Performance Characteristics of Upper Airway Critical Collapsing Pressure Measurements during Sleep

Jason P. Kirkness, PhD[1]; Leigh A. Peterson, MHS[1]; Samuel B. Squier, BS[1]; Brian M. McGinley, MD[1]; Hartmut Schneider, MD, PhD[1]; Adrian Meyer[2]; Alan R. Schwartz, MD[1]; Philip L. Smith, MD[1]; Susheel P. Patil, MD, PhD[1]

[1]Johns Hopkins Sleep Disorders Center, Johns Hopkins School of Medicine, Baltimore, MD; [2]Hals-Nasen-Ohrenklinik, Kantonsspital St.Gallen, St Gallen, Switzerland

Objective: The critical pressure (P_{CRIT}), a measurement of upper airway collapsibility, is a determinant of the severity of upper airway obstruction during sleep. We examined the performance characteristics of the passive and active P_{CRIT} by examining both within-night and between-night variability in the measurements.

Methods: We studied 54 sleep apnea patients (39 men, 15 women) and 34 normal subjects (20 men, 14 women) on either 1 or 2 nights during sleep. The P_{CRIT} was measured during relative hypotonia ("passive" state) or during periods of sustained upper airway obstruction used to recruit upper airway neuromuscular responses ("active" state) within- and between-nights. In a subgroup of 10 normal subjects, we performed repeated measurements during hypnotic-induced sleep. Bland-Altman analyses were used to determine the within-night and between-night reliability of the P_{CRIT} measurements.

Results: There were no significant within-night or between-night differences for the mean passive P_{CRIT}. The active P_{CRIT} was ~1 cm H_2O more collapsible on the second night than on the first night. The limits of agreement, which bound the passive and active P_{CRIT}, was ~ ± 3 cm H_2O and was reduced to ~ ± 1 cm H_2O for the passive P_{CRIT} with hypnotic-induced sleep.

Conclusion: Passive and active P_{CRIT} measurements are reasonably reliable within and between nights. An approximately 3 cm H_2O change in passive or active P_{CRIT} appears to represent the minimally significant change in P_{CRIT} necessary to assess the effect of an intervention (e.g., positional therapy, surgical interventions, oral appliance effects, and pharmacotherapy) on upper airway mechanical loads or neuromuscular responses.

Keywords: Pharyngeal collapsibility, obstructive sleep apnea, sleep disordered breathing, neuromuscular compensation, upper airway mechanics

Citation: Kirkness JP; Peterson LA; Squier SB; McGinley BM; Schneider H; Meyer A; Schwartz AR; Smith PL; Patil SP. Performance characteristics of upper airway critical collapsing pressure measurements during sleep. *SLEEP* 2011;34(4):459-467.

INTRODUCTION

Obstructive sleep apnea (OSA) is an increasingly common disorder associated with comorbid conditions, including cardiovascular disease and metabolic disorders.[1-5] OSA is characterized by recurrent episodes of complete or partial upper airway obstruction during sleep. The primary defect is one of increased collapsibility during sleep, which increases susceptibility and severity to obstructive sleep apnea. The critical pressure (P_{CRIT}), a measurement of upper airway collapsibility, is a determinant of the severity of upper airway obstruction during sleep.[6-11] P_{CRIT} also describes a continuum of pharyngeal collapsibility from health to varying degrees of upper airway obstruction including snoring, hypopneas, and apneas.[9,12] In normal subjects, the P_{CRIT} is markedly negative compared with sleep apnea patients in whom the P_{CRIT} is closer to atmospheric pressure or above.

Current evidence suggests that defects in upper airway mechanical (passive) and neuromuscular (active) control play a role in the pathogenesis of obstructive sleep apnea. Methods to quantify P_{CRIT} during sleep have been adapted to assess the relative contribution of these properties towards upper airway collapse.[8,13-28] Specifically, measurements of P_{CRIT} during the passive state (relative hypotonia) assess the contribution of mechanical loads on upper airway collapsibility. Measurements of P_{CRIT} during the active state represent the combination of mechanical loads and neural reflex responses. Investigators have increasingly utilized measurements of passive and active P_{CRIT} to elucidate the pathogenesis of obstructive sleep apnea.[7,8,10,13-39] In particular, studies have been conducted to manipulate passive and active upper airway properties with treatments such as stimulation of upper airway dilator muscles,[40] upper airway surgery,[41] exogenous surfactant,[42] or weight loss[43] to effect reductions in P_{CRIT} and disease severity.

Physiologic protocols have been established to assess upper airway pressure-flow relationships during sleep and derive measurements of P_{CRIT} under the passive and active conditions. Establishing the reliability of P_{CRIT} would guide clinical investigators in deploying these measurements in physiologic studies and treatment trials. The major goal of the current study was to examine the performance characteristics of the passive and active P_{CRIT} by examining both within- and between-night reliability in the measurements.

METHODS

Subjects

A total of 54 sleep apnea subjects (39 men, 15 women) and 34 subjects without sleep apnea (20 men, 14 women; for both control and sedation groups; see Table 1) from the Johns Hopkins Sleep Disorders Center and the general community (Tables 1A-C) were included in this retrospective analysis of previously collected studies of upper airway collapsibility. Sleep apnea was defined as a NREM respiratory disturbance index (RDI) > 10 events/h. Subjects were excluded if they had a history of a concurrent sleep disorder or other confounding

Submitted for publication July, 2010
Submitted in final revised form October, 2010
Accepted for publication November, 2010
Address correspondence to: Jason P. Kirkness, PhD, Johns Hopkins Sleep Disorders Center, 5501 Hopkins Bayview Circle, Baltimore, MD 21224; Tel: (410) 550-2184; Fax: (410) 550-8368; E-mail: Jason.Kirkness@jhmi.edu

Table 1—Subject demographics

(A) Within-night repeatability of passive P_{CRIT} and R_{US}

	Control (n = 14)	OSA (n = 18)	Hypnotic (n = 10)
Age (years)	40 ± 7	45 ± 11	27 ± 8*
BMI (kg/m^2)	41 ± 12	40 ± 12	24 ± 2*
Men:Women (n)	5:9	10:8	6:4
NREM AHI (events/h)	3 ± 2	55 ± 20*	2 ± 2
REM AHI (events/h)	9 ± 5	68 ± 37*	6 ± 8

(B) Between-night passive P_{CRIT} and R_{US} measurement reproducibility

	Control (n = 7)	OSA (n = 26)
Age (years)	40 ± 12	47 ± 11*
BMI (kg/m^2)	28 ± 5	34 ± 8*
Men:Women (n)	6:2	21:5
NREM AHI (events/h)	2 ± 1	46 ± 5*
REM AHI (events/h)	11 ± 9	51 ± 32*

(C) Between-night active P_{CRIT} and R_{US} measurement reproducibility

	Control (n = 3)	OSA (n = 10)
Age (years)	50 ± 7	44 ± 12
BMI (kg/m^2)	25 ± 1	30 ± 7
Men:Women (n)	3:0	8:2
NREM AHI (events/h)	3 ± 1	48 ± 16*
REM AHI (events/h)	11 ± 8	44 ± 35

OSA, obstructive sleep apnea; BMI, body mass index; AHI, apnea/hypopnea index; P values are OSA or Hypnotic vs Control. *P < 0.05.

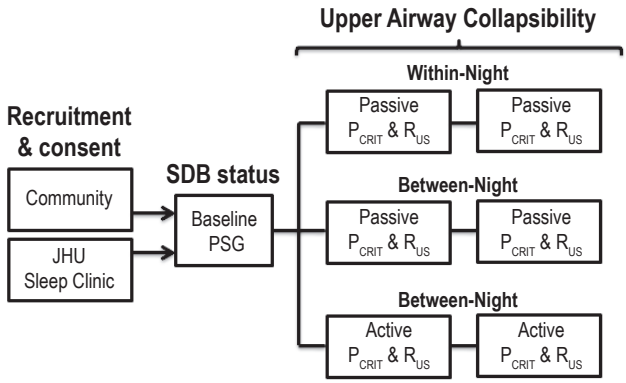

Figure 1—Study design. The sleep apnea status of subjects recruited from the clinic or community was confirmed with a baseline polysomnographic (PSG) study. Additionally, each subject underwent either 1 or 2 nights in the sleep laboratory for determination of passive and/or active upper airway collapsibility (P_{CRIT}) and up-stream resistance (R_{US}). During stable, NREM (stage 2) sleep, measurements were conducted during periods of relative hypotonia ("passive" state) or following extended periods of stable flow-limitation and upper airway muscle activity ("active" state). Repeated measurements were made either within-nights or between nights.

medical condition (e.g., narcolepsy, restless legs syndrome, previous upper airway surgery, or significant pulmonary disease). The protocol was approved by the Johns Hopkins Institutional Review Board, and informed written consent was obtained from each subject.

Experimental Procedures

Baseline polysomnographic measurements

All subjects slept in the sleep laboratory at the Johns Hopkins Sleep Disorders Center or the Clinical Research Unit at the Johns Hopkins Bayview Medical Center. Standard polysomnographic recording techniques were employed using a full montage acquisition system (Embla N7000, Somnologica, Medcare, Buffalo, NY). The signals acquired included: electroencephalograms (C_3-A_2, C_3-O_1, F_3-A_2), left and right electroculograms, electrocardiogram, submental electromyogram, oxyhemoglobin saturation, airflow via a nasal cannula and oronasal thermistor. Thoracic and abdominal movements were monitored by inductance plethysmography, and posture was continuously recorded using a body position monitor and confirmed via infrared video camera.

Pressure-airflow measurements

To determine the passive and active critical collapsing pressure (P_{CRIT}), nasal pressure was manipulated to induce or alleviate upper airway obstruction and responses in airflow were recorded via a nasal mask as previously described.[8] Airflow was measured using a pneumotachograph (Hans Rudolph model #4830, Hans Rudolph, Kansas City, MO) attached to pneumotachograph amplifier (Hans Rudolph model #1, Series 1110) in series with a nasal continuous positive airway pressure (CPAP) mask (Profile Lite Nasal Gel Mask, Respironics, Murraysville, PA). Nasal pressure (P_N) was measured using a pressure transducer (Embla N7000 Patient Unit Pressure Sensor, Medcare, Buffalo, NY) attached via tubing to a pressure port on the nasal mask. Pressure was delivered to the nasal mask throughout the night from a remotely controlled modified continuous positive airway pressure device (ResMed Ltd, Bella Vista, NSW, Australia) capable of delivering negative and positive pressures over a range of −20 to +20 cm H_2O.

Experimental Protocols

Protocols for assessment of upper airway collapsibility

Each subject underwent baseline polysomnogram (PSG) assessment of sleep disordered breathing status followed by an additional 1 or 2 nights in the sleep laboratory for upper airway characterization (Figure 1). We measured P_{CRIT} during conditions of hypotonia (passive P_{CRIT}) and increased neuromuscular activity (active P_{CRIT}). Passive P_{CRIT} measurements were made within the same night and between nights. Active P_{CRIT} measurements could only be made between nights. Measurements were obtained during periods when subjects slept in the supine position with one pillow underneath their head.

Passive upper airway critical collapsing pressure (passive P_{CRIT})

Participants were titrated to a holding P_N at which inspiratory airflow limitation was eliminated and neuromuscular activity was attenuated, as reported previously.[7,13,44,45] A minimum holding pressure of 4 cm H_2O was applied to prevent re-breathing for control subjects. During stable, stage N2 sleep, P_N was re-

duced rapidly by 1-2 cm H_2O to a level where airflow became flow-limited for 5 breaths and then returned to holding pressure for 1-2 min before continuing with subsequent pressure drops. P_N was repeatedly lowered in 1-2 cm H_2O increments until complete (zero flow) or near complete (< 50 mL/s) upper airway closure was observed. A minimum of 2 series of stepwise reductions in P_N by 1–2 cm H_2O that eventually encompassed zero airflow (P_{CRIT}) was collected for each assessment of passive P_{CRIT}.

Active upper airway critical collapsing pressure (active P_{CRIT})

Dynamic neuromuscular responses to upper airway obstruction were determined by assessment of the active P_{CRIT}, as previously described.[8,44] Briefly, P_N was reduced stepwise from holding pressure by 1-2 cm H_2O until constant airflow limitation was exhibited for 10 min during NREM sleep. P_N was subsequently further reduced stepwise by 1-2 cm H_2O for 10 min during NREM sleep until recurrent obstructive apneas were observed or until sleep was no longer maintained. At pressures lower than 4 cm H_2O, a continuous airflow of between 8-10 L/min was added through the nasal mask to prevent re-breathing.

Passive P_{CRIT} sources of variability

In a group (n = 10) of separate control subjects (Table 1A), within-night passive P_{CRIT} measurements were obtained in the supine position while controlling head position (head comfortably fixed in the same position) during hypnotic-induced sleep (0.50 mg triazolam, Pfizer Inc, NY, NY).

Analyses

Polysomnography

All polysomnography studies were analyzed for sleep stage, arousals, and respiratory-related events according to the standard published criteria.[46-49]

Upper airway critical closing pressure (P_{CRIT}) and up-stream resistance (R_{US})

A passive and active pressure-flow curve were separately constructed using flow-limited breaths, as previously described.[8] A spline analysis was performed to identify the sloped, flow-limited portion of the pressure-flow curve. Median regression was performed using data from the flow-limited portion of the pressure-flow curve to obtain the x-intercept (P_{CRIT}), and 1/slope (upstream resistance; R_{US}) for measurements of passive and active P_{CRIT} and R_{US}.[7]

Statistical Analysis

In a larger database of P_{CRIT} measurements at our center, we examined our ability to successfully obtain a passive and active P_{CRIT} measurement in previously recruited subjects. A successful P_{CRIT} measurement was defined as a P_{CRIT} value extrapolated no more than 3 cm H_2O from the lowest nasal pressure level successfully applied during sleep. We then examined the reliability of passive and active P_{CRIT} and R_{US} measurements using several approaches. First, since differences in within-night and between-night measurements and subject characteristics were normally distributed, statistical significance was assessed using paired *t*-tests. Second, the intraclass-correlation (ICC) between measurements, an assessment of the within-individual variation, was determined using the method of Deyo et al.[50] An ICC of 1.0 would indicate an absence of within-individual variability for the measurement. Third, Bland-Altman plots of the difference in measurements vs. the average of the 2 measurements were examined for evidence of systematic bias, the presence of heteroscedasticity, and to identify the limits of agreement that bound the mean difference between P_{CRIT} and R_{US} measurements (mean difference ± 2 SD). Linear regression analyses were performed to determine whether differences in passive and active P_{CRIT} and R_{US} measurements were a function of time within-night and between-nights. To examine if there was any evidence of a systematic bias on the reproducibility of the passive or active P_{CRIT} due to the median regression approach, we compared the fitted x-intercept to the lowest pressure level obtained in a subgroup of 21 individuals. Linear regression analyses were also performed to determine the strength of any cross-sectional associations between the repeated measurements of P_{CRIT} and R_{US} with age or BMI, stratified by disease status. Between-group differences by sleep apnea status were assessed using unpaired *t*-tests. Statistical significance was defined a priori at a $P \leq 0.05$ and data are presented as mean ± SD, unless otherwise specified. Statistical analyses were performed using STATA 10.0 (College Station, TX).

RESULTS

In a larger database of previously collected passive and active P_{CRIT} measurements at our center, we examined our ability to obtain a P_{CRIT} measurement. In 148 subjects in whom measurements of passive P_{CRIT} were attempted, we obtained a successful passive P_{CRIT} in 86%. For the active P_{CRIT}, however, we were only able to obtain a valid measurement of active P_{CRIT} in 48%.

Table 1 describes the subject characteristics for the groups in the current study for the within-night passive P_{CRIT} and R_{US} measurement (Table 1A) analysis, and the between-night analyses for both passive (Table 1B) and active (Table 1C) P_{CRIT} and R_{US}.

Within-Night Reliability of Passive P_{CRIT} and R_{US}: Natural Sleep

Thirty-two subjects (Table 1A) had within-night repeated measurements separated by an average of 134 ± 91 min (range: 4–304 min). The mean holding pressure for the first series of measurements was similar for the second series of measurements (8.6 ± 2.4 cm H_2O vs. 8.6 ± 2.3 cm H_2O, respectively; P = 0.75). For all subjects, there was no difference between the first and the second passive P_{CRIT} (P = 0.93) or R_{US} (P = 0.40) measurements (Table 2). The ICC was 0.90 and 0.66 for comparisons of within-night passive P_{CRIT} and R_{US}, respectively. The Bland-Altman analysis did not demonstrate a systematic bias between the first and second measurements of passive P_{CRIT}, with a mean difference of −0.1 ± 1.6 cm H_2O; P = 0.93 (see Figure 2A) and lower and upper limits of agreement of −3.2 and +3.0 cm H_2O, respectively. Similarly, no significant group mean differences between the within-night repeated measurement of passive R_{US} (3.0 ± 3.6 cm H_2O/L/s; P = 0.40; Figure 2B) were observed, with lower and upper limits of agreement of −20.5 and +26.5 cm H_2O, respectively.

No association between the time interval (in minutes) and repeated measurements was observed for either the passive P_{CRIT} ($r^2 = 0.09$, P = 0.10; Figure 3) or R_{US} ($r^2 = 0.03$, P = 0.37). When

Table 2—Repeatability and reproducibility of P_{CRIT} and R_{US}

Within-night repeated measurements

		P_{CRIT} (cm H_2O)			R_{US} (cm H_2O/L/s)		
	Group	1st value	2nd value	ΔP_{CRIT}	1st value	2nd value	ΔR_{US}
Passive	Control	−2.5 ± 3.0	−2.5 ± 2.6	0.0 ± 2.0	28 ± 18	24 ± 17	4 ± 15
	OSA	1.0 ± 3.1*	1.1 ± 3.1*	−0.1 ± 1.1	21 ± 9	19 ± 13	2 ± 9
	All	−0.6 ± 3.5	−0.5 ± 3.4	−0.1 ± 1.6	24 ± 14	21 ± 15	3 ± 12
	Hypnotic	−3.4 ± 3.2	−3.4 ± 3.5	−0.1 ± 0.6	18 ± 4	17 ± 4	1 ± 3

Between-night measurement reproducibility

		P_{CRIT} (cm H_2O)			R_{US} (cm H_2O/L/s)		
		1st night	2nd night	ΔP_{CRIT}	1st night	2nd night	ΔR_{US}
Passive	Control	−3.9 ± 2.1	−4.8 ± 2.7	0.9 ± 3.0	21 ± 8	31 ± 15	−10 ± 16
	OSA	0.8 ± 2.8*	1.0 ± 3.1*	−0.1 ± 1.2	17 ± 9	15 ± 7	2 ± 8
	All	−0.3 ± 3.3	−0.4 ± 3.8	0.1 ± 1.8	18 ± 9	19 ± 11	−1 ± 11
		P_{CRIT} (cm H_2O)			R_{US} (cm H_2O/L/s)		
		1st night	2nd night	ΔP_{CRIT}	1st night	2nd night	ΔR_{US}
Active	Control	−6.5 ± 1.8	−5.9 ± 1.8	−0.7 ± 0.8	16 ± 8	14 ± 6	2 ± 6
	OSA	−1.8 ± 3.9*	−0.7 ± 3.3*	−1.1 ± 1.8	22 ± 12	19 ± 10	3 ± 5
	All	−2.9 ± 4.0	−1.9 ± 3.8	−1.0 ± 1.6†	21 ± 11	18 ± 9	3 ± 5

Passive, hypotonic state; Active, state during neuromuscular compensation to airflow obstruction; P_{CRIT}, critical collapsing pressure, R_{US}, up-stream resistance; Δ = 1st − 2nd. *P < 0.05 OSA vs Control. †P < 0.05 1st vs 2nd night.

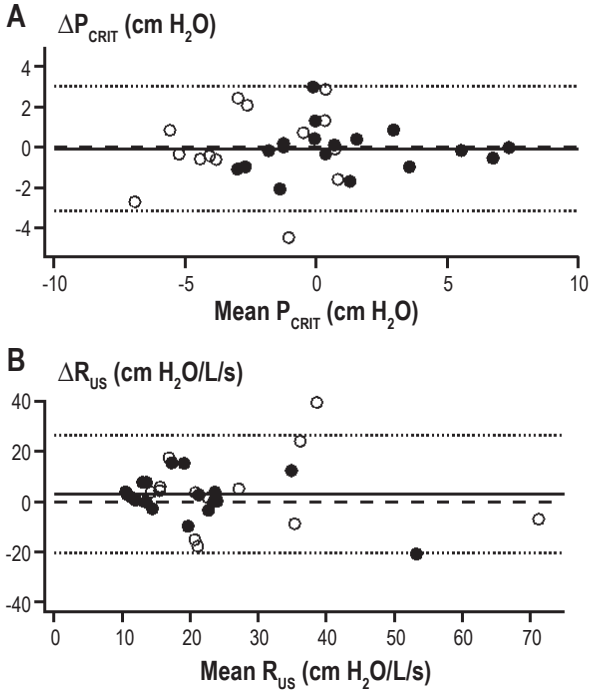

Figure 2—Within-night passive P_{CRIT} Bland-Altman plot. Bland-Altman plots displaying the difference of repeated measurements of **(A)** passive P_{CRIT} and **(B)** passive R_{US} plotted against the average of the repeated measurements. The mean difference (−0.1 ± 1.6 cm H_2O; solid line) was not different from zero (dashed line) and the limits of agreement (dotted lines) are represented as ± 2 standard deviations. The upper and lower limits of agreement were +3.0 and 3.2 cm H_2O for passive P_{CRIT} and +26.5 to −20.5 cm H_2O/L/s for R_{US}. The intraclass correlation coefficient (ICC) for between-night measurements during sleep was 0.90 for passive P_{CRIT} and 0.66 for R_{US}. The subject demographics of healthy control (open circles) and sleep apnea (closed circles) subjects are provided in Table 1A.

subjects were stratified based on the median time between repeated measurements (≤ 159 min [n = 17; mean = 63 minutes] and > 159 min [n = 15; mean = 216 min]), there was no change in the mean difference in passive P_{CRIT} or R_{US}. The mean difference in both passive P_{CRIT} and R_{US} measurements over time was the same for OSA and control subjects.

Within-Night Reliability of Passive P_{CRIT} and R_{US}: Hypnotic-Induced Sleep

During sleep with sedation, the average time between repeated passive P_{CRIT} measurements was 78 ± 59 min (range: 5–189 min). P_{CRIT} and R_{US} were not different between the first and second measurements (Table 2) with ICCs of 0.99 and 0.66, respectively. No systematic bias between P_{CRIT} measurements were observed (mean difference −0.1 ± 0.6 cm H_2O; P = 0.76) with upper and lower confidence intervals of +1.1 and −1.2 cm H_2O (Figure 4). Similarly, no systematic differences in R_{US} measurements were observed (mean difference 3 ± 12 cm H_2O/L/s; P = 0.44) with upper and lower confidence intervals of +6.5 and −5.0 cm H_2O/L/s. No association between the time interval and repeated measurements of P_{CRIT} (r^2 = 0.21, P = 0.17) or R_{US} (r^2 = 0.32, P = 0.086) were observed in all participants or when stratified by OSA status.

Between-Night Passive P_{CRIT} and R_{US} Reliability

Twenty-five of the 33 subjects for the between-night passive P_{CRIT} and R_{US} analysis were studied on consecutive nights. The remaining 9 subjects had their second study night a median of 3.5 months later (range: 2 weeks to 2 years) and there was no significant change in BMI with the time between the measurements in this group (P = 0.64). No significant difference in between-night passive P_{CRIT} and R_{US} was observed between night 1 and night 2 (Table 2). The ICC was 0.87 and 0.41 for comparisons of between-night passive P_{CRIT} and R_{US}, respectively. Bland-Altman plots did not demonstrate a systematic bias in the between-night passive P_{CRIT} measurements (mean difference 0.1 ± 1.8 cm H_2O; P = 0.73; Figure 5A) with lower and upper limits of agreement of −3.5 and +3.7 cm H_2O, nor in the between-night passive R_{US} (mean difference −1 ± 11 cm H_2O/L/s; P = 0.65; Figure 5B), with lower and upper limits of agreement of −23.1 and +21.3 cm H_2O/L/s.

The number of days between passive P_{CRIT} measurements was not associated with the differences between the measurements for the entire group (r^2 = 0.03, P = 0.30) or for the subgroup that had > 1 day between measurements (r^2 = 0.001, P = 0.93). Similarly, for passive R_{US} measurements there was no association of time between measurements and the difference in passive R_{US} for the entire group (r^2 = 0.01, P = 0.61) or

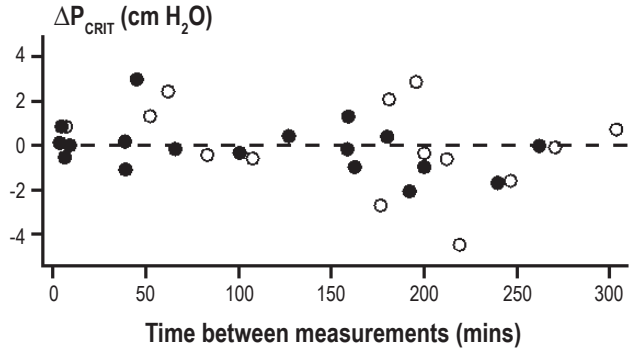

Figure 3—Difference between repeated passive P_{CRIT} measurements vs. time between the measurements. Scatter-plot showing the difference between repeated passive P_{CRIT} measurements (ΔP_{CRIT}) and the time in minutes between the measurements. The time between measurements did not systematically alter the magnitude of ΔP_{CRIT} ($r^2 = 0.09$, $P < 0.07$). The subject demographics of healthy control (open circles) and sleep apneic (closed circles) subjects are provided in Table 1A.

for the subgroup with > 1 day between measurements ($r^2 = 0.06$, $P = 0.54$). To examine the variability between repeated passive P_{CRIT} measurements that may be due to the median regression approach, we examined the lowest observed pressure measurement compared to the calculated P_{CRIT}. The difference between passive P_{CRIT} and the lowest pressure level was the same on the first (−0.2 ± 0.6 cm H_2O) and second (−0.5 ± 0.5 cm H_2O) nights ($P = 0.08$).

Between-Night Active P_{CRIT} and R_{US} Reliability

Active P_{CRIT} measurements were performed on 18 of the subjects who had passive P_{CRIT} measurements repeated between nights; however, adequate data were obtained from 13 of 18 subjects (70%). The active P_{CRIT} was 1.0 ± 1.6 cm H_2O lower (less collapsible) on night 1 than night 2 ($P = 0.04$; Table 2). Moreover, R_{US} exhibited a nonsignificant trend to be higher on night 1 compared to night 2 ($P = 0.08$; Table 2). Ten of 13 subjects had active P_{CRIT} and R_{US} measurements on consecutive nights, and 3 had a second study night between 1 and 9 months (median 113 days). As participant characteristics may change over time and affect upper airway properties, a subanalysis was performed of the 10 subjects in whom active P_{CRIT} measurements were obtained on consecutive nights. There was no significant between-night active P_{CRIT} (−0.8 ± 1.2 cm H_2O; $P = 0.07$) or R_{US} (2 ± 5 cm H_2O/L/s; $P = 0.16$) difference. For the entire group the ICC was 0.95 and 0.87 for comparisons of between-night active P_{CRIT} and R_{US}, respectively. Bland-Altman plots also demonstrated the small systematic difference between the first night and second night active P_{CRIT} measurements of −1.0 ± 1.6 cm H_2O ($P = 0.04$; Table 2) with the lower and upper limits of agreement for between-night active P_{CRIT} at −4.2 and +2.2 cm H_2O, respectively (Figure 6A). Similarly, a small systematic difference in active R_{US} was exhibited between nights that did not reach statistical significance (mean difference 3 ± 5 cm H_2O/L/s; $P = 0.06$; Figure 6B) with lower and upper limits of agreement of −7.4 and +13.3 cm H_2O/L/s, respectively. Similar to the passive P_{CRIT} there was no difference between active P_{CRIT} and the lowest pressure level on the first

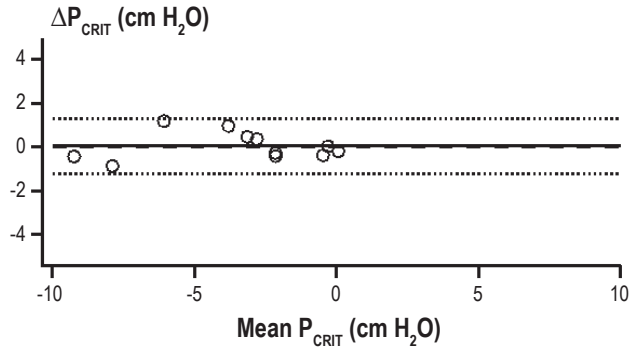

Figure 4—Within-night passive P_{CRIT} during hypnotic induced sleep. Bland-Altman plots displaying the difference of repeated measurements of passive P_{CRIT} plotted against the average of the repeat measurements. The mean difference (−0.1 ± 0.6 cm H_2O; solid line) was not different from zero (dashed line) and the limits of agreement (dotted lines) are represented as ± 2 standard deviations. The upper and lower limits of agreement were +1.1 and −1.2 cm H_2O for passive P_{CRIT}. The intraclass correlation coefficient (ICC) for between-night measurements during hypnotic-induced sleep was 0.99 for passive P_{CRIT} and 0.66 for R_{US}. The subject demographics of the subjects, none of whom had OSA (open circles) are provided in Table 1A.

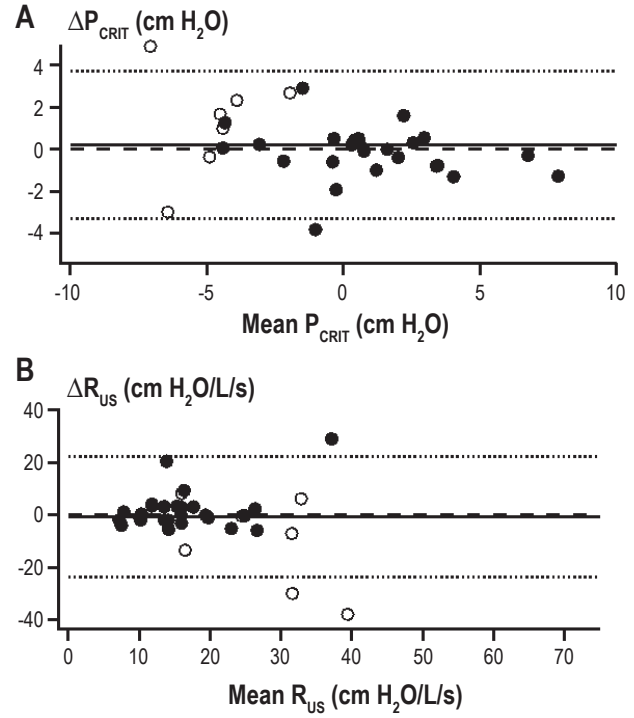

Figure 5—Between-night passive P_{CRIT} and R_{US} measurement reproducibility. Bland-Altman plots displaying the difference between night 1 and night 2 measurements of **(A)** passive P_{CRIT} and **(B)** passive R_{US} plotted against the average of both measurements. The mean difference (0.1 ± 1.8 cm H_2O; solid line) is not different from zero and the limits of agreement (dashed lines) are represented as ± 2 standard deviations. The upper and lower limits of agreement for between-night passive P_{CRIT} were −3.3 and +3.5 cm H_2O and for R_{US} were −23.5 and +20.7 cm H_2O/L/s, respectively. The intraclass correlation coefficient (ICC) for between-night measurements was 0.87 for passive P_{CRIT} and 0.41 for R_{US}. The subject demographics of healthy control (open circles) and sleep apneic (closed circles) subjects are provided in Table 1B.

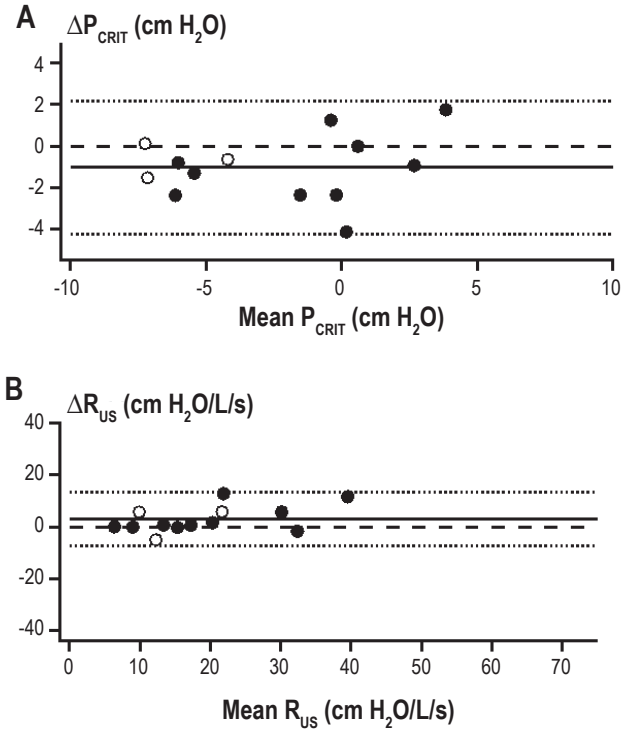

Figure 6—Between-night active P_{CRIT} and R_{US} measurement reproducibility. Bland-Altman plots displaying the difference between night 1 and night 2 measurements of **(A)** active P_{CRIT} and **(B)** active R_{US} plotted against the average of both measurements. The mean difference (solid line) shows a small systematic bias (−1.0 ± 1.6 cm H_2O) and the limits of agreement (dashed lines) are represented as ± 2 standard deviations. The upper and lower limits of agreement for between-night passive P_{CRIT} were –4.2 and +2.2 cm H_2O and for R_{US} were -7.4 and +13.3 cm H_2O/L/s, respectively. The intraclass correlation coefficient (ICC) for between-night measurements was 0.95 for passive P_{CRIT} and 0.87 for R_{US}. The subject demographics of healthy control (open circles) and sleep apneic (closed circles) subjects are provided in Table 1C.

(−0.9 ± 0.3 cm H_2O) compared to the second (−0.5 ± 0.4 cm H_2O) night (P = 0.28).

DISCUSSION

The findings in this study demonstrate that the passive P_{CRIT} measurement is more readily obtained than the active P_{CRIT} measurement. Furthermore, when passive and active P_{CRIT} and R_{US} measurements were collected on multiple occasions, these measurements were reliable within the same night and between nights, using several approaches. First, comparison of repeated measures of P_{CRIT} and R_{US} demonstrated negligible differences in group mean effects for passive measurements. Furthermore, no systematic differences in active measurements were observed when made on consecutive nights. Second, intra-class correlation between measurements for P_{CRIT} and R_{US} were high. Third, examination of Bland-Altman plots demonstrated agreement between repeated passive P_{CRIT} measurements both within and between nights and for active P_{CRIT} measurements between nights. Specifically, no significant or minimal systematic bias in the mean difference between measurements, over a range of P_{CRIT} or R_{US} measurements was observed, and relatively narrow limits of agreement were present. Furthermore, hypnotic-induced sleep and careful control of head and neck posture further reduced the variability of within-night repeated measurements of passive P_{CRIT}.

Reliability of Passive P_{CRIT} and R_{US} Measurements

The current study reports the reliability in repeated passive P_{CRIT} and R_{US} measurements, a measure of the contribution of mechanical loads towards the development of upper airway obstruction. We observed negligible mean differences in repeated measurements of the passive P_{CRIT} within- and between-nights and excellent ICC agreement (0.87–0.90), suggesting minimal within-individual variability in this measurement. Similarly, passive R_{US} demonstrated negligible mean differences in repeated measurements within and between nights, although the ICC agreement was more modest (0.41–0.66). The Bland-Altman analyses for within- and between-night passive P_{CRIT} demonstrated similar limits of agreement, at ≈ ± 3 cm H_2O and most likely represents the minimally significant change in passive P_{CRIT} necessary to assess the effects of an intervention on upper airway mechanical loads. The use of a hypnotic to induce stable sleep and careful control of head, neck, and body posture further reduced the variability in the measurement of passive P_{CRIT}. Under these carefully controlled conditions, the minimally significant change would be as little as ≈ ± 1 cm H_2O. Others have demonstrated that measurement of a hypnotic P_{CRIT} during hypnotic-induced sleep are strongly correlated when measurements are made during natural sleep.[28] Our findings suggest that repeated measurements of passive P_{CRIT} have validity within- and between-nights and have sufficient reliability to assess potential significant effects of interventions on modifying upper airway mechanical properties.

Reliability of Active P_{CRIT} and R_{US} Measurements

The current study also evaluated the reliability of repeated active P_{CRIT} and R_{US} measurements, a global measure of upper airway collapsibility that assesses the contribution of mechanical loads and neuromuscular responses towards the development of upper airway obstruction. In subjects in whom active P_{CRIT} measurements were performed on consecutive nights, there was no significant between-night difference. However, when all subjects with active measurements were considered (i.e., the addition of 3 individuals studied a median of 113 days apart), we observed a small but statistically significant increase in the mean active P_{CRIT} by 1.0 cm H_2O (i.e., more collapsible) during the second night compared to the first night. Nevertheless, excellent ICC agreement (0.95) was present for active P_{CRIT} measurements. We speculate that the small systematic change in active P_{CRIT} between nights may be due to changes in participant characteristics in the 3 individuals studied a median of 113 days apart. Other possibilities might include an improved tolerance of the nasal mask and sleep testing conditions resulting in improved sleep quality on the second night, thereby decreasing arousability and increasing airway collapsibility. This hypothesis, however, could not be tested in the context of the study design. Alternatively, the between-night difference could be due to a type I error, with a 5% chance that this systematic difference was a false positive finding. The active R_{US} demonstrated negligible mean differences in repeated measurements between-nights. In contrast to the passive R_{US}, the active R_{US} demonstrated a stronger ICC (0.87). We hypothesize that the

higher ICC for the active R_{US} may in part be related to the availability of adequate active pressure-flow measurements primarily in a sample of sleep apnea subjects, with only a few control subjects included.

The Bland-Altman analyses for between-night active P_{CRIT} demonstrated limits of agreement, at ≈ ± 3 cm H_2O, similar to the passive P_{CRIT}, and most likely represents the minimally significant change in active P_{CRIT} necessary to assess the global effects (an integration of mechanical loads and neuromuscular responses) of an intervention on upper airway collapsibility. Quantitative differences in active P_{CRIT} of approximately 4-5 cm H_2O, generally distinguish between groups over the continuum of normal breathing (< −10 cm H_2O), snoring (between −5 to −10 cm H_2O), obstructive hypopneas (between −5 to 0 cm H_2O), and obstructive apneas (> 0 cm H_2O),[8,9,12] with a threshold of approximately −5 cm H_2O separating individuals with primarily snoring or normal breathing (no disease) from those with hypopneas and apneas (disease).[8,12,43] The night-to-night variability in active P_{CRIT} was greatest around a mean active P_{CRIT} of 0 cm H_2O, suggesting that the measurement is less reliable in predicting disease status in this range. However, with limits of agreement of ≈ ± 3 cm H_2O, the active P_{CRIT} would range from −3 cm H_2O to +3 cm H_2O, which is above the threshold of −5 cm H_2O that is generally associated with the development of apneas and hypopneas.[8,9,51] Therefore, repeated measurements of active P_{CRIT} are reliable in predicting the severity of upper airway obstruction (i.e. apneas and hypopneas from snoring and normal breathing), and interventions which alter the active P_{CRIT} beyond a ± 3 cm H_2O threshold are very likely to correspond to significant changes in the severity of upper airway obstruction. The influence of sedation and control of head and neck posture on the variability of active P_{CRIT} measurements was not determined in this study, however, we would hypothesize that the variability in the measurement would be further reduced, similar to what was observed with the passive P_{CRIT}.

Sources of Variability in the Measurement of P_{CRIT}

Several factors may explain the variability observed in the passive and active P_{CRIT}. Sleep state has been shown to have small effects on the passive P_{CRIT}, with an increase by 1 cm H_2O in REM sleep compared to NREM sleep,[13,30,35] and no significant difference between stage N2 or N3 sleep.[35] In contrast, little is known about the effects of sleep state on the active P_{CRIT}. Recent studies have reported a decrease in sleep apnea severity during stage N3 sleep when compared with stages N1 or N2, suggesting that the active P_{CRIT} may be reduced during stage N3 sleep.[52]

Other sources that may contribute to variability of upper airway collapsibility measurements include changes in body posture[13,53] as well as head, neck, and jaw position.[31,38] Previous studies during sedation have shown that jaw opening as well as head and neck position can change the passive P_{CRIT} by 4-8 cm H_2O.[17,18] Furthermore, sleep apnea severity can change as the night progresses, which would suggest alterations in the passive and/or active P_{CRIT} during the night. In the current study, we found no significant differences in passive P_{CRIT} over time within the same night, suggesting that such changes are rather small. We could not exclude significant within-night changes in the active P_{CRIT} since this was not assessed.

We examined whether the analytic approach of calculating P_{CRIT} using a median regression contributed to the between measurement variability. There was a trend for the calculated passive P_{CRIT} to be between ~0.2 to 0.5 cm H_2O lower than the lowest observed pressure level and the active P_{CRIT} to be between ~0.5 and 0.9 cm H_2O lower. The difference between P_{CRIT} and the lowest pressure level is small and would therefore contribute to no greater than ~0.4 cm H_2O of the variability in between-night measurements.

Changes in lung volume could also represent another source of variability in repeated P_{CRIT} measurements.[54] We have recently shown that changing the trans-respiratory pressure by 10 cm H_2O elevates end-expiratory lung volume by one liter and decreases passive P_{CRIT} by 1-2 cm H_2O.[54] A P_{CRIT} difference between measurements would translate into a 0.3 L change in lung volume thereby accounting for 0.3–0.6 cm H_2O (10% to 20%) of the variability. These data imply that while changes in lung volume modify the upper airway collapsibility, only a relatively small portion of between measurement variability could be attributed to a change in lung volume.

Methodological Limitations

There are several additional limitations of the current study. First, the study was a retrospective analysis of sleep studies utilizing a convenience sample that included subjects who had a minimum of two passive and active P_{CRIT} measurements, and may have resulted in an overestimation in the frequency of obtaining a valid P_{CRIT} measurement. Indeed, analysis of our database of previously collected P_{CRIT} measurements demonstrated that we obtained a passive P_{CRIT} measurement in 86% of subjects and active P_{CRIT} in 48%. Furthermore, review of the subjects that we were unable to obtain an active P_{CRIT} measurement in the current study demonstrated that these subjects tended to be control subjects and/or female subjects.[8,44] One explanation for this observation is that sleep disruption may occur at progressively lower nasal pressures and limit the ability to obtain an active P_{CRIT} on successive occasions. Our estimates of successful P_{CRIT} measurement may represent a minimum yield that could be improved with approaches to enhancing sleep continuity (e.g., use of a hypnotic).[16] Second, in the current study we were not able to investigate the within-night variability of the active P_{CRIT}, since the time taken to perform each measurement with stable sleep precluded our ability to obtain two series of active measurements in the same night. Third, although participants maintained a supine posture for measurements of $P_{CRIT,}$ head, neck, and jaw position were not rigorously controlled (see 'Sources of Variability in the Measurement of P_{CRIT}') and could account for some of the variability observed between measurements of passive and active P_{CRIT}. The combination of hypnotic-induced sleep and control of body posture and head and neck position reduced the standard deviation for repeated measurements of passive P_{CRIT} to almost one-third, suggesting that greater precision in P_{CRIT} measurement can be attained by physical control of postural factors and control of sleep state. Our study, however, more likely simulates real world conditions with respect to minor variation in head and neck position while an individual sleeps; therefore, assessment of reliability of P_{CRIT} measurements under these real world conditions are important in establishing

the minimal significant difference in P_{CRIT} measurements with interventions.

Implications and Conclusion

Data regarding the performance characteristics of passive and active P_{CRIT} measurements are important for adequately powering cohort and treatment studies. For example, based on an effect size of 1.0 with a standard deviation (SD: 1.6), a sample of thirteen subjects would be required to obtain 90% power to detect a within-subject passive or active P_{CRIT} difference of 1.6 cm H_2O or R_{US} difference of 11 cm H_2O/L/s. Furthermore, a 15 or 50% attrition rate should be incorporated into the study design for the passive or active P_{CRIT}, respectively, to ensure adequate recruitment. Since the reliability is greater for repeated passive P_{CRIT} measurements during hypnotic-induced sleep, only five subjects would provide equal or greater power to detect the same change in P_{CRIT} or R_{US}. Agreement between repeated measurements of both P_{CRIT} techniques indicates that these methods can reliably quantify mechanical and neuromuscular properties that modify airway collapsibility. The present findings provide critical information required to plan studies examining pathogenic mechanisms and predicting clinical responses to therapeutic interventions such as positional therapy, surgical interventions, oral appliance effects, and pharmacotherapy.

In conclusion, the agreement between repeated measurements of passive and active P_{CRIT} and R_{US} during sleep suggests that upper airway collapsibility can be reliably used to characterize the relative contribution of mechanical and neuromuscular factors to upper airway collapse and could be used to characterize responses to interventions and determine appropriate sample sizes for clinical trial interventions. We anticipate that an approach utilizing measurements of upper airway collapsibility may complement the traditional approach to measurement of sleep apnea severity, the AHI, in defining factors and identifying therapies that predict successful therapeutic outcomes.

ACKNOWLEDGMENTS

The authors would like to thank Drs. Adam Benjafield and Glenn Richards from ResMed Science Center for providing the pressure generators used to measure P_{CRIT}. Support for this study was provided by NHLBI–HL50381, HL37379, and HL077137.

DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Kirkness has received donated CPAP equipment and research support from ResMed Science Center. Dr, Schwartz has received donated CPAP equipment and research support from ResMed Science Center and has consulted for Apnex, Cardiac Concepts and Sora Pharmaceuticals. Dr. Smith has consulted for Apnex. Dr. Patil has received donated CPAP equipment and research support from ResMed Science Center. Dr. Schneider has consulted for Fisher & Paykel and TNI Medical. The other authors have indicated no financial conflicts of interest.

REFERENCES

1. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: A population health perspective. Am J Respir Crit Care Med 2002;165:1217-39.
2. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378-84.
3. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 2000;283:1829-36.
4. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med 2002;165:677-82.
5. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001;163:19-25.
6. Kirkness JP, Schwartz AR, Schneider H, et al. Contribution of male sex, age, and obesity to mechanical instability of the upper airway during sleep. J Appl Physiol 2008;104:1618-24.
7. 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;170:86-93.
8. Patil SP, Schneider H, Marx JJ, Gladmon E, Schwartz AR, Smith PL. Neuromechanical control of upper airway patency during sleep. J Appl Physiol 2007;102:547-56.
9. Schwartz AR, Smith PL, Wise RA, Gold AR, Permutt S. Induction of upper airway occlusion in sleeping individuals with subatmospheric nasal pressure. J Appl Physiol 1988;64:535-42.
10. Smith PL, Wise RA, Gold AR, Schwartz AR, Permutt S. Upper airway pressure-flow relationships in obstructive sleep apnea. J Appl Physiol 1988;64:789-95.
11. Younes M. Contributions of upper airway mechanics and control mechanisms to severity of obstructive apnea. Am J Respir Crit Care Med 2003;168:645-58.
12. 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;143:1300-3.
13. Boudewyns A, Punjabi N, Van de Heyning PH, et al. Abbreviated method for assessing upper airway function in obstructive sleep apnea. Chest 2000;118:1031-41.
14. Fregosi RF, Quan SF, Morgan WL, et al. Pharyngeal critical pressure in children with mild sleep-disordered breathing. J Appl Physiol 2006.
15. Gold AR, Marcus CL, Dipalo F, Gold MS. Upper airway collapsibility during sleep in upper airway resistance syndrome. Chest 2002;121:1531-40.
16. Hoshino Y, Ayuse T, Kurata S, et al. The compensatory responses to upper airway obstruction in normal subjects under propofol anesthesia. Respir Physiol Neurobiol 2009;166:24-31.
17. Ikeda H, Ayuse T, Oi K. The effects of head and body positioning on upper airway collapsibility in normal subjects who received midazolam sedation. J Clin Anesth 2006;18:185-93.
18. Inazawa T, Ayuse T, Kurata S, et al. Effect of mandibular position on upper airway collapsibility and resistance. J Dent Res 2005;84:554-8.
19. Jordan AS, Wellman A, Edwards JK, et al. Respiratory control stability and upper airway collapsibility in men and women with obstructive sleep apnea. J Appl Physiol 2005;99:2020-7.
20. Litman RS, McDonough JM, Marcus CL, Schwartz AR, Ward DS. Upper airway collapsibility in anesthetized children. Anesth Analg 2006;102:750-4.
21. Oliven A, O'Hearn DJ, Boudewyns A, et al. Upper airway response to electrical stimulation of the genioglossus in obstructive sleep apnea. J Appl Physiol 2003;95:2023-9.
22. Owens RL, Malhotra A, Eckert DJ, White DP, Jordan AS. The influence of end-expiratory lung volume on measurements of pharyngeal collapsibility. J Appl Physiol 2010;108:445-51.
23. Rowley JA, Zhou X, Vergine I, Shkoukani MA, Badr MS. Influence of gender on upper airway mechanics: upper airway resistance and Pcrit. J Appl Physiol 2001;91:2248-54.
24. Series F, Cote C, Simoneau JA, St, Marc I. Upper airway collapsibility, and contractile and metabolic characteristics of musculus uvulae. FASEB J 1996;10:897-904.
25. Sforza E, Petiau C, Weiss T, Thibault A, Krieger J. Pharyngeal critical pressure in patients with obstructive sleep apnea syndrome. Clinical implications. Am J Respir Crit Care Med 1999;159:149-57.
26. Isono S, Tanaka A, Tagaito Y, Ishikawa T, Nishino T. Influences of head positions and bite opening on collapsibility of the passive pharynx. J Appl Physiol 2004;97:339-46.

27. Tagaito Y, Isono S, Remmers JE, Tanaka A, Nishino T. Lung volume and collapsibility of the passive pharynx in patients with sleep-disordered breathing. J Appl Physiol 2007;103:1379-85.
28. Morrison DL, Launois SH, Isono S, Feroah TR, Whitelaw WA, Remmers JE. Pharyngeal narrowing and closing pressures in patients with obstructive sleep apnea. Am Rev Respir Dis 1993;148:606-11.
29. Issa FG, Sullivan CE. Upper airway closing pressures in obstructive sleep apnea. J Appl Physiol 1984;57:520-7.
30. Schwartz AR, O'Donnell CP, Baron J, et al. The hypotonic upper airway in obstructive sleep apnea: role of structures and neuromuscular activity. Am J Respir Crit Care Med 1998;157:1051-7.
31. Ayuse T, Inazawa T, Kurata S, et al. Mouth-opening increases upper-airway collapsibility without changing resistance during midazolam sedation. J Dent Res 2004;83:718-22.
32. Marcus CL, McColley SA, Carroll JL, Loughlin GM, Smith PL, Schwartz AR. Upper airway collapsibility in children with obstructive sleep apnea syndrome. J Appl Physiol 1994;77:918-24.
33. Meurice JC, Marc I, Carrier G, Series F. Effects of mouth opening on upper airway collapsibility in normal sleeping subjects. Am J Respir Crit Care Med 1996;153:255-9.
34. Odeh M, Schnall R, Gavriely N, Oliven A. Dependency of upper airway patency on head position: the effect of muscle contraction. Respir Physiol 1995;100:239-44.
35. Penzel T, Moller M, Becker HF, Knaack L, Peter JH. Effect of sleep position and sleep stage on the collapsibility of the upper airways in patients with sleep apnea. Sleep 2001;24:90-5.
36. Philip-Joet F, Marc I, Series F. Effects of genioglossal response to negative airway pressure on upper airway collapsibility during sleep. J Appl Physiol 1996;80:1466-74.
37. Seelagy MM, Schwartz AR, Russ DB, King ED, Wise RA, Smith PL. Reflex modulation of airflow dynamics through the upper airway. J Appl Physiol 1994;76:2692-700.
38. Walsh JH, Maddison KJ, Platt PR, Hillman DR, Eastwood PR. Influence of head extension, flexion, and rotation on collapsibility of the passive upper airway. Sleep 2008;31:1440-7.
39. Katz ES, Marcus CL, White DP. Influence of airway pressure on genioglossus activity during sleep in normal children. Am J Respir Crit Care Med 2006;173:902-9.
40. Oliven A, Odeh M, Geitini L, et al. Effect of coactivation of tongue protrusor and retractor muscles on pharyngeal lumen and airflow in sleep apnea patients. J Appl Physiol 2007;103:1662-8.
41. Schwartz AR, Schubert N, Rothman W, et al. Effect of uvulopalatopharyngoplasty on upper airway collapsibility in obstructive sleep apnea. Am Rev Respir Dis 1992;145:527-32.
42. Kirkness JP, Madronio M, Stavrinou R, Wheatley JR, Amis TC. Surface tension of upper airway mucosal lining liquid in obstructive sleep apnea/hypopnea syndrome. Sleep 2005;28:457-63.
43. Schwartz AR, Gold AR, Schubert N, et al. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. Am Rev Respir Dis 1991;144:494-8.
44. McGinley BM, Schwartz AR, Schneider H, Kirkness JP, Smith PL, Patil SP. Upper airway neuromuscular compensation during sleep is defective in obstructive sleep apnea. J Appl Physiol 2008;105:197-205.
45. Schwartz AR, Eisele DW, Smith PL. Pharyngeal airway obstruction in obstructive sleep apnea: pathophysiology and clinical implications. Otolaryngol Clin North Am 1998;31:911-8.
46. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. US Government Printing Office., 1968.
47. Atlas Task Force. EEG Arousals: Scoring Rules and Examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992;15:174-84.
48. American Academy of Sleep Medicine. The international classification of sleep disorders: diagnostic and coding manual. 2nd ed. Westchester, IL: American Academy of Sleep Medicine, 2005.
49. Punjabi NM, O'hearn DJ, Neubauer DN, et al. Modeling hypersomnolence in sleep-disordered breathing. A novel approach using survival analysis. Am J Respir Crit Care Med 1999;159:1703-9.
50. Deyo RA, Diehr P, Patrick DL. Reproducibility and responsiveness of health status measures. Statistics and strategies for evaluation. Control Clin Trials 1991;12:142S-58S.
51. Gold AR, Schwartz AR. The pharyngeal critical pressure. The whys and hows of using nasal continuous positive airway pressure diagnostically. Chest 1996;110:1077-88.
52. Ratnavadivel R, Chau N, Stadler D, Yeo A, McEvoy RD, Catcheside PG. Marked reduction in obstructive sleep apnea severity in slow wave sleep. J Clin Sleep Med 2009;5:519-24.
53. McEvoy RD, Sharp DJ, Thornton AT. The effects of posture on obstructive sleep apnea. Am Rev Respir Dis 1986;133:662-6.
54. Squier SB, Patil SP, Schneider H, Kirkness JP, Smith PL, Schwartz AR. Effect of end-expiratory lung volume on upper airway collapsibility in sleeping men and women. J Appl Physiol 2010.