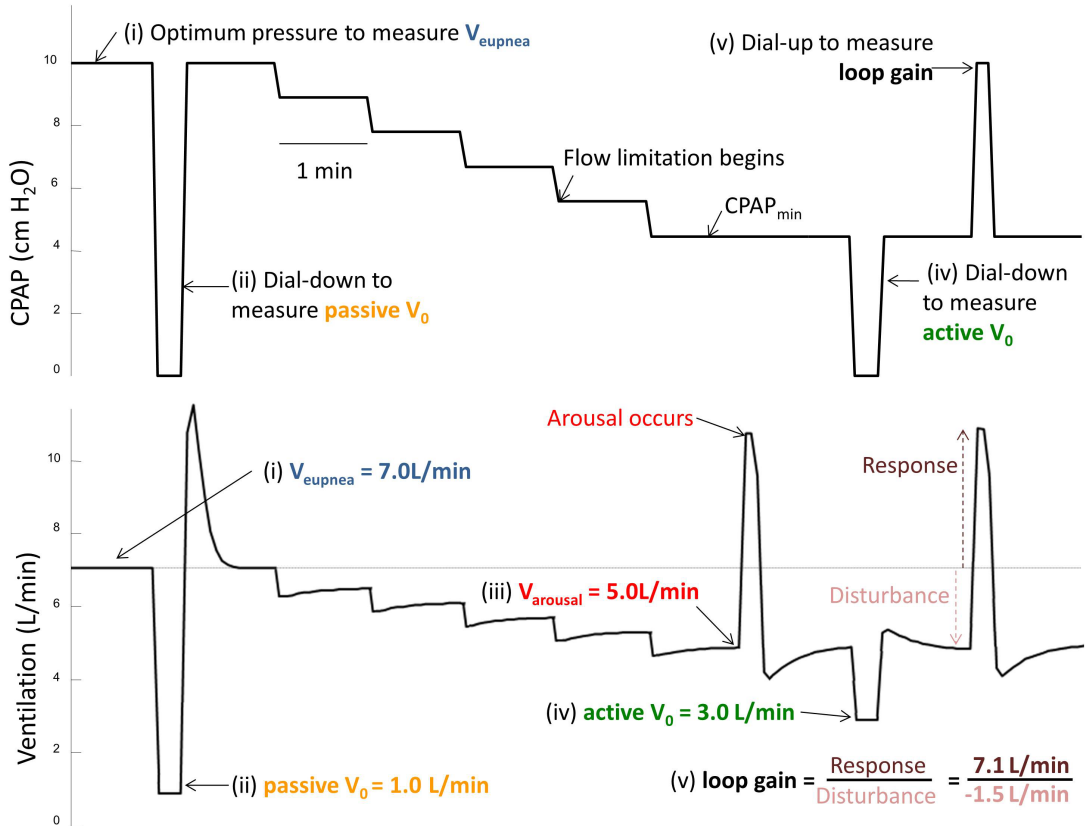

Figure 1—CPAP dial-down method for measuring phenotypic traits. **(i)** V_{eupnea}, ventilation at optimal CPAP with no evidence of snoring or flow limited breathing; **(ii)** passive V_0, ventilation at CPAP = 0 cm H_2O with completely relaxed pharyngeal muscles; **(iii)** $V_{arousal}$, the ventilation just prior to a respiratory-induced arousal; **(iv)** active V_0, ventilation at CPAP = 0 cm H_2O with maximally activated pharyngeal muscles; **(v)** loop gain, the ratio of ventilatory overshoot (response) above V_{eupnea} when returning to optimal CPAP pressure from a period of sub-optimal CPAP with reduced ventilation (disturbance).

to occur $V_{arousal}$ (iii). This level of pressure was termed the $CPAP_{min}$. At $CPAP_{min}$, during periods of relatively arousal-free breathing, a series of dial downs to 0 cm H_2O was performed to measure active V_0 (iv). An additional maneuver which involved a series of dial ups to the optimal CPAP level from the $CPAP_{min}$ was then performed in order to determine loop gain (v). If the patient experienced awakening (i.e., an increase in EEG activity > 15 sec) at any time such as at $CPAP_{min}$, during the slow decreases in CPAP or subsequent to a dial up or dial down from $CPAP_{min}$, the CPAP was returned to the optimal pressure, and once sleep was reinstated, the sequence was repeated. Several reduction sequences such as that demonstrated in Figure 1 were achieved across the night.

In order to model the interaction between the various traits to determine the predisposition to OSA, the 5 "ventilations": (i) V_{eupnea}, (ii) passive V_0, (iii) $V_{arousal}$, (iv) active V_0, and (v) loop gain; were plotted on a graph of ventilation (L/min) versus ventilatory drive (L/min). One advantage of this method is that it enables a normalization of the trait measurements to ventilatory drive. The graph also allows the calculation of (vi) arousal threshold, and (vii) upper airway gain (see Figure 2 with the sequential numbering matching that of Figure 1). First, V_{eupnea} was determined by averaging several minutes of ventilation on optimal CPAP, was plotted (Figure 2i and Figure 1i). The value was placed along the line of identity between ventilation and ventilatory drive, as it indicates that the patient's ventilatory demand is being fully met with the airway completely patent on optimal CPAP. Second, the passive V_0, which is the ventilation at CPAP = 0 cm H_2O when the upper airway muscles are passive, was plotted (Figure 2ii and Figure 1ii). This value was determined by averaging the ventilation of breaths 3 and 4 (without arousal) following a rapid dial down from optimal CPAP to 0 cm H_2O. Third, $V_{arousal}$, which is the ventilation that leads to a respiratory arousal, was plotted (Figure 2iii and Figure 1iii). This value was determined from the mean ventilation of the 5 breaths prior to a respiratory-induced arousal. Fourth, active V_0, which is the ventilation at CPAP = 0 cm H_2O when the pharyngeal muscles are active, was plotted (Figure 2iv and Figure 1iv). This value was determined by averaging the ventilation of breaths 3 and 4 following a dial down in CPAP pressure from $CPAP_{min}$ to 0 cm H_2O (if $CPAP_{min}$ is a negative pressure then the pressure is dialled "up" to 0 cm H_2O). Fifth, the reciprocal of loop gain line was plotted (Figure 2v and Figure 1v). The slope of the line was determined by calculating how much increased ventilatory drive (horizontal vector of the line) was created by a reduction in ventilation (vertical vector of line). That is, loop gain = response (increase or overshoot in ventilation above eupnea) ÷ disturbance (reduction in ventilation below eupnea)—in this case loop gain = 7.1L/min ÷ −1.5L/min = −4.7 (note that loop gain is dimensionless). The slope of the line plotted is 1/LG or in this case 1/−4.7.

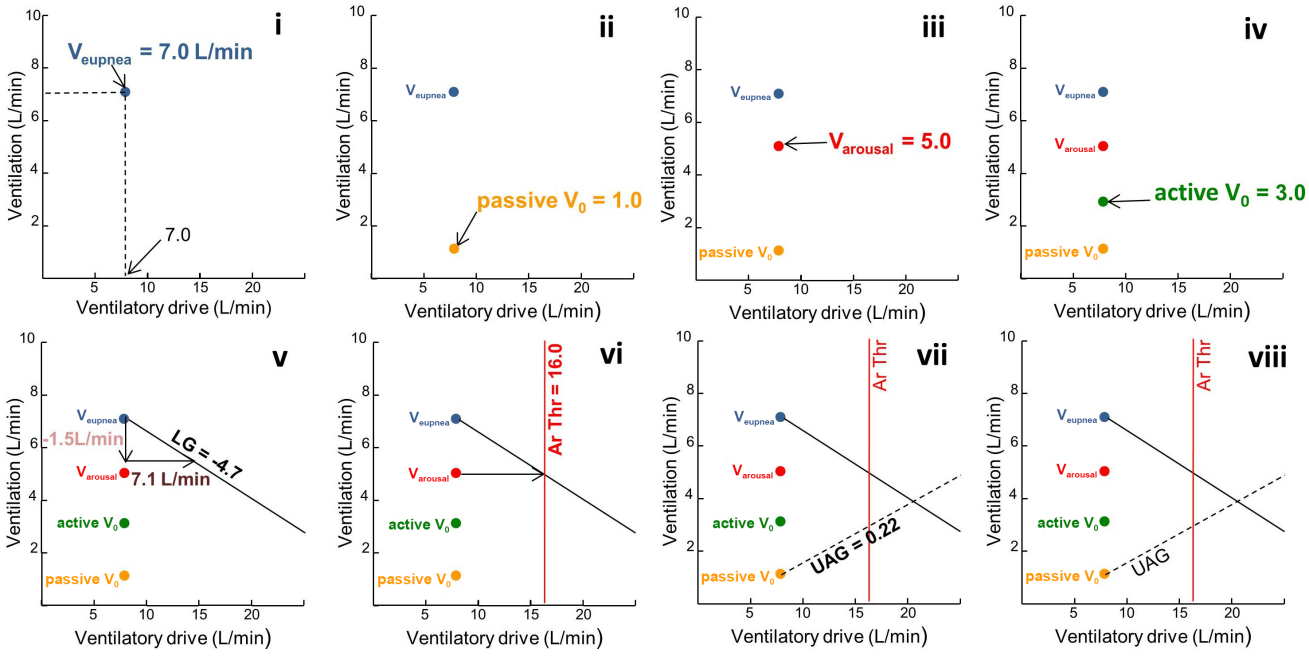

Figure 2—Plotting the phenotypic trait variables. Lower case roman numerals correspond with numbering in Figure 1.

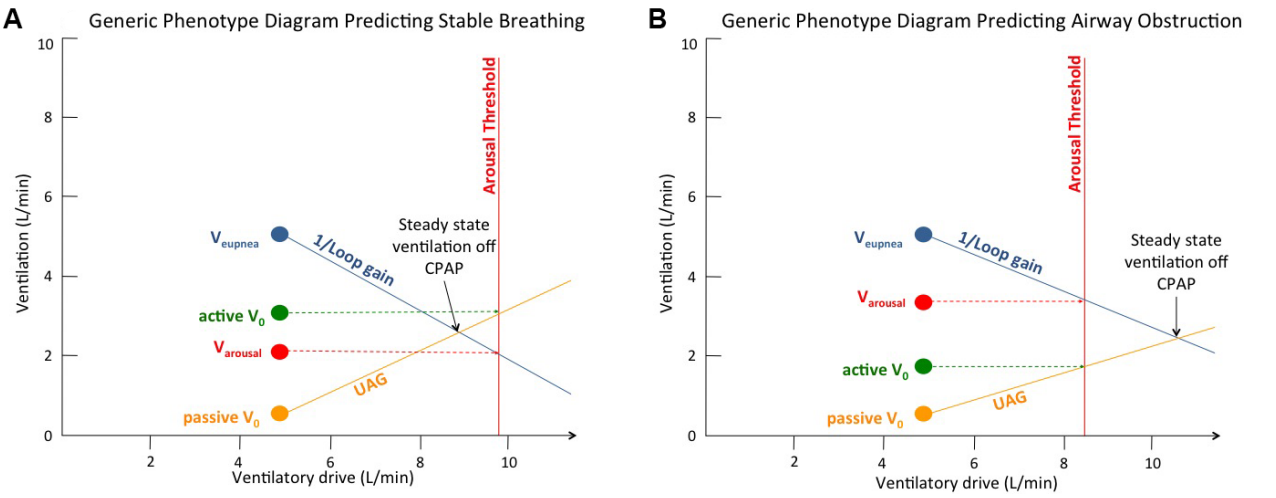

Figure 3—Generic phenotype diagram. **(A)** Model predicting stable breathing with loop gain line and UAG line intersecting to the left of the arousal threshold line. **(B)** Model predicting airway obstruction with the loop gain line and UAG line intersecting to the right of the arousal threshold line. UAG, upper airway gain.

Once the loop gain is known, the arousal threshold, which is the level of ventilatory drive at which a patient will arouse from sleep, could be determined from the intersection of a horizontal line through $V_{arousal}$ and the loop gain line (Figure 2vi). Lastly, the upper airway gain (UAG) was determined as follows (Figure 2vii): A horizontal line was drawn through the active V_0 and its intersection with the arousal threshold line. The passive V_0 point was then connected with this intersection point. The slope of this line is called the upper airway gain (UAG) (UAG = change in ventilation/change in ventilatory drive). The UAG represents the ability of the upper airway muscles to activate and restore ventilation in response to increases in ventilatory drive. Figure 2viii depicts visually how the traits interact and illustrates whether the combination predicts the presence or absence of OSA.[27] The generic phenotype diagram depicted in Figure 3 demonstrates how the model predicts airway obstruction. If a steady state ventilation off CPAP (determined by the intersection of the loop gain line and the upper airway gain line) is achieved below the arousal threshold (i.e., if the loop gain and UAG lines intersect to the left of the arousal threshold line [Figure 3A]), the patient will be able to achieve stable breathing, whereas if this intersection occurs to the right of the arousal threshold line (Figure 3B), the patient will experience a respiratory arousal, and thus OSA.

In addition to the measurements reported above, for consistency with previous data, we also measured the passive critical

Table 1—Patient demographics.

	All Patients (n = 20, 15M, 5F)	Supine OSA (n = 7)	Position-Independent OSA (n = 13)
Age (y)	54.9 ± 11.9	54.86 ± 14.90	54.85 ± 10.56
BMI (kg/m^2)	34.7 ± 6.3	32.63 ± 4.53	35.76 ± 7.01
Neck circumference (cm)	43.2 ± 3.1	42.29 ± 3.04	43.62 ± 3.07
Chest circumference (cm)	113.5 ± 8.6	108.57 ± 7.74	116.08 ± 8.03
Waist circumference (cm)	114.3 ± 13.8	108.43 ± 13.02	117.38 ± 13.58
Hip circumference (cm)	114.5 ± 14.0	109.29 ± 9.72	117.31 ± 15.50
AHI (events/h)	57.0 ± 23.8	48.54 (20.35)*	75.19 (50.14)*
Supine AHI (events/h)	69.9 ± 27.0	65.16 ± 21.91	72.38 ± 29.95
Non-supine AHI (events/h)	36.7 ± 31.9	4.52 (12.13)*,^	55.28 (47.82)*,^
Non-REM (events/h)	54.35 ± 24.31	42.57 ± 12.92	60.69 ± 20.99
REM AHI (events/h)	45.02 ± 27.88	22.05 ± 12.06^	57.39 ± 26.06^
Apnea index (events/h)	39.68 ± 26.07	23.99 ± 16.14°	48.12 ± 26.92°
Hypopnea index (events/h)	15.74 ± 8.92	18.40 ± 12.78	14.31 ± 6.16

*Values are nonparametric and are expressed as median (interquartile range). ^Significant difference between the supine OSA group and position-independent group with P < 0.01. °Significant difference between the supine OSA group and position independent group with P < 0.05. M, males; F, females; BMI, body mass index; AHI, apnea-hypopnea index; REM, rapid eye movement.

collapsing pressure or Pcrit.[28] In brief, while the patient was in NREM sleep receiving optimal CPAP, the mask pressure was rapidly reduced for 5 breaths before being returned to optimal CPAP. The reduction in mask pressure was performed in sequenced drops to a level of CPAP (positive or negative) that produced flow limitation. Each run of pressure drops included ≥ 3 drops that produced flow limitation. Peak inspiratory flow was taken from breaths 3–5 in a drop in which flow limitation was observed. The data points were plotted on a flow vs mask pressure graph and a linear regression line was plotted. The intersection of the regression line with the x-axis gives the Pcrit.

Statistics

Data were collated on an Excel spreadsheet (2010, Version 14.0.6129.5000, Microsoft Corporation) and analyzed using IBM SPSS 22 (2013, Release 22.0.0, IBM Corporation). Positional changes on the traits were analyzed using a paired t-test. Mean values between 2 groups (i.e., supine vs. position-independent OSA) were analyzed using an unpaired t-test. We examined both the absolute lung volumes and the positional lung volume expressed as a percentage of the seated lung volume in order to standardize the magnitude of change. All results are given as mean ± standard deviation unless otherwise stated. A P value < 0.05 was considered statistically significant.

RESULTS

The patient demographics are listed in Table 1. The mean value for each phenotypic trait measurement was compared from the supine night to the lateral night, with the results presented in Table 2 and Figure 4.

There was a similar number of phenotype measurements made in each condition. There was a significant increase when moving from supine to lateral in the passive V_0 and active V_0, and a significant decrease in Pcrit. The remaining traits (V_{eupnea}, $V_{arousal}$, loop gain, AT, and UAG) were unaltered by a change in position. The awake FRC was also significantly increased in the lateral position by a mean of 110 mL (8%). The model of the group data (Figure 4) demonstrated that although there was an increase in passive V_0 and active V_0, the loop gain line and UAG line still intersected to the right of the arousal threshold line when the patients lay in the lateral position. Therefore the model predicted that although lateral sleep increased both the passive anatomy (passive V_0, Pcrit) and the achievable ventilation once the upper airway muscles are activated (active V_0), it still did not resolve OSA as the intersection of the loop gain and UAG lines lies to the right of the arousal threshold line. Such a prediction is in line with the mean lateral AHI being 36.7 ± 31.9 events/h. The individual phenotype diagrams for each of the 20 patients are included in section 3 of the supplemental material.

We compared the phenotype trait values for patients who had supine OSA with those patients with position-independent OSA; the full results are listed in section 4 of the supplemental material.

Table 2—Phenotype values from supine to lateral.

	Supine	Lateral	Paired t-test
V_{eupnea} (L/min)	6.84 ± 0.86	6.95 ± 1.03	0.490
Passive V_0 (L/min)	0.33 ± 0.76	3.56 ± 2.94	< 0.001
$V_{arousal}$ (L/min)	5.47 ± 1.09	6.16 ± 1.37	0.074
Active V_0 (L/min)	1.10 ± 1.97	4.71 ± 3.08	< 0.001
Loop gain	−2.29 ± 1.13	−2.70 ± 1.85	0.288
AT (L/min)	9.72 ± 2.27	8.60 ± 3.00	0.075
UAG	0.24 ± 1.20	0.54 ± 2.71	0.510
Pcrit (cm H_2O)	2.02 ± 2.55	−1.92 ± 3.87	< 0.001
FRC (L)	1.31 ± 0.56	1.42 ± 0.62	0.046
Percent FRC (%)	79.25 ± 13.24	87.05 ± 18.01	0.011

AT, arousal threshold; UAG, upper airway gain; FRC, functional residual capacity; Pcrit, pharyngeal critical closing pressure; Percent FRC, the FRC expressed as a percentage of the seated value.

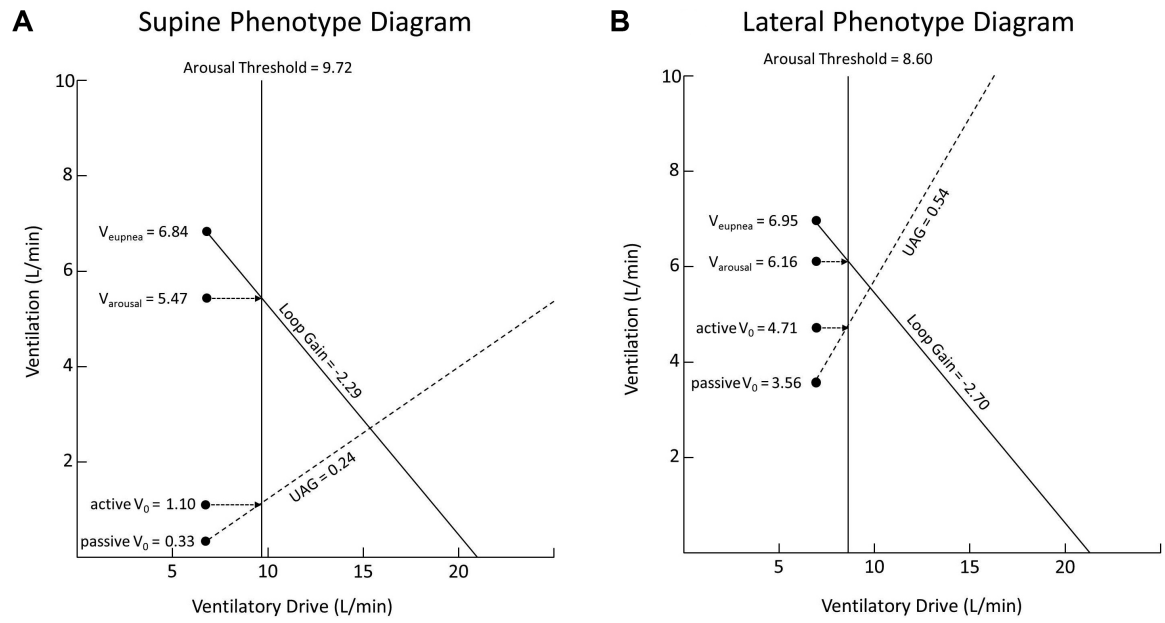

Figure 4—Summary phenotype diagrams for patients with severe OSA when moving from the supine sleeping position to the lateral sleeping position. UAG, upper airway gain.

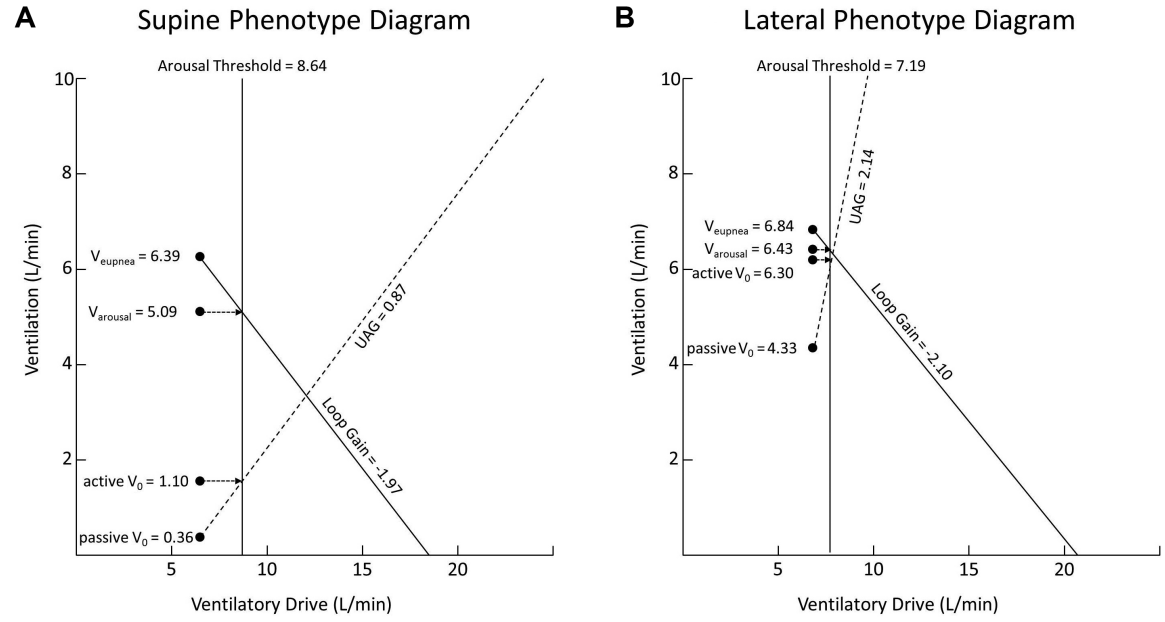

Figure 5—Phenotype diagrams for supine and lateral position in patients who have a supine to non-supine AHI ratio of > 4:1. UAG – upper airway gain.

There were 7 patients in the supine OSA group and 13 in the position-independent group. There were no significant differences in any of the anthropomorphic or demographic features between the 2 groups. The lateral UAG was significantly increased and the lateral Pcrit significantly decreased in the supine OSA group compared to the lateral UAG and Pcrit in the position-independent group (2.14 ± 2.53 vs −0.32 ± 2.48, P = 0.049 and −4.63 ± 3.33 cm H_2O vs −0.50 ± 3.40 cm H_2O, P = 0.02, respectively). There was also a strong trend to a significantly increased active V_0 in the lateral position in the supine OSA group compared to the position-independent group (6.30 ± 0.74 vs 3.85 ± 0.91, P = 0.052).

A within-group analysis of the supine OSA group demonstrated a significant improvement when moving from supine to lateral in passive V_0 (0.36 ± 0.94 L/min vs 4.33 ± 2.83 L/min, P = 0.007), active V_0 (1.56 ± 2.37 L/min vs 6.30 ± 0.74 L/min, P = 0.01), and Pcrit (3.00 ± 2.32 cm H_2O vs −4.63 ± 3.33 cm H_2O, P = 0.001). For patients with supine OSA, the increase in active V_0, passive V_0, and UAG brought the intersection of the loop gain line and UAG line very close to the arousal threshold

(Figure 5). This is in keeping with the known low lateral AHI in this group of patients of 4.52 events/h (reported with an interquartile range of 12.13, as these data were not normally distributed).

DISCUSSION

Our study demonstrates for the first time that when patients with severe OSA shift from the supine to lateral position, they experience a significant increase in awake FRC, passive V_0, and active V_0, and a significant decrease in Pcrit. On their own, these improvements are not large enough to prevent OSA in the lateral position in all patients because two other traits that predispose to OSA, loop gain and arousal threshold, are not altered by changes in body position. Furthermore, we demonstrate for the first time that the subgroup of OSA patients who have a supine predominant OSA (defined by a supine to non-supine AHI ratio of > 4:1) have significantly more favorable UAG and Pcrit, and a trend to significant improvement in active V_0 in the lateral position compared to other patients with OSA. This improvement is large enough to almost completely avert OSA in the lateral position in these patients. Our findings demonstrate that, in a subpopulation of OSA patients with supine OSA, the preservation of airway function in the lateral position arises from an ability to stiffen and dilate the airway more effectively (improved UAG and active V_0) than patients with position-independent OSA. Additionally, our findings suggest that patients with supine OSA exhibit a dynamic change in their collapsibility with positional changes. In a subset of patients who display a relatively less collapsible airway in the lateral position, we speculate that these individuals will be more likely to respond to therapies targeting the non-anatomical traits (i.e., loop gain and arousal threshold)—as those with position-independent OSA will need to have their anatomy altered before any non-anatomical therapy is likely to be of benefit.

The observed improvements in the passive and active V_0 observed in all patients in the lateral sleeping position likely result from a combination of: (1) a more effective airway dilatation in the lateral position, (2) improved caudal traction of the trachea secondary to improved lung volume, (3) the inherent folding qualities of the lateral pharyngeal walls, and (4) a change in the direction of gravity through upper airway structures.

The improvements observed in active V_0 in the lateral position indicate that the airway is able to stiffen or dilate more effectively in that position. In addition to the improvements of lateral positioning on passive characteristics of the airway listed above (i.e., improvement in passive V_0 and Pcrit), it may be that the function or effectiveness of pharyngeal dilator muscles is also improved in this position. Previous studies have demonstrated that the genioglossus muscle is at its most active when OSA patients and normal subjects lie in the supine sleeping position.[29,30] This is likely the result of the muscle having to work harder to overcome the unfavorable passive anatomy in the supine position (i.e., a higher Pcrit when supine). With the improvement in passive qualities and change in the direction of gravity through soft tissue structures it may be that the genioglossus has to work less to achieve greater stiffening and dilating in the lateral position. In our study, the subgroup of patients with supine-predominant OSA demonstrated a significant improvement in UAG and a trend towards a significant improvement ($P = 0.052$) in active V_0 in the lateral position, despite no significant differences in passive V_0. In this group of patients, the function of pharyngeal dilator muscles appears to be the main difference determining almost complete resolution of OSA in the lateral position.

In our patients, the awake FRC increased when they shifted from supine to lateral—an effect already reported[31] and shown to be associated with a reduced upper airway collapsibility that may result from an increase in caudal tracheal traction and reduced tissue pressures around the upper airway.[32–34] Whether the size of the volume change we observed (110 mL) is sufficient to explain an improved Pcrit of 3.9 cm H_2O (from 2.0 ± 2.5 cm H_2O supine to -1.9 ± 3.9 cm H_2O lateral) is questionable in view of earlier studies. For instance, Jordan et al. demonstrated that increasing end-expiratory lung volume by 500 mL improved the Pcrit from 2.2 ± 0.7 cm H_2O to -1.0 ± 0.5 cm H_2O. Of note, the improvement in Pcrit observed in our study of −3.9 cm H_2O in the lateral position is larger than that observed in previous studies (2.2–2.9 cm H_2O).[20–22] The most likely explanation for the larger Pcrit improvement observed in lateral sleep compared to previous reports is that the proportion of supine-related OSA patients in our cohort (7/20) is greater than in other cohorts of severe OSA patients.[9] A larger proportion of patients with supine-related OSA will bias the results to a greater improvement in Pcrit in the lateral position compared to previous studies.

The folding characteristics of the lateral pharyngeal airway may also play an important role in determining collapse in the supine sleeping position. With the airway adopting a laterally oriented ellipsoid shape with the patient supine,[35] collapse is most likely to occur initially at the lateral walls before propagating medially.[36,37] Modeling of the human airway, using both physical[38] and mathematical[39] models, indicates that the folding geometry of the lateral airway is critically important in determining collapsibility of the airway. When a patient with OSA lies in the lateral position, there is an opening up of the lateral portions of the airway, so that the overall shape of the velopharynx becomes more circular.[35] Coupled with a change in the direction of gravity through the upper airway soft tissues, the altered geometry of the lateral airway when the patient lies in the lateral position may explain part of the improvement seen in passive V_0 in that position.

When lying in the supine position, the bulk of the soft tissue structures such as the tongue and soft palate lie anterior to the velopharyngeal airway.[40] In this position, gravitational pull favors posterior collapse of the bulky soft tissue structures. With the patient lying in the lateral position, the tongue and soft palate now lie perpendicular to the gravitational pull (i.e., they now constitute the lateral wall of a 90° rotated airway). It is now the smaller volume of soft tissue that constitutes the lateral pharyngeal wall that lies in the anterior position, resulting in an airway that is less likely to collapse when passive and in the lateral position.[40]

Implication for an Alternative to CPAP Treatment of OSA

A number of strategies may be employed to prevent patients with OSA from sleeping in the supine position.[41] In certain

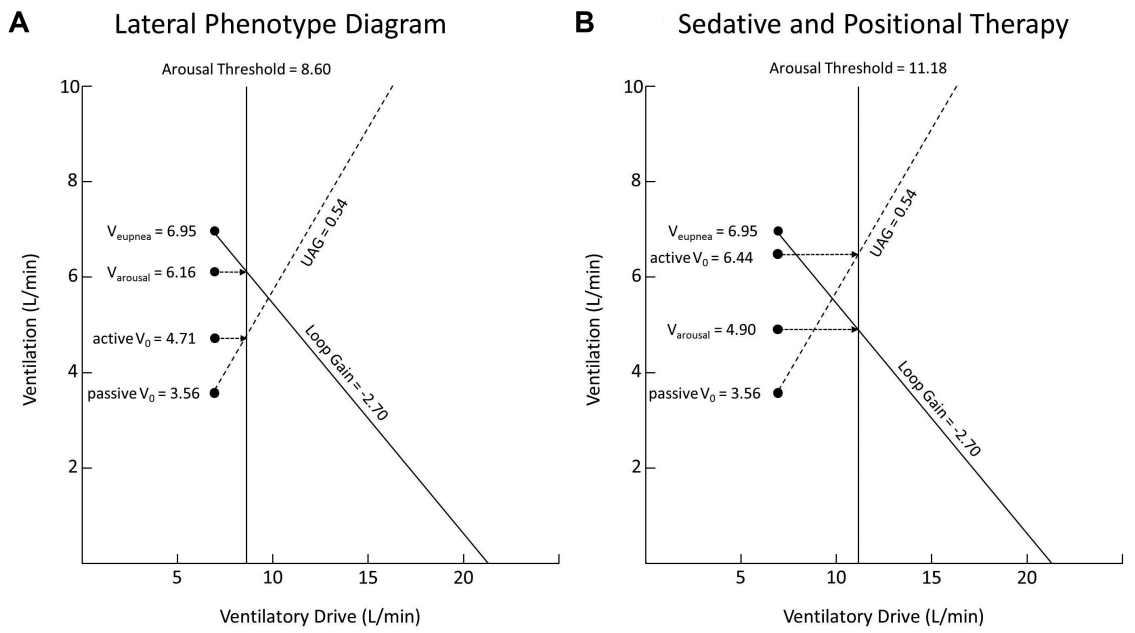

Figure 6—(A) Data of the 20 patients in our study in the lateral position. **(B)** Predicted effect of combination therapy with lateral positioning and non-muscle relaxant sedative to improve arousal threshold.

patients, where the lateral AHI is low from night to night, and the propensity for supine airway collapse is repeatable,[23] positional therapy could normalize the AHI.[42] Our study demonstrates why positional therapy does not work for all OSA patients. Only some patients improve their active (active V_0) and passive (passive V_0 and Pcrit) anatomy sufficiently when moving to the lateral position, particularly when considering the interaction between airway anatomy and the other physiological traits predisposing to OSA. We show for the first time that arousal threshold and loop gain are not significantly affected by moving to the lateral position and continue to predispose the airway to collapse.

Several studies have addressed the contribution of a high loop gain and low arousal threshold to OSA severity.[43–45] From these studies, it has been estimated that a low arousal threshold contributes to OSA in up to 50% of patients with the disease,[46] and that the administration of a non-muscle relaxant sedative can elevate the arousal threshold by 28% to 48%.[44,47] In addition, the administration of acetazolamide reduces the loop gain in OSA sufferers by 41% without altering any of the other pathophysiological traits measured.[45] Altering these traits has been shown to lead to a partial improvement in OSA.

Given that lateral sleep improves passive V_0 and active V_0 but not loop gain or arousal threshold, we considered the effect combining these treatments would have on patients with OSA (i.e., the effect of lateral positioning combined with treatment of loop gain or arousal threshold). By using our data demonstrating the phenotypic trait values of all 20 patients when lying in the lateral position (see Figure 6A, copied from Figure 4B above) and applying an improvement in arousal threshold of 30% (from previously published data) to our data, we can demonstrate that the model now predicts complete resolution of obstructive events (see Figure 6B). That is, in Figure 6A the model predicts obstructive events with the loop gain line and UAG line intersecting to the right of the arousal threshold line, while in Figure 6B, with the improvement in arousal threshold applied, the model predicts stable breathing with the loop gain line and arousal threshold line intersecting to the left of the arousal threshold line. By contrast, an improvement in loop gain of 40% applied on its own is not enough to resolve obstructive events (Figure 7). Figure 7A is the data from our 20 patients in the lateral position (again, copied from Figure 4B above), with the model predicting obstructive events. In this instance, the model still predicts obstructive events despite the applied improvement in loop gain (see Figure 7B where the loop gain line and UAG line still intersect to the right of the arousal threshold line).

This analysis suggests that the potential combination of positional modification and non-muscle relaxant sedatives as an alternative to CPAP therapy in severe OSA sufferers is a fruitful strategy for further investigation.

Limitations

The first limitation of our study is that it included only a small cohort of patients, all of whom had severe OSA, limiting its applicability to the OSA population as a whole, particularly patients of varying OSA severity.

For technical reasons, we limited our measurements of the pathophysiological traits to NREM sleep. The interaction of the variables measured in REM sleep and the effect of lateral position on the variables has not been demonstrated, although we know from previous studies that positional effects on the AHI do occur in REM sleep.[22,48]

The lung volume measurements we made were during wakefulness. Measurements of both supine and lateral lung volumes have not been made during sleep in individuals with OSA, and no studies have compared these values with awake values in the same postures. We therefore cannot be certain of how our

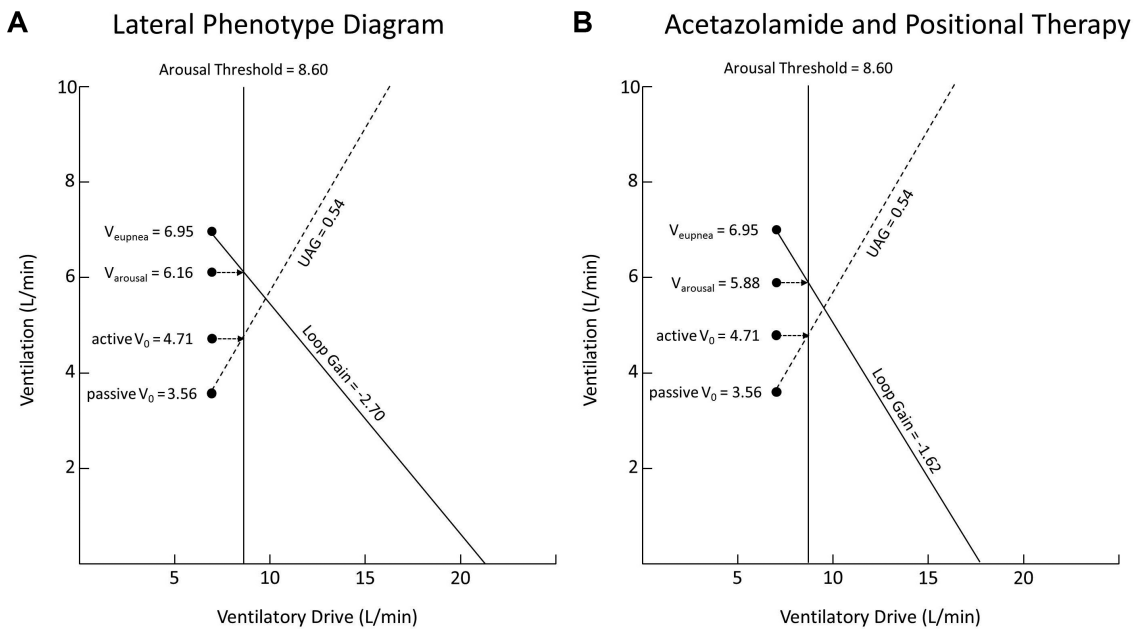

Figure 7—(A) Data of the 20 patients in our study in the lateral position. **(B)** Predicted effect of combination therapy with lateral positioning and acetazolamide treatment of ventilatory control instability (loop gain).

awake measurements of FRC relate to the actual FRC during sleep, and this is a limitation of the data presented.

CONCLUSION

We have demonstrated for the first time that patients with severe OSA who move from the supine to lateral position have a significant improvement in awake FRC, passive upper airway collapsibility (passive V_0 and Pcrit), and the ability of the airway to dilate and stiffen (active V_0), but there is no significant change in the respiratory arousal threshold or loop gain. In a subgroup of OSA patients with supine OSA (a supine to non-supine AHI ratio > 4:1), the improvement in OSA in the lateral position appears to be the result of an improvement in the ability of the airway to stiffen and dilate in that position, possibly as a function of more effective pharyngeal dilation in that position (i.e., improved UAG and trend to significant improvement in active V_0). Our data suggest that, although positional therapy alone will not resolve obstruction in the majority of patients with severe OSA, it could be combined with treatments that improve arousal threshold and loop gain as an alternative to CPAP in patients with severe OSA.

DISCLOSURE STATEMENT

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Section 1: Description of Method for Lung Volume Nitrogen Gas Washout Method

The patient's head and neck position were controlled in the supine and lateral position using a series of pillows. Briefly, patients breathed through a mouthpiece that facilitated the measurement of ventilation and carbon dioxide (CO_2) (NICO Cardiopulmonary Management System) and oxygen (O_2) (Ametek S-3A/I, Ametek Process Instruments, Pittsburgh, PA). Fractional expired nitrogen was calculated from the fractional expired O_2 and CO_2 levels (expired FN_2 = 1- expired FO_2- expired FCO_2). Once patients were acclimatized (~2–3 min) to the breathing circuit, we switched the inspired gas from room air (79% nitrogen, N_2) to 100% O_2 (0% N_2), facilitated by a low resistance non-rebreathing valve (Medium T shape 2-Way NRBV, Hans-Rudolph, Kansas City, MO). When a steady-state expired FN_2 was achieved, participants were switched back to room air ("wash-in" phase) until a steady state was reached (constant FiN_2 within 1.5% between breaths, ~5–7 min). The time course of the rise in N_2 was used to measure FRC according to the equation $FRC = \Delta VolN_2/\Delta FN_2$; where $\Delta VolN_2$ is the change in alveolar N_2 volume from the start to end of the test (area under the curve of expired FN_2 versus cumulative expired volume), and ΔFN_2 is the change in alveolar N_2 concentration during this time (final FN_2 − initial FN_2). The "wash-in" phase of the test, rather than the "washout" phase, was used to avoid the transient reduction in ventilation that can occur with a rapid rise in PO_2 at the onset of the washout.

Section 2: Algorithm For Performing CPAP Dial-Down

In order to model the interaction between the various traits to determine the predisposition to OSA, the five "ventilations" (V_{eupnea}, passive V_0, $V_{arousal}$, active V_0, and ventilatory response/ventilatory disturbance) are plotted on a graph of ventilation versus ventilatory drive. This graph also allows the calculation of the arousal threshold and the responsiveness of the upper airway muscles (Figure 2-main manuscript). First, V_{eupnea}, which is the subject's asleep ventilatory requirement, determined by averaging several minutes of ventilation on optimal CPAP, is plotted (Figure 2i and Figure 1i-main manuscript). The value is placed along the line of identity between ventilation and ventilatory drive as it indicates that the patient's ventilatory demand is being fully met with the airway totally patent on optimal CPAP. Second, the passive V_0, which is the ventilation at CPAP = 0 cm H_2O when the upper airway muscles are passive, is plotted (Figure 2ii and Figure 1ii-main manuscript). This value is determined by averaging the ventilation of breaths 3 and 4 (without arousal) following a rapid dial down from optimal CPAP to 0 cm H_2O. Third, $V_{arousal}$, which is the ventilation that leads to a respiratory arousal is plotted (Figure 2iii and Figure 1iii-main manuscript). This value is determined from the mean ventilation of the 5 breaths prior to a respiratory-induced arousal. Fourth, active V_0, which is the ventilation at CPAP = 0 cm H_2O when the pharyngeal muscles are active, is plotted (Figure 2iv and Figure 1iv-main manuscript). This value is determined by averaging the ventilation of breaths 3 and 4 following a dial down in CPAP pressure from $CPAP_{min}$ to 0 cm H_2O (if $CPAP_{min}$ is a negative pressure then the pressure is dialled "up" to 0 cm H_2O). Fifth, the reciprocal of loop gain line is plotted (Figure 2v and Figure 1v-main manuscript). The slope of the line is determined by calculating how much increased ventilatory drive (horizontal vector of the line) is created by a reduction in ventilation (vertical vector of line). That is, loop gain = response (increase or overshoot in ventilation above eupnea) ÷ disturbance (reduction in ventilation below eupnea), in this case loop gain = 7.1 L/min ÷ −1.5 L/min = −4.7 (note that loop gain is dimensionless). The slope of the line plotted is 1/LG or in this case 1/−4.7.

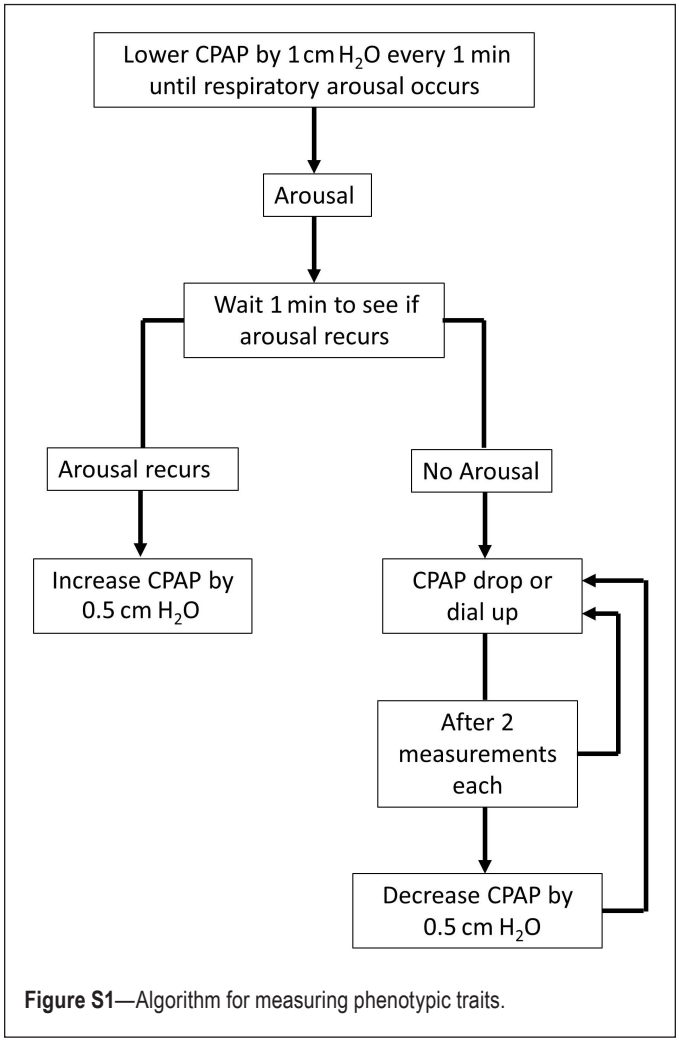

Figure S1—Algorithm for measuring phenotypic traits.

Once the loop gain is known, the arousal threshold, which is the level of ventilatory drive at which a patient will arouse from sleep, can now be determined from the intersection of a horizontal line through $V_{arousal}$ and the loop gain line (Figure 2vi-main manuscript). Lastly, the upper airway gain (UAG) can be determined as follows (Figure 2vii-main manuscript): a horizontal line is drawn through the active V_0 and its intersection with the arousal threshold line. The passive V_0 point is then connected with this intersection point. The slope of this line is called the UAG (UAG = change in ventilation/change

in ventilatory drive). The UAG represents the ability of the upper airway muscles to activate and restore ventilation in response to increases in ventilatory drive. Figure 2viii (main manuscript) depicts visually how the traits interact. The model is able to predict OSA in that if a steady state ventilation off CPAP (determined by the intersection of the loop gain line and the upper airway gain line) is achieved below the arousal threshold (if the LG and UAG lines intersect to the left of the arousal threshold line) then the patient will be able to achieve stable breathing, whereas if this intersection occurs to the right of the arousal threshold line, the patient will experience a respiratory arousal, and thus OSA.

Section 3: Individual Phenotype Diagrams

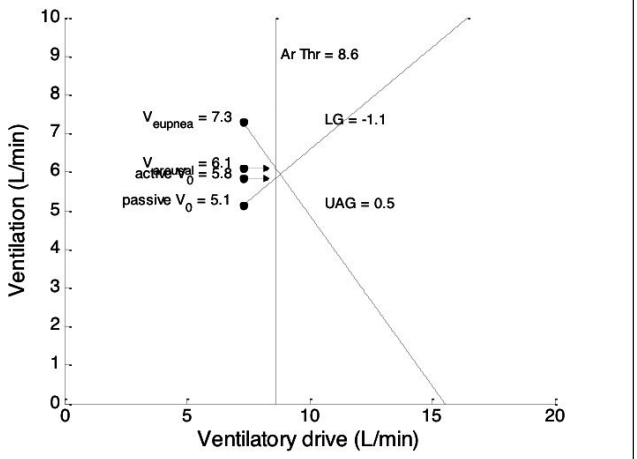

Figure S2—Lateral 1.

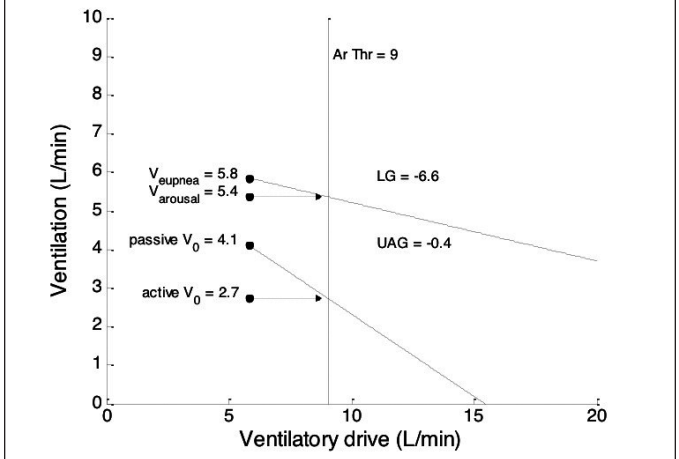

Figure S4—Lateral 2.

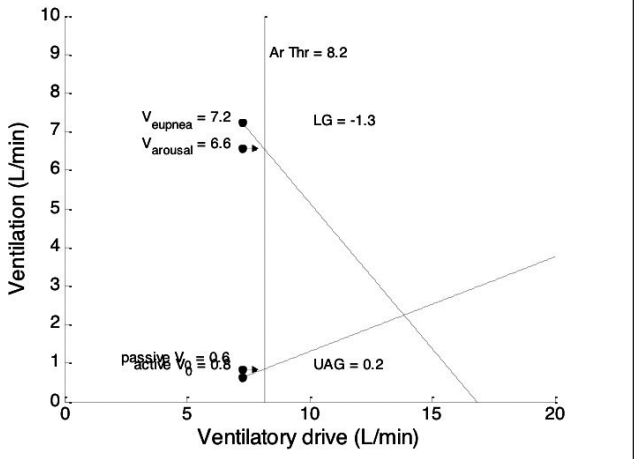

Figure S3—Supine 1.

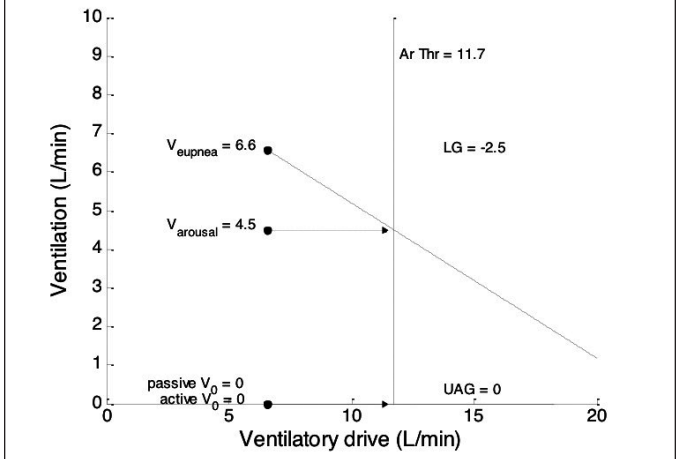

Figure S5—Supine 2.

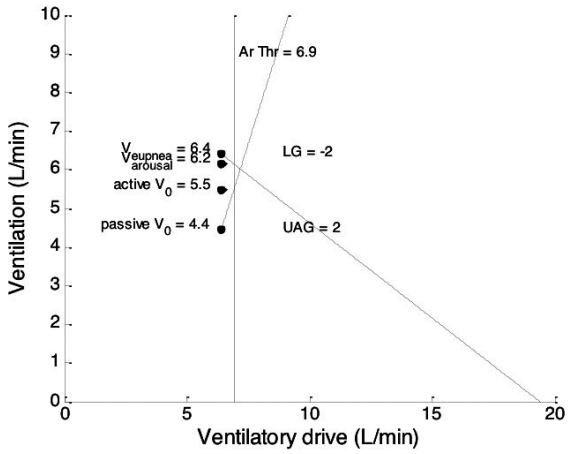

Figure S6—Lateral 3.

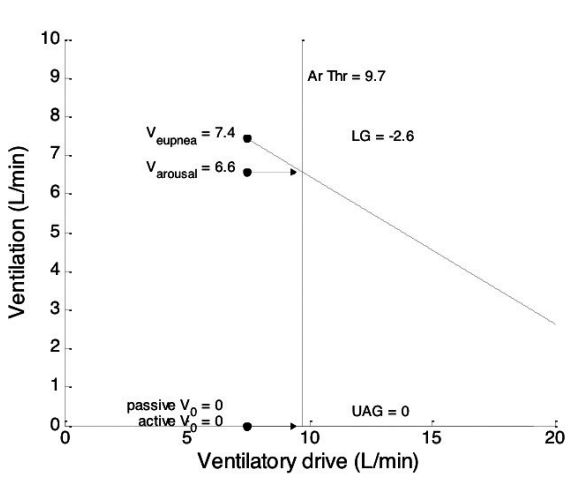

Figure S7—Supine 3.

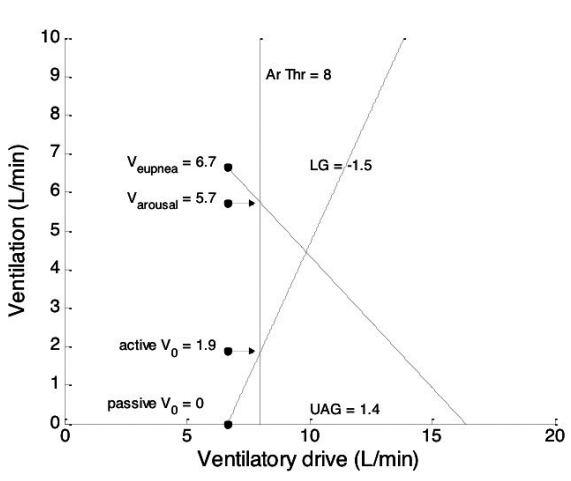

Figure S8—Lateral 4.

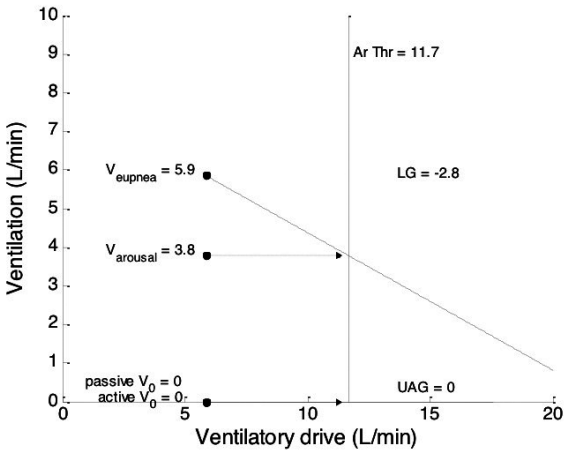

Figure S9—Supine 4.

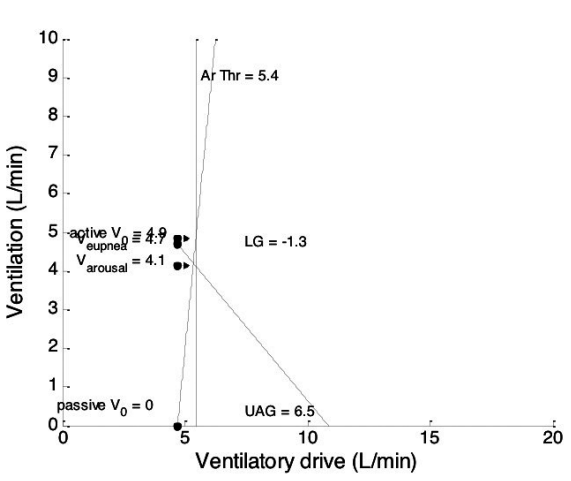

Figure S10—Lateral 5.

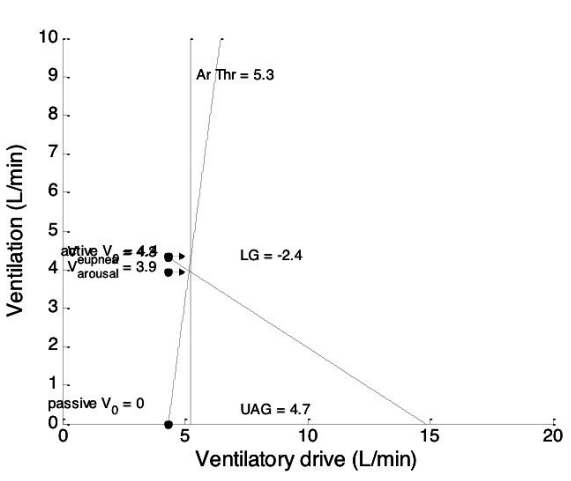

Figure S11—Supine 5.

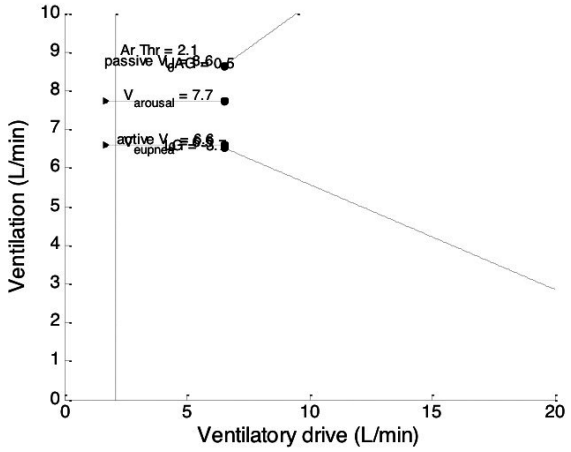

Figure S12—Lateral 6.

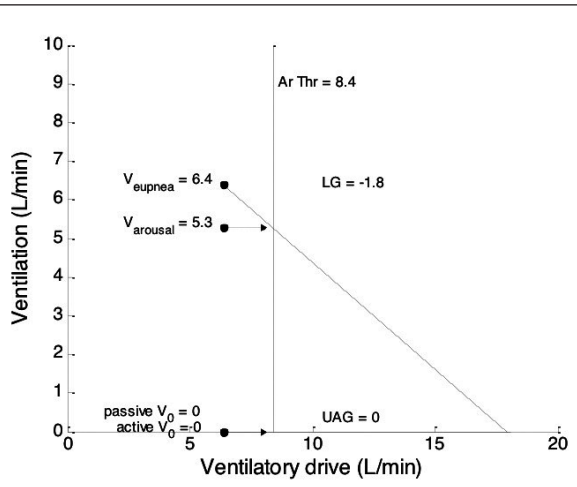

Figure S13—Supine 6.

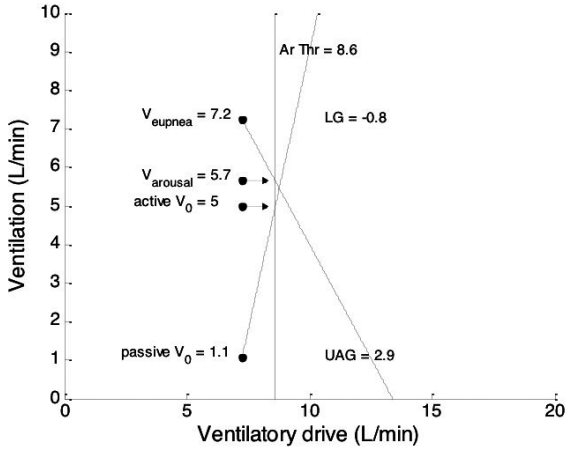

Figure S14—Lateral 7.

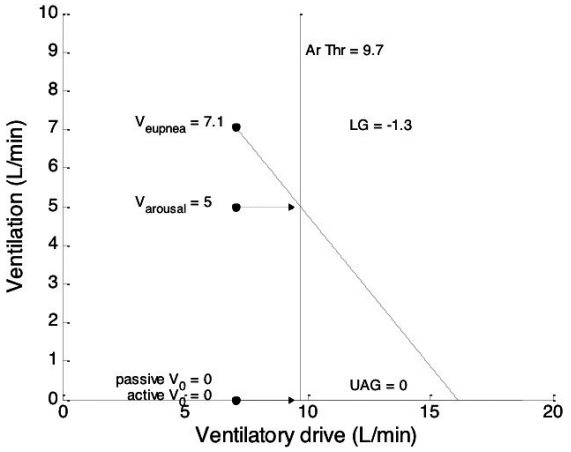

Figure S15—Supine 7.

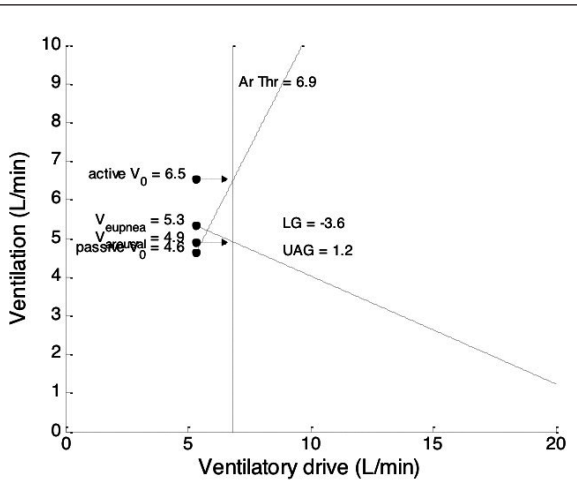

Figure S16—Lateral 8.

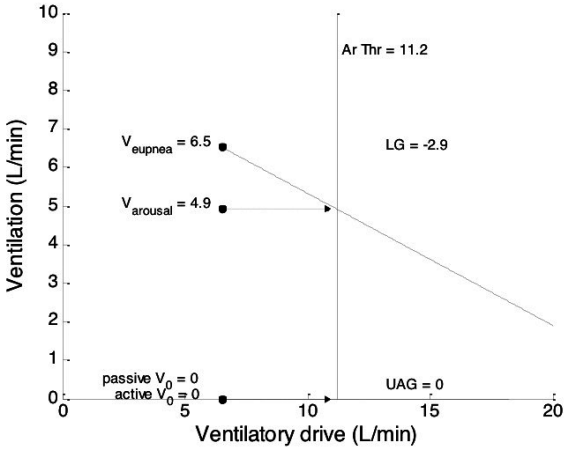

Figure S17—Supine 8.

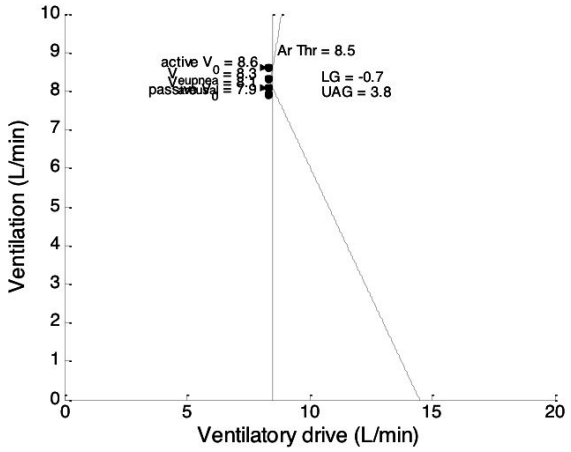

Figure S18—Lateral 9.

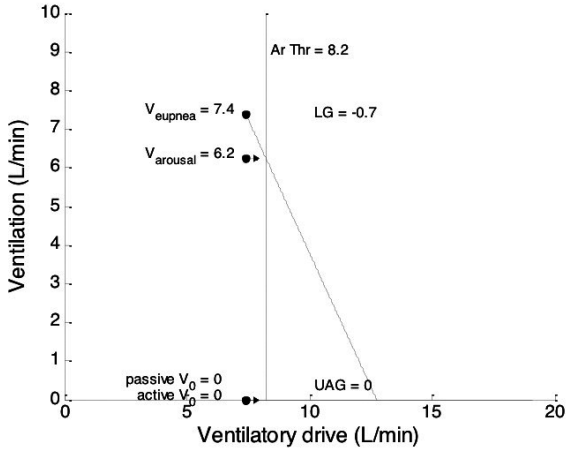

Figure S19—Supine 9.

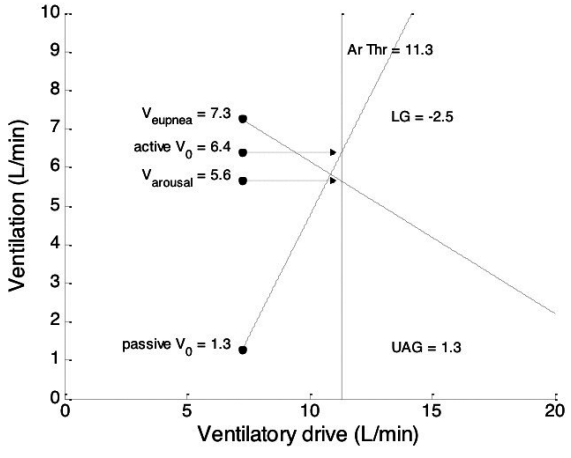

Figure S20—Lateral 10.

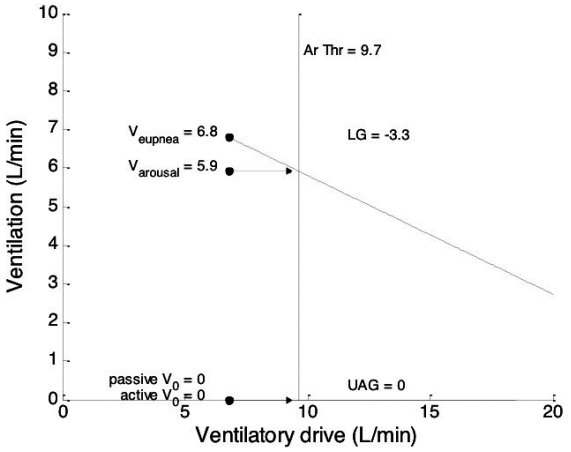

Figure S21—Supine 10.

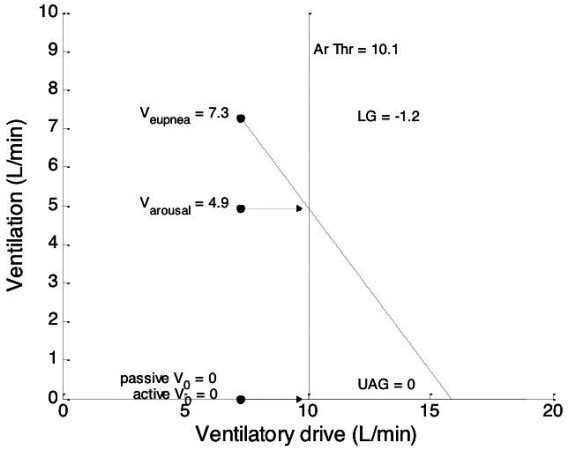

Figure S22—Lateral 11.

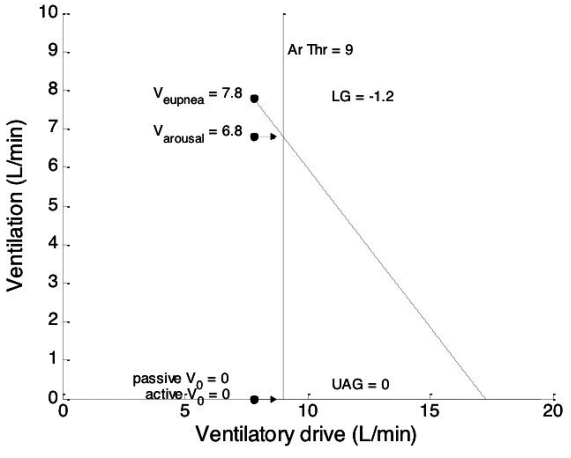

Figure S23—Supine 11.

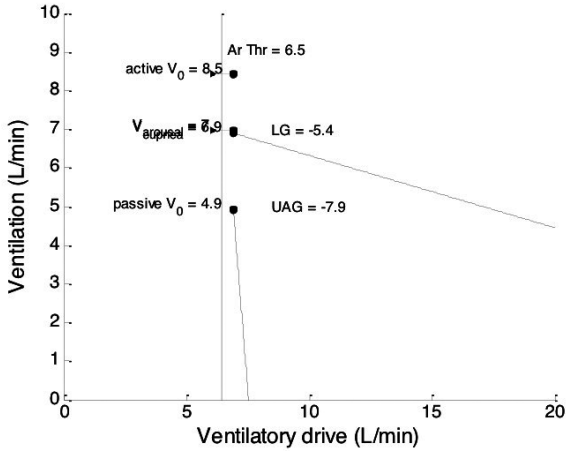

Figure S24—Lateral 12.

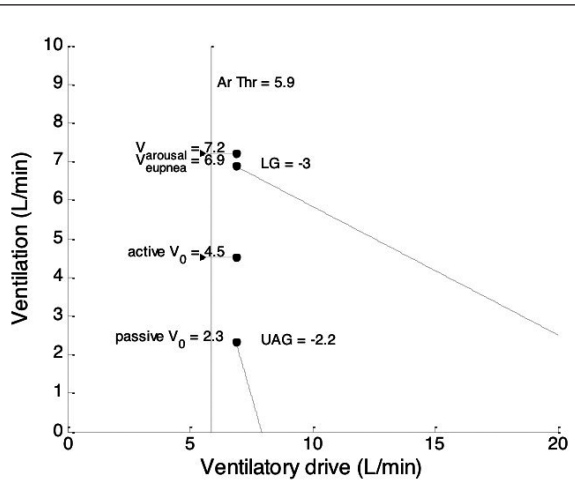

Figure S25—Supine 12.

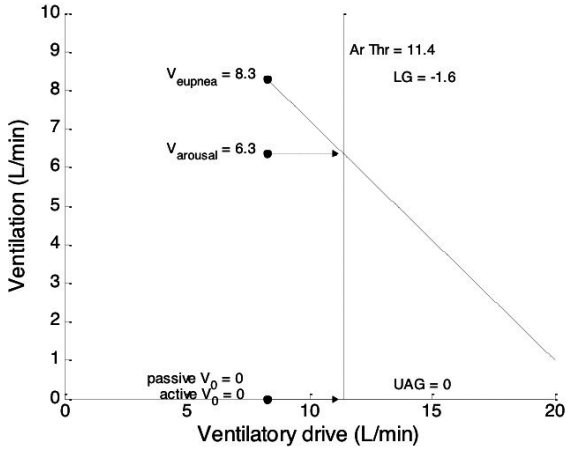

Figure S26—Lateral 13.

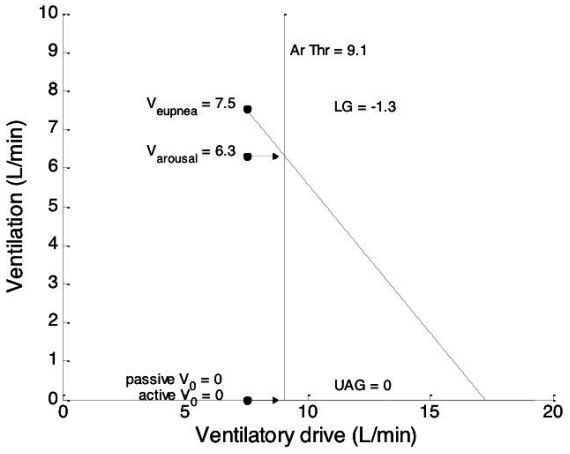

Figure S27—Supine 13.

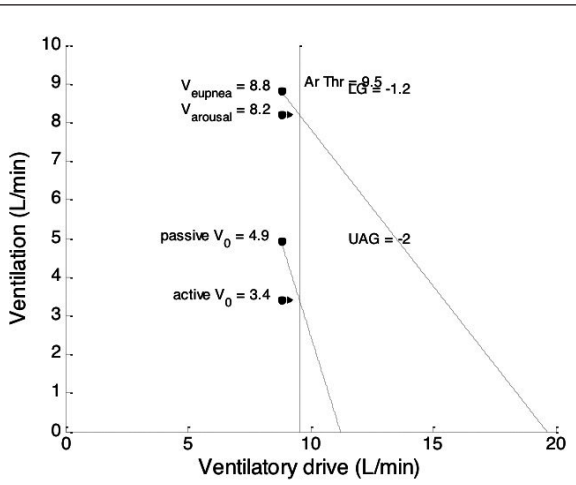

Figure S28—Lateral 14.

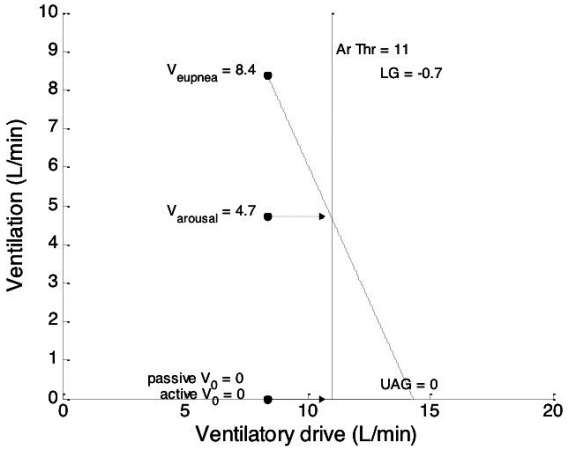

Figure S29—Supine 14.

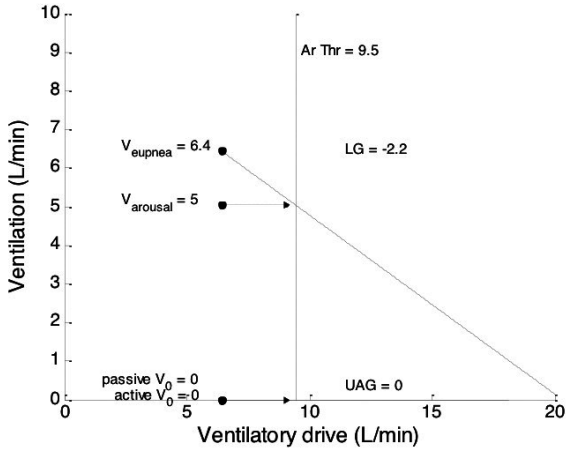

Figure S30—Lateral 15.

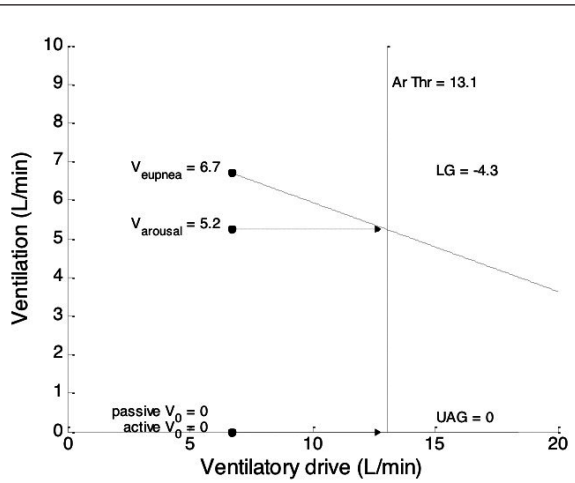

Figure S31—Supine 15.

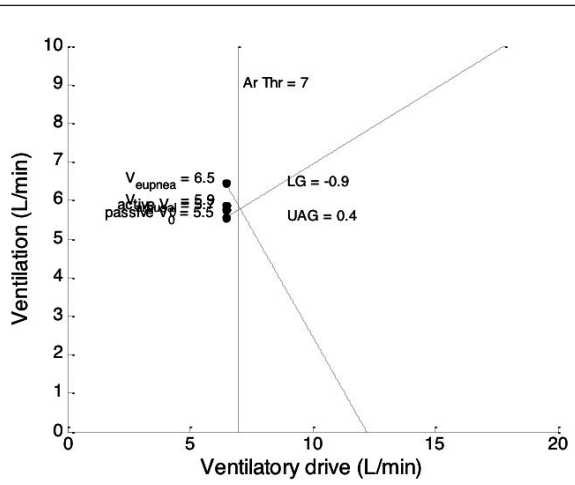

Figure S32—Lateral 16.

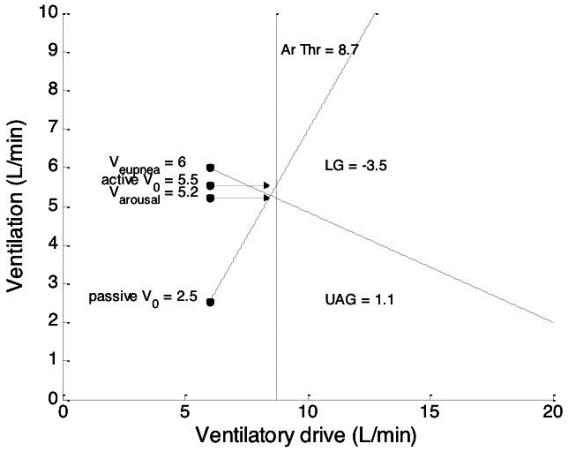

Figure S33—Supine 16.

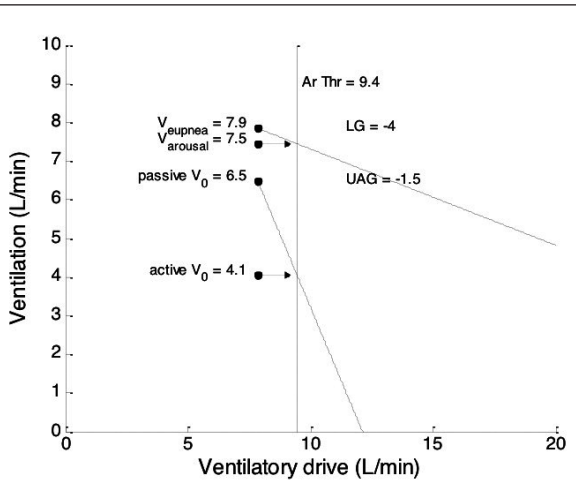

Figure S34—Lateral 17.

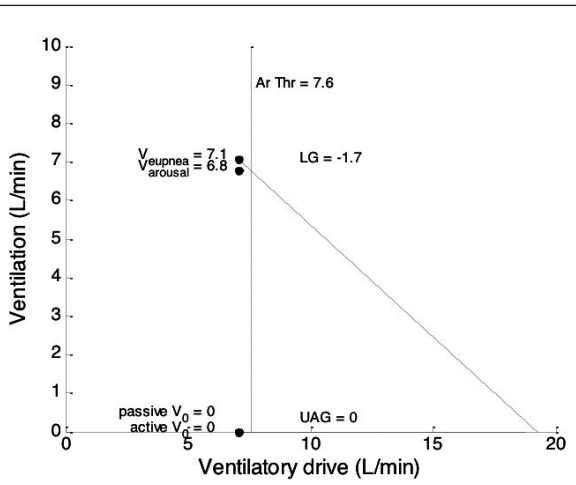

Figure S35—Supine 17.

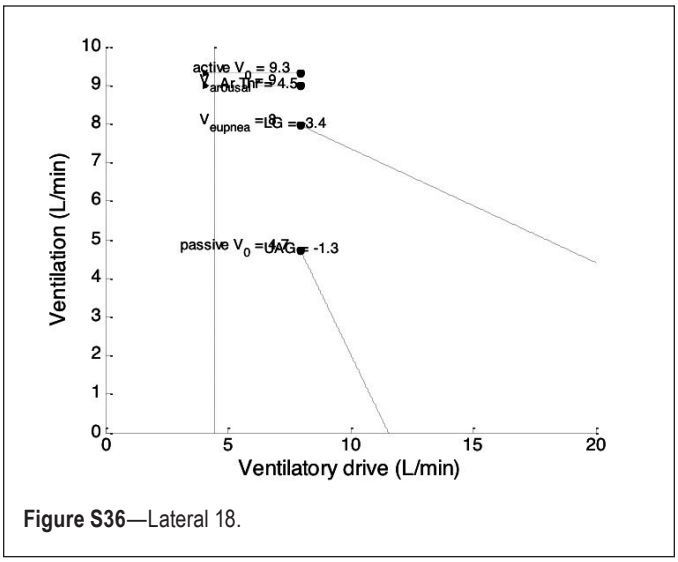

Figure S36—Lateral 18.

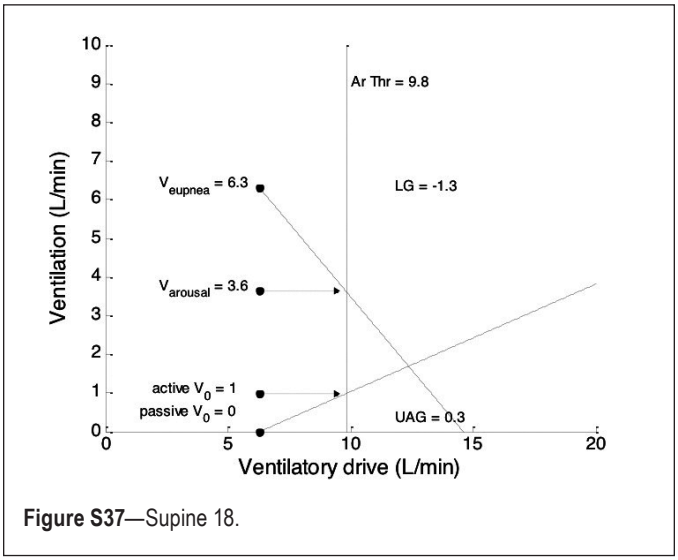

Figure S37—Supine 18.

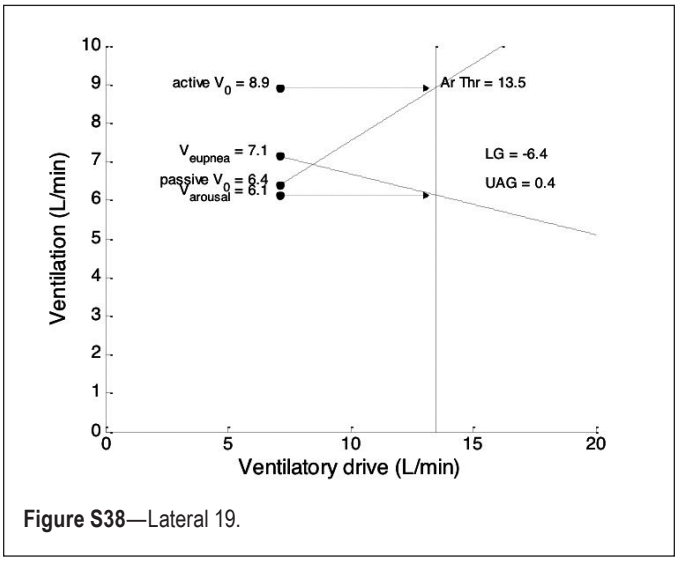

Figure S38—Lateral 19.

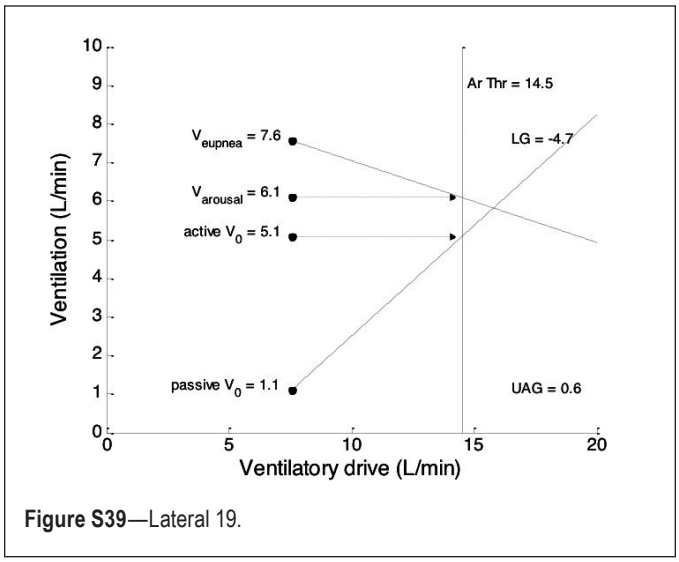

Figure S39—Lateral 19.

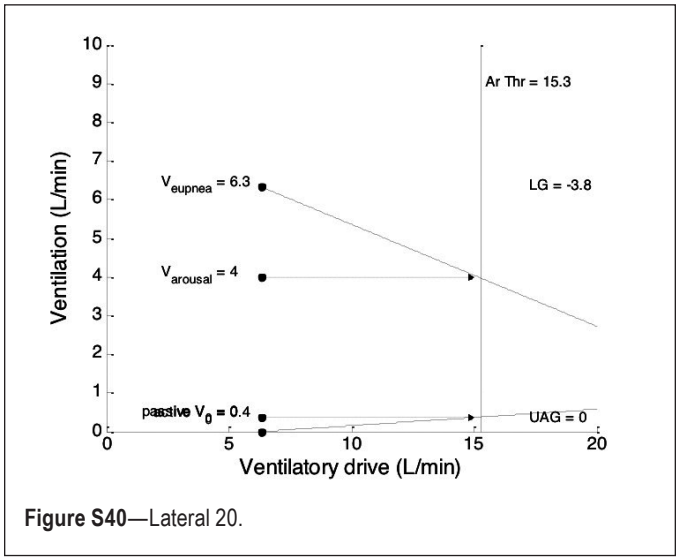

Figure S40—Lateral 20.

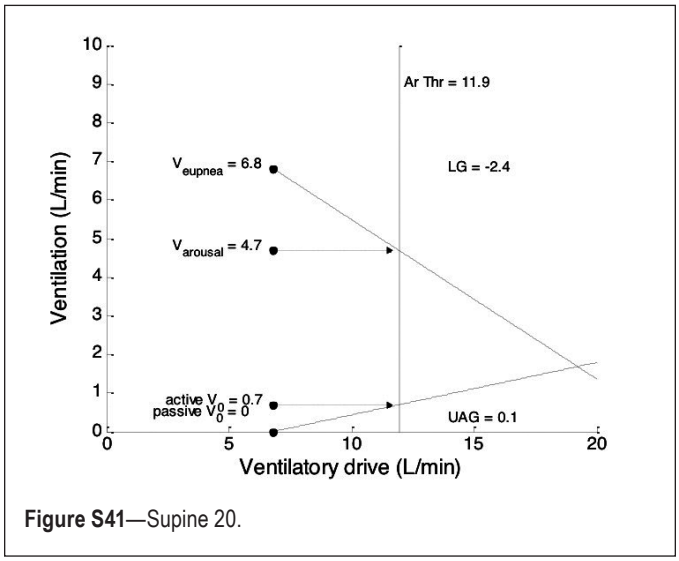

Figure S41—Supine 20.

Section 4: Comparison of Supine OSA Group and Position-Independent OSA Groups

Table S1—Comparison of patients with supine to non-supine AHI ratio of > 4:1 to all other patients.

	Supine OSA (n = 7)		Position-Independent OSA (n = 13)		P value (unpaired t-test)	
Phenotype Traits	**Supine**	**Lateral**	**Supine**	**Lateral**	**Supine vs Supine**	**Lateral vs Lateral**
V_{eupnea} (L/min)	6.39 ± 1.05	6.84 ± 1.40	7.08 ± 0.66	7.01 ± 0.83	0.09	0.743
Passive V_0 (L/min)	0.36 ± 0.94†	4.33 ± 2.83†	0.31 ± 0.68‡	3.14 ± 3.02‡	0.89	0.403
$V_{arousal}$ (L/min)	5.09 ± 1.14	6.43 ± 1.80	5.67 ± 1.04	6.02 ± 1.14	0.26	0.536
AT(L/min)	8.64 ± 1.89	7.19 ± 1.79	10.30 ± 2.30	9.36 ± 3.30	0.12	0.125
Active V_0 (L/min)	1.56 ± 2.37†	6.30 ± 0.74†	0.85 ± 1.78‡	3.85 ± 0.91‡	0.46	0.052
Loop gain	−1.97 ± 1.00	−2.10 ± 1.49	−2.45 ± 1.20	−3.02 ± 1.99	0.38	0.302
UAG	0.87 ± 0.66	2.14 ± 2.53	−0.10 ± 0.18	−0.32 ± 2.48	0.20	0.049
Pcrit (cm H_2O)	3.00 ± 2.32†	−4.63 ± 3.33†	1.49 ± 2.60‡	−0.50 ± 3.40‡	0.22	0.020
FRC (L)	1.16 ± 0.51	1.27 ± 0.45	1.39 ± 0.58	1.51 ± 0.69	0.39	0.441
Percent FRC (%)	79.71 ± 14.85	89.71 ± 12.72	79.00 ± 12.93	85.62 ± 20.65	0.91	0.640

†Statistically significant paired t-test within the supine OSA subgroup comparing the supine mean value to the lateral mean value within that group. ‡Statistically significant paired t-test within the position-independent OSA subgroup comparing the supine mean value to the lateral mean value within that group. BMI, body mass index; Circ., circumference; AHI_{SUP}, supine AHI; AHI_{LAT}, non-supine AHI; Pcrit, pharyngeal critical closing pressure; FRC, functional residual capacity; Percent FRC, FRC expressed as a percentage of the seated FRC value; AHI, apnea-hypopnea index; AT, arousal threshold; UAG, upper airway gain.

Section 5: Lung Volume Variability

Table S2—Lung volume variability, seated position.

	N	Mean	Std. Deviation	Variance
Patient 1	4	1.0110	0.69257	0.480
Patient 2	4	1.7813	0.56997	0.325
Patient 3	4	0.7175	0.90500	0.819
Patient 4	4	2.5105	1.02265	1.046
Patient 5	2	1.8525	0.06435	0.004
Patient 6	4	1.1158	0.20560	0.042
Patient 7	4	1.1038	0.19323	0.037
Patient 8	4	2.0052	0.17270	0.030
Patient 9	4	1.1038	0.19323	0.037
Patient 10	4	0.8725	0.06336	0.004
Patient 11	3	2.5743	0.24492	0.060
Patient 12	4	1.5803	0.10847	0.012
Patient 13	4	1.3420	0.32469	0.105
Patient 14	4	1.3475	0.11968	0.014
Patient 15	4	2.1203	0.08250	0.007
Patient 16	4	0.4453	0.53981	0.291
Patient 17	4	0.8910	0.59810	0.358
Patient 18	4	1.6815	0.23928	0.057
Patient 19	2	1.7495	0.20153	0.041
Patient 20	4	2.0333	1.38514	1.919

Table S3—Lung volume variability, lateral position.

	N	Mean	Std. Deviation	Variance
Patient 1	4	0.7818	0.53004	0.281
Patient 2	3	1.7137	0.16449	0.027
Patient 3	4	0.8443	0.56467	0.319
Patient 4	4	2.6008	0.72420	0.524
Patient 5	2	1.2850	0.19092	0.036
Patient 6	4	0.6010	0.08835	0.008
Patient 7	4	0.8970	0.11915	0.014
Patient 8	4	1.3290	0.89755	0.806
Patient 9	4	0.8970	0.11915	0.014
Patient 10	4	0.6570	0.07616	0.006
Patient 11	4	2.9550	0.90541	0.820
Patient 12	4	1.7965	0.26832	0.072
Patient 13	3	0.8537	0.21537	0.046
Patient 14	4	1.2783	0.04939	0.002
Patient 15	4	2.0233	0.29523	0.087
Patient 16	4	0.6828	0.45793	0.210
Patient 17	4	1.3440	0.17005	0.029
Patient 18	4	1.5085	0.08408	0.007
Patient 19	2	1.6450	0.07495	0.006
Patient 20	4	0.8063	0.93404	0.872

Table S4—Lung volume variability, supine position.

	N	Mean	Std. Deviation	Variance
Patient 1	4	0.9985	0.23259	0.054
Patient 2	4	1.4700	0.51801	0.268
Patient 3	3	1.0817	0.31734	0.101
Patient 4	4	2.3495	0.49222	0.242
Patient 5	2	1.1000	0.01414	0.000
Patient 6	4	0.7457	0.06718	0.005
Patient 7	4	0.7633	0.07690	0.006
Patient 8	4	1.8413	0.08370	0.007
Patient 9	4	0.7633	0.07690	0.006
Patient 10	4	0.5018	0.04345	0.002
Patient 11	4	2.1850	0.20744	0.043
Patient 12	4	1.3592	0.43421	0.189
Patient 13	3	0.7067	0.04163	0.002
Patient 14	4	1.0885	0.11458	0.013
Patient 15	4	1.9878	0.36651	0.134
Patient 16	4	0.4153	0.49321	0.243
Patient 17	3	1.0913	0.22584	0.051
Patient 18	3	1.4540	0.19879	0.040
Patient 19	2	1.6735	0.13506	0.018
Patient 20	3	1.4217	1.25061	1.564

Table S5—Lung volume variability, seated position: night 1.

	N	Mean	Std. Deviation	Variance
Patient 1	2	0.5890	0.83297	0.694
Patient 2	2	2.2605	0.07283	0.005
Patient 3	2	1.4350	0.63074	0.398
Patient 4	2	3.3605	0.49710	0.247
Patient 5	2	1.8525	0.06435	0.004
Patient 6	2	1.0285	0.31042	0.096
Patient 7	2	1.0105	0.27506	0.076
Patient 8	2	2.0230	0.26870	0.072
Patient 9	2	1.0105	0.27506	0.076
Patient 10	2	0.8900	0.01273	0.000
Patient 11	2	2.4760	0.24890	0.062
Patient 12	2	1.5445	0.16051	0.026
Patient 13	2	1.4640	0.31254	0.098
Patient 14	2	1.3220	0.07778	0.006
Patient 15	2	2.1390	0.00000	0.000
Patient 16	2	0.0000	0.00000	0.000
Patient 17	2	1.2365	0.02333	0.001
Patient 18	2	1.8265	0.29204	0.085
Patient 19	0			
Patient 20	2	2.9125	0.00778	0.000

Table S6—Lung volume variability, seated position: night 2.

	N	Mean	Std. Deviation	Variance
Patient 1	2	1.4330	0.12800	0.033
Patient 2	2	1.3020	0.15900	0.051
Patient 3	2	0.0000	0.00000	0.000
Patient 4	2	1.6605	0.01350	0.000
Patient 5	0			
Patient 6	2	1.2030	0.00200	0.000
Patient 7	2	1.1970	0.02800	0.002
Patient 8	2	1.9875	0.08950	0.016
Patient 9	2	1.1970	0.02800	0.002
Patient 10	2	0.8550	0.07300	0.011
Patient 11	1	2.7710		
Patient 12	2	1.6160	0.04700	0.004
Patient 13	2	1.2200	0.28200	0.159
Patient 14	2	1.3730	0.13100	0.034
Patient 15	2	2.1015	0.09750	0.019
Patient 16	2	0.8905	0.20150	0.081
Patient 17	2	0.5455	0.54550	0.595
Patient 18	2	1.5365	0.03450	0.002
Patient 19	2	1.7495	0.14250	0.041
Patient 20	2	1.1540	1.15400	2.663

Table S7—Lung volume variability, lateral position: night 1.

	N	Mean	Std. Deviation	Variance
Patient 1	2	0.4565	0.64559	0.417
Patient 2	2	1.7920	0.13152	0.017
Patient 3	2	0.5830	0.82449	0.680
Patient 4	2	3.1730	0.44123	0.195
Patient 5	2	1.2850	0.19092	0.036
Patient 6	2	0.6030	0.14849	0.022
Patient 7	2	0.8120	0.08202	0.007
Patient 8	2	0.8105	1.14622	1.314
Patient 9	2	0.8120	0.08202	0.007
Patient 10	2	0.6380	0.11738	0.014
Patient 11	2	3.4400	1.21622	1.479
Patient 12	2	1.7390	0.22203	0.049
Patient 13	2	0.9440	0.20930	0.044
Patient 14	2	1.3020	0.01273	0.000
Patient 15	2	1.9350	0.44972	0.202
Patient 16	2	0.9105	0.08697	0.008
Patient 17	2	1.3465	0.21991	0.048
Patient 18	2	1.4505	0.06010	0.004
Patient 19	0			
Patient 20	2	1.6125	0.13081	0.017

Table S8—Lung volume variability, lateral position: night 2.

	N	Mean	Std. Deviation	Variance
Patient 1	2	1.1070	0.05374	0.003
Patient 2	1	1.5570		
Patient 3	2	1.1055	0.06152	0.004
Patient 4	2	2.0285	0.26234	0.069
Patient 5	0			
Patient 6	2	0.5990	0.03677	0.001
Patient 7	2	0.9820	0.08344	0.007
Patient 8	2	1.8475	0.16617	0.028
Patient 9	2	0.9820	0.08344	0.007
Patient 10	2	0.6760	0.04667	0.002
Patient 11	2	2.4700	0.19799	0.039
Patient 12	2	1.8540	0.39174	0.153
Patient 13	1	0.6730		
Patient 14	2	1.2545	0.07000	0.005
Patient 15	2	2.1115	0.16758	0.028
Patient 16	2	0.4550	0.64347	0.414
Patient 17	2	1.3415	0.19587	0.038
Patient 18	2	1.5665	0.06435	0.004
Patient 19	2	1.6450	0.07495	0.006
Patient 20	2	0.0000	0.00000	0.000

Table S9—Lung volume variability, supine position: night 1.

	N	Mean	Std. Deviation	Variance
Patient 1	2	0.8020	0.05515	0.003
Patient 2	2	1.9050	0.00707	0.000
Patient 3	2	0.9075	0.13930	0.019
Patient 4	2	2.6615	0.57205	0.327
Patient 5	2	1.1000	0.01414	0.000
Patient 6	2	0.7545	0.04455	0.002
Patient 7	2	0.7140	0.04808	0.002
Patient 8	2	1.7850	0.08061	0.006
Patient 9	2	0.7140	0.04808	0.002
Patient 10	2	0.4825	0.04879	0.002
Patient 11	2	2.1700	0.05657	0.003
Patient 12	2	1.0305	0.04738	0.002
Patient 13	2	0.7000	0.05657	0.003
Patient 14	2	1.1560	0.06505	0.004
Patient 15	2	2.0295	0.56215	0.316
Patient 16	2	0.0000	0.00000	0.000
Patient 17	2	0.9750	0.14425	0.021
Patient 18	2	1.3400	0.03253	0.001
Patient 19	0			
Patient 20	2	0.9565	1.35270	1.830

Table S10—Lung volume variability, supine position: night 2.

	N	Mean	Std. Deviation	Variance
Patient 1	2	1.1950	0.06930	0.005
Patient 2	2	1.0350	0.21920	0.048
Patient 3	1	1.4300		
Patient 4	2	2.0375	0.10112	0.010
Patient 5	0			
Patient 6	2	0.7370	0.10607	0.011
Patient 7	2	0.8125	0.07566	0.006
Patient 8	2	1.8975	0.04313	0.002
Patient 9	2	0.8125	0.07566	0.006
Patient 10	2	0.5210	0.04243	0.002
Patient 11	2	2.2000	0.35355	0.125
Patient 12	2	1.6880	0.36204	0.131
Patient 13	1	0.7200		
Patient 14	2	1.0210	0.13011	0.017
Patient 15	2	1.9460	0.28284	0.080
Patient 16	2	0.8305	0.20011	0.040
Patient 17	1	1.3240		
Patient 18	1	1.6820		
Patient 19	2	1.6735	0.13506	0.018
Patient 20	1	2.3520		