Lung Volume and Continuous Positive Airway Pressure Requirements in Obstructive Sleep Apnea

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Previous studies have demonstrated that lung volume during wakefulness influences upper airway size and resistance, particularly in patients with sleep apnea. We sought to determine the influence of lung volume on the level of continuous positive airway pressure (CPAP) required to prevent flow limitation during non-REM sleep in subjects with sleep apnea. Seventeen subjects (apnea–hypopnea index, 42.6 ± 6.2 [SEM]) were studied during stable non-REM sleep in a rigid head-out shell equipped with a positive/negative pressure attachment for manipulation of extrathoracic pressure. An epiglottic pressure catheter plus a mask/pneumotachometer were used to assess flow limitation. When lung volume was increased by 1,035 ± 22 ml, the CPAP level could be decreased from 11.9 ± 0.7 to 4.8 ± 0.7 cm H_2O ($p < 0.001$) without flow limitation. The decreased CPAP at the same negative extrathoracic pressure yielded a final lung volume increase of 421 ± 36 ml above the initial value. Conversely, when lung volume was reduced by 732 ± 74 ml ($n = 8$), the CPAP level had to be increased from 11.9 ± 0.7 to 17.1 ± 1.0 cm H_2O ($p < 0.001$) to prevent flow limitation, with a final lung volume decrease of 567 ± 78 ml. These results demonstrate that relatively small changes in lung volume have an important effect on the upper airway in subjects with sleep apnea during non-REM sleep.

Keywords: airflow limitation; continuous positive airway pressure; lung volume; sleep apnea; upper airway

Obstructive sleep apnea (OSA) syndrome is a common disorder that occurs in approximately 4% of middle-aged men and 2% of women (1). OSA is characterized by repetitive pharyngeal collapse during sleep, leading to sleep disruption, arousals, and arterial oxygen desaturation. However, the mechanisms leading to pharyngeal collapse are not completely understood. Previous investigators have suggested that this airway collapse involves a combination of anatomic narrowing of the upper airway by pharyngeal structures and sleep-induced decrements in pharyngeal dilator muscle activity (2–5).

During sleep, in normal subjects, upper airway resistance increases and functional residual capacity (FRC) decreases (6–8). These sleep-induced decrements in lung volume are believed to increase upper airway collapsibility and contribute to inspiratory flow limitation, although the exact mechanisms are not entirely clear. Animal data, using mongrel dogs, have suggested that thoracic inflation increases upper airway pharyngeal size and stiffness through caudal traction on the trachea. These forces, independent of upper airway muscle activity, increase the size of the upper airway and decrease resistance to airflow (9, 10).

Studies in adult humans (without OSA) have shown that, during wakefulness, passive changes in lung volume have a substantial influence on pharyngeal airway size and collapsibility (11, 12). In addition, our group has recently demonstrated that, in normal subjects during sleep, there is increased pharyngeal collapsibility and airflow resistance despite increased genioglossus muscle activation, when lung volume is lowered by extrathoracic positive pressure (13).

Other investigators, comparing normal subjects and patients with OSA, have reported a greater lung volume dependence of the upper airway in the latter group, such that patients with OSA have larger changes in upper airway size over the normal tidal breathing range (14, 15). These studies suggest that patients with OSA have a greater propensity for pharyngeal collapse at low lung volumes, compared with weight-matched control subjects.

Continuous positive airway pressure (CPAP) is recognized to be an effective treatment for sleep apnea (16). It is believed to act by pneumatically "splinting" the pharyngeal airway, thereby preventing its collapse during sleep (17, 18). However, CPAP is also known to increase lung volume (19). CPAP could therefore also prevent sleep apnea and hypopnea by increasing upper airway stiffness through caudal traction of the trachea (because of an increase in lung volume).

We therefore hypothesized that an increase in lung volume would stabilize the upper airway and reduce the need for CPAP in patients with sleep apnea. Conversely, a reduction in lung volume should decrease upper airway size and stiffness, leading to an increase in the CPAP level required to prevent upper airway flow limitation. Some of the results of this study have been previously reported in abstract form (20).

METHODS

Subjects

We studied 17 subjects with sleep apnea (Table 1) with moderate to severe OSA syndrome (mean apnea–hypopnea index [AHI], 42.6 ± 6.2 [SEM] events/hour of sleep) determined by overnight polysomnogram using American Academy of Sleep Medicine–defined criteria (21). The subjects were currently treated with CPAP. The protocol was approved by the Human Subjects Committee at Brigham and Women's Hospital. All subjects provided written consent before participation in the study. Subjects with medical disorders potentially affecting chest compliance or the upper or lower airway (other than OSA and obesity) were excluded.

Techniques

Airway pressure was recorded at the level of the epiglottis with a pressure-tipped catheter (Millar MPC-500; Millar Instruments, Inc., Houston, TX). Before insertion of the catheter, both nostrils were decongested with 0.05% oxymetazoline hydrochloride, and one nostril was anesthetized with two to four sprays of 4% lidocaine topical spray. Subjects breathed through a nasal mask (Respironics, Murraysville, PA)

(*Received in original form April 27, 2004; accepted in final form April 4, 2005*)

Supported by grants HL48531, HL60292, NIH/NHLBI T32 HL07901, NIH/RR01032 from the National Institutes of Health, and by the Fond National Suisse de la Recherche Scientifique, Fondation SICPA, and the Société Academique Vaudoise.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 172. pp 114–117, 2005
Originally Published in Press as DOI: 10.1164/rccm.200404-552OC on April 7, 2005
Internet address: www.atsjournals.org

TABLE 1. DEMOGRAPHIC DATA ON THE 17 SUBJECTS INCLUDED IN THE STUDY

	Mean	SEM	Range
Age, yr	47.6	2.1	33–57
BMI, kg/m^2	31.9	1.3	25.1–44.4
AHI, events/h	42.6	6.2	13.4–107.0
Men, %	65%		

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index.

with airflow measured with a pneumotachograph (Hans Rudolph, Kansas City, MO) and pressure transducer (Validyne Corp., Northridge, CA). End-tidal CO_2 was sampled at the mask using a calibrated infrared CO_2 analyzer (BCI Corp., Waukesha, WI).

Lung volume was manipulated with the subject lying supine in a head-out rigid shell (Porta-lung, Inc., Murraysville, PA) adapted with a vacuum/blower attachment (ShopVac, Williamsport, PA) to increase or decrease extrathoracic pressure. Changes in end-expiratory lung volume were measured with two pairs of magnetometers (EOL Eberhard, Oberwil, Switzerland) placed in the anteroposterior axis of the chest and abdomen. Magnetometers were calibrated to volumes obtained from a pneumotachograph and changes in end-expiratory lung volumes were determined using a previously validated formula (22, 23). Wakefulness and sleep stages were determined using standard EEG, chin EMG, and electrooculogram.

Protocol

The CPAP was initially set at the patient's prescribed level. After achieving stable non-REM sleep, the CPAP was adjusted to the minimal level required to prevent flow limitation. This was accomplished by modulating the CPAP level until the flow signal (pneumotachograph) and the pressure signal at the epiglottis consistently demonstrated similar inspiratory curves (measured for 7.3 ± 1.2 minutes during the initial titration and 3.3 ± 0.4 minutes for the subsequent CPAP titrations). Flow limitation was defined as at least a 1-cm H_2O decrement in epiglottic pressure without an associated increase in inspiratory flow (Figure 1) (24). In all subjects, lung volume was then increased by approximately 1,000 ml by applying a negative extrathoracic pressure. Subsequently, the CPAP was again titrated to the lowest level required to prevent flow limitation. End-expiratory lung volume was monitored continuously. In eight subjects, we also determined the CPAP level required to prevent flow limitation after a lung volume decrease of approximately 750 ml. All experiments were conducted during stage 2 or 1 non-REM sleep.

We used a one-way repeated measures analysis of variance with a *post hoc* Tukey test to determine if there was a significant difference between CPAP levels in patients who were studied under the three conditions. A paired *t* test was used to compare the required CPAP level for the 17 subjects between baseline and the 1-L increase in lung volume. All data are reported as means ± SE. Linear regression using mixed models was performed to estimate the effect of lung volume on CPAP pressure (*see* the online supplement for details on data analysis and lung volume measurements).

RESULTS

Seventeen patients completed the protocol (6 women, 11 men; Table 1). The mean CPAP level required to prevent flow limitation in the upper airway without manipulation of lung volume was 11.9 ± 0.7 cm H_2O. This was defined as "baseline CPAP lung volume."

When lung volume was increased by 1,035 ± 22 ml with a mean negative extrathoracic pressure of 9.7 ± 0.6 cm H_2O, the CPAP level required to prevent upper airway flow limitation decreased from 11.9 ± 0.7 to 4.8 ± 0.7 cm H_2O ($p < 0.001$). The final lung volume increase (after retitration of the CPAP) was 421 ± 36 ml above the initial baseline CPAP lung volume. We considered this latter volume as the true lung volume increase.

In eight of the subjects, lung volume was also decreased by 732 ± 74 ml, with a mean positive extrathoracic pressure of 9.4 ± 1.0 cm H_2O. The CPAP level required to prevent flow limitation was 17.1 ± 1.0 cm H_2O ($p < 0.001$). The final lung volume decrease after CPAP retitration was 567 ± 78 ml below the initial baseline CPAP lung volume. These results are summarized in Figures 2 and 3.

The relationships between CPAP requirement and lung volume, and between CPAP requirements and extrathoracic pressure, were inverse but both highly significant ($p < 0.0001$). Using a Pearson test, the correlation coefficients were, respectively, −0.82 (required CPAP level and lung volume) and 0.89 (required CPAP level and extrathoracic pressure).

Using mixed-effect models, we found a significant relationship between the required CPAP level and lung volume ($p < 0.0001$). The slope of this relationship was –11. 44 ± 1.54 cm H_2O/L. We tested for possible nonlinear effects by adding a quadratic term to the model. This term was nonsignificant ($p = 0.19$). This model suggests that the CPAP level required to prevent flow limitation varies by 11.44 cm H_2O for 1-L change in (final) lung volume.

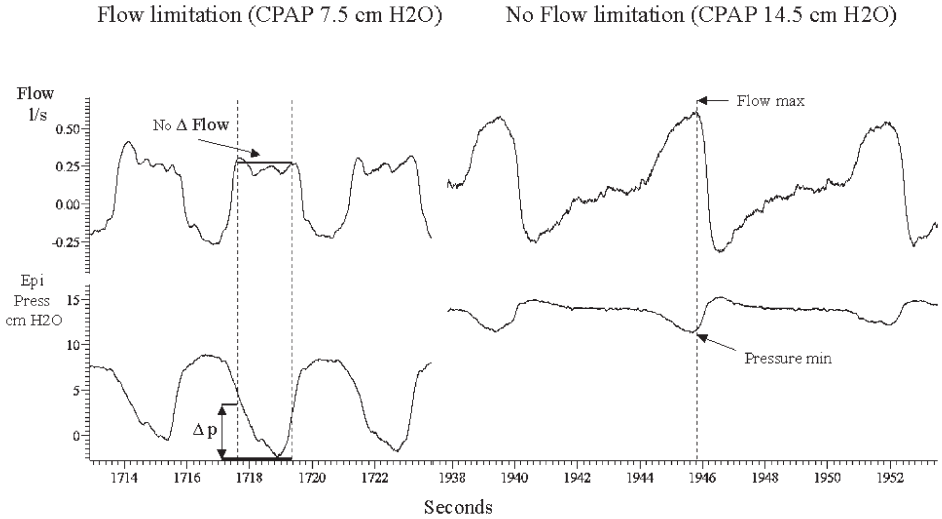

Figure 1. Demonstration of the presence and absence of flow limitation as determined by an epiglottic catheter at two continuous positive airway pressures (CPAP). On the *left*, there is a further decrease in epiglottic pressure (Δp) when the flow reaches a plateau (no Δ flow). On the *right* (no flow limitation), the nadir of epiglottic pressure (pressure min) corresponds to the peak flow (flow max).

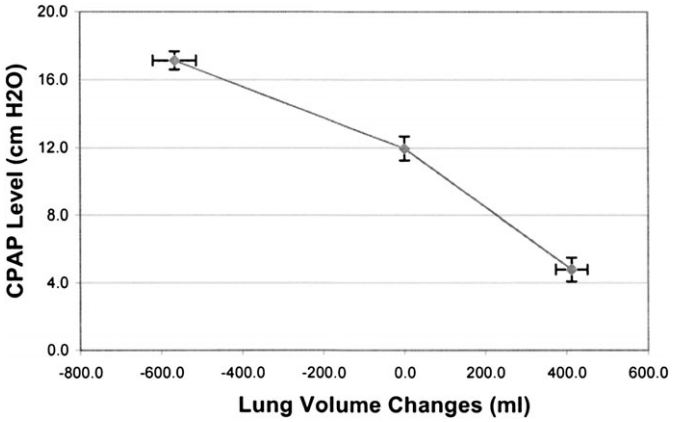

Figure 2. The relationship between the "final" lung volume (after CPAP retitration) and the CPAP level required to prevent flow limitation.

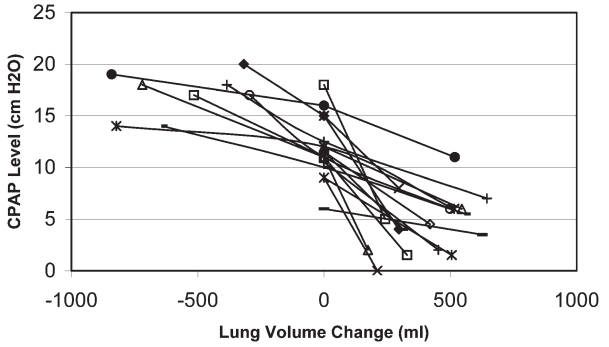

Figure 3. Individual results for CPAP requirements versus change in lung volume are depicted. The lung volume represents the "final" lung volume after CPAP retitration.

DISCUSSION

These results demonstrate the influence of lung volume on upper airway mechanics in patients with sleep apnea during non-REM sleep. The CPAP level required to prevent upper airway flow limitation can be substantially reduced when lung volume is increased. Moreover, the CPAP level had to be considerably increased when lung volume was decreased. Such a marked effect of relatively minor lung volume changes (+421, −567 ml) on the upper airway has not been previously reported. The modeling of these results supports the concept of a direct relationship between lung volume and upper airway collapsibility during non-REM sleep in patients with OSA. These results also suggest that increments in lung volume may be an important mechanism by which CPAP reduces or eliminates disordered breathing during sleep. The animal and human studies previously described suggest that the mechanism underlying this association is probably an increase in upper airway stiffness with increased lung volume caused by caudal traction from the trachea.

OSA is clearly a "sleep-dependent" disorder, because even patients with severe apnea only have obstructed breathing events during sleep. This state effect is believed to be mediated primarily by the loss of neuromuscular reflexes that keep the upper airway patent during wakefulness (25–27). However, if one considers the physiologic decrease in FRC that occurs in normal subjects when they fall asleep (190–440 ml decrease in FRC between wakefulness and stage 2 non-REM sleep [7, 8]), it seems probable that this decrement in lung volume may also importantly contribute to the increase in upper airway collapsibility. This effect may be even more important in supine, obese subjects with large abdominal mass.

CPAP is believed to act as a pneumatic "splint," thereby preventing upper airway collapse (17, 18). However, it is also known to increase lung volume (19). Our results suggest that the effect of CPAP on lung volume may be an important mechanism by which it prevents upper airway collapse. Further work is necessary to precisely determine the relative importance of lung volume versus airway pressure on CPAP efficacy.

The fact that one of the ways by which CPAP mediates its effect on the upper airway is via changes in lung volume remains controversial, however, and is not supported by all previous literature. In 1990, Series and coworkers (28) eliminated the increments in lung volume which occur with CPAP by applying an identical positive extrathoracic pressure in normal subjects during wakefulness. They observed upper airway resistance to be slightly higher with CPAP plus positive extrathoracic pressure than with CPAP alone. However, this difference was not significant, and they concluded that splinting of the upper airway is the principal mechanism of action of CPAP. However, these subjects were awake and probably modulated upper airway resistance behaviorally with pharyngeal muscles, thus preventing important changes in resistance. Normal subjects also have a less collapsible airway than individuals with OSA. This group also determined the effect of a 500-ml increase in lung volume in patients with apnea during sleep, using a poncho-type respirator with a constant negative extrathoracic pressure (29). No reduction in AHI or improvement in sleep architecture was observed, although there was a reduction in the severity of oxygen desaturation. However, they did not measure lung volume during sleep and induced smaller changes in lung volume than occurred in the present study. They also used a very different outcome variable than was used in our protocol (AHI vs. flow limitation). One could argue that the improved sensitivity of flow limitation over AHI in assessing pharyngeal mechanics facilitated our demonstration of a lung volume effect in the present study.

Interestingly, Akshay and colleagues (30), in 1983, were able to dramatically reduce apnea frequency and oxygen desaturation in nine patients with sleep apnea by applying positive expiratory airway pressure without positive inspiratory pressure (30). Because positive expiratory airway pressure is supposed to increase lung volume without providing inspiratory upper airway splinting, these results support the hypothesis that end-expiratory lung volume may have a substantial effect on upper airway physiology and sleep apnea severity.

Several methodologic issues need to be addressed. First, it is possible that factors such as sex, body mass index, or AHI could influence the effect of lung volume on the upper airway. A separate analysis of the effect of an increase in lung volume in men only ($n = 11$) and women only ($n = 6$) demonstrated a significant effect in both sexes (respectively, $p < 0.001$ and $p = 0.001$). However, the sample size doesn't allow us to study body mass index or AHI as covariates. Second, we chose to titrate CPAP to eliminate flow limitation, as previously performed by other investigators (31, 32), rather than assessing AHI at varying lung volumes across an entire night. Either would likely yield valid results. However, many factors contribute to AHI (i.e., cycle frequency) of which upper airway collapsibility is only one; therefore, we believe the minimal CPAP level required to prevent flow limitation is probably a better measure. Third, when the CPAP level is titrated down (after lung volume was increased), it could be argued that (*1*) upper airway muscle

activation slowly adapts to the new condition allowing for lower CPAP levels and (*2*) that a hysteresis of the upper airway could also allow us to lower CPAP level without observing flow limitation. However, because we always incremented the CPAP level once flow limitation was observed, substantial muscle recruitment was unlikely and hysteresis of the upper airway should not be a problem. Fourth, decreasing lung volume was difficult as rising upper airway resistance often led to arousal. This explains the considerable variability in lung volume decrement in our subjects (range, 550–1,043 ml) because some tolerated this better than others. Moreover only 8 of the 17 subjects were studied with a decrease and an increase in lung volume. However, these eight subjects were not different compared with the others (sex, AHI, body mass index), and we therefore chose to report these data together. Finally, it could be argued that our results may be the consequence of a direct effect of the iron lung pressure on the neck and upper airway. However, we took special care to prevent any pressure on the neck as described in METHODS in the online supplement. We therefore believe our results to be a product of changing lung volume and not a result of direct pressure around the neck.

In conclusion, these results demonstrate that lung volume has an important effect on upper airway collapsibility and suggest that it may be one of the mechanisms by which CPAP prevents upper airway obstruction in patients with sleep apnea. Further work will be required to explore the therapeutic potential of lung volume manipulation.

Conflict of Interest Statement: R.C.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.L.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; R.B.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; S.R.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.S.J. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; K.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; D.P.W. is a consultant and receives research grants from Respironics, Alfred E. Mann Foundation, Cephalon, WideMed, and Itamar Medical, and is a consultant to Aspire Medical.

References

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;32:1230–1235.
2. Haponik E, Smith P, Bohlman M, Allan R, Goldman S, Bleecker E. Computerized tomography in obstructive sleep apnea: correlation of airway size with physiology during sleep and wakefulness. *Am Rev Respir Dis* 1983;127:221–226.
3. Suratt PM, Dee P, Atkinson RL, Armstrong P, Wilhoit SC. Fluoroscopic and computed tomographic features of the pharyngeal airway in obstructive sleep apnea. *Am Rev Respir Dis* 1983;127:487–492.
4. Schwab RJ, Gupta KB, Gefter WB, Metzger LJ, Hoffman EA, Pack AI. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing: significance of the lateral pharyngeal walls. *Am J Respir Crit Care Med* 1995;152:1673–1689.
5. Mezzanotte WS, Tangel DJ, White DP. Waking and sleeping upper airway muscle activity in apnea patients versus normal control. *Am J Respir Crit Care Med* 1996;153:1880–1887.
6. Kay A, Trinder J, Kim Y. Progressive changes in airway resistance during sleep. *J Appl Physiol* 1996;81:282–292.
7. Ballard RD, Irvin CG, Martin JR, Pak J, Pandey R, White DP. Influence of sleep on lung volume in asthmatic patients and normal subjects. *J Appl Physiol* 1990;68:2034–2041.
8. Hudgel DW, Devatta P. Decrease in functional residual capacity during sleep in normal humans. *J Appl Physiol* 1984;57:1319–1322.
9. Van de Graaff WB. Thoracic influence on upper airway patency. *J Appl Physiol* 1988;65:2124–2131.
10. Van de Graaff WB. Thoracic traction on the trachea: mechanisms and magnitude. *J Appl Physiol* 1991;70:1328–1363.
11. Series F, Marc I. Influence of lung volume dependance of upper airway resistance during continuous negative airway pressure. *J Appl Physiol* 1994;77:840–844.
12. Series F, Cormier Y, Desmeules M. Influence of passive changes of lung volume on upper airways. *J Appl Physiol* 1990;68:2159–2164.
13. Stanchina ML, Malhotra A, Fogel RB, Trindler J. Edwards Jk, Schory K, White DP. The influence of lung volume on pharyngeal mechanics, collapsibility and genioglossus muscle activation during sleep. *Sleep* 2003;26:851–856.
14. Hoffstein V, Zamel N, Phillipson EA. Lung volume dependence of pharyngeal cross-sectional area in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1984;130:175–178.
15. Fogel RB, Malhotra A, Dalagiorgou G, Robinson MK, Jakab M, Kikinis R, Pittman SD, White DP. Anatomic and physiologic predictors of apnea severity in morbidly obese subjects. *Sleep* 2003;26:150–155.
16. Jenkinson C, Davies RJ, Mullins R, Stradling JR. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. *Lancet* 1999;353:2100–2105.
17. Schwab RJ, Pack AI, Gupta KB, Metzger LJ, Oh E, Getsy JE, Hoffman EA, Gefter WB. Upper airway and soft tissue structural changes induced by CPAP in normal subjects. *Am J Respir Crit Care Med* 1996; 154:1106–1116.
18. Abbey NC, Block AJ, Green D, Mancuso A, Hellard DW. Measurement of pharyngeal volume by digitized magnetic resonance imaging: effect of nasal continuous positive airway pressure. *Am Rev Respir Dis* 1989; 140:717–723.
19. O'Donoghue FJ, Catcheside PG, Jordan AS, Bersten AD, McEvoy RD. Effect of CPAP on intrinsic PEEP, inspiratory effort, and lung volume in severe stable COPD. *Thorax* 2002;57:533–539.
20. Stanchina ML, Malhotra A, Fogel RB, Millman JK, Edwards JK, Schory K, White DP. The influence of lung volume changes during sleep on pharyngeal mechanics in obstructive sleep apnea (OSA) patients [abstract]. *Am J Respir Crit Care Med* 2003;167:A303.
21. American Academy of Sleep Medicine. Sleep related breathing disorders in adults: recommendations for syndrome definition and measurements techniques in clinical research. *Sleep* 1999;22:667–689.
22. Banzett RB, Mahan ST, Garner DM, Brughera A, Loring SH. A simple and reliable method to calibrate respiratory magnetometers and Respitrace. *J Appl Physiol* 1995;79:2169–2176.
23. Konno K, Mead J. Measurement of the separate volume changes of rib cage and abdomen during breathing. *J Appl Physiol* 1967;22:407–422.
24. Clark S, Wilson C, Satoh M, Pegelow D, Dempsey J. Assessment of inspiratory flow limitation invasively and noninvasively during sleep. *Am J Respir Crit Care Med* 1998;158:713–722.
25. Wheatley J, Tangel D, Mezzanotte W, White D. Influence of sleep on response to negative airway pressure of tensor palatini muscle and retropalatal airway. *J Appl Physiol* 1993;75:2117–2124.
26. Horner R, Innes J, Morrell M, Shea S, Guz A. The effect of sleep on reflex genioglossus muscle activation by stimuli of negative airway pressure in humans. *J Physiol* 1994;476:141–151.
27. Younes M, Ostrowski M, Thompson W, Leslie C, Shewchuk W. Chemical control stability in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2001;163:1181–1190.
28. Series F, Cormier Y, Couture J, Desmeules M. Changes in upper airway resistance with lung inflation and positive airway pressure. *J Appl Physiol* 1990;68:1075–1079.
29. Series F, Cormier Y, Lampron N, La Forge J. Influence of lung volume in sleep apnea. *Thorax* 1989;44:52–57.
30. Akshay K, Mahadevia AK, Onal E, Lopata M. Effects of expiratory positive airway pressure on sleep induced respiratory abnormalities in patients with hypersomnia-sleep apnea syndrome. *Am Rev Respir Dis* 1983;128:708–711.
31. Condos R, Norman RG, Krishnasamy I, Peduzzi N, Goldring RM, Rapoport DM. Flow limitation as a noninvasive assessment of residual upper-airway resistance during continuous positive airway pressure therapy of obstructive sleep apnea. *Am J Respir Crit Care Med* 1994; 150:475–480.
32. Series F, Marc I. Effects of inspiratory and expiratory positive pressure difference on airflow dynamics during sleep. *J Appl Physiol* 1998;85: 1855–1862.