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EFFECT OF NASAL RESISTANCE ON DELIVERED CONTINUOUS POSITIVE AIRWAY PRESSURE IN THE TREATMENT OF SLEEP APNEA-HYPOPNEA SYNDROME

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EFFECT OF NASAL RESISTANCE ON DELIVERED CONTINUOUS POSITIVE AIRWAY PRESSURE IN THE TREATMENT OF SLEEP APNEA-HYPOPNEA SYNDROME

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ABBREVIATIONS

AHI: Apnea-hypopnea index

AR: Acoustic rhinometry

CPAP: Continuous positive airway pressure

CSA: Cross-sectional area

C-Flex: Flexible positive airway pressure

NOSE: Nasal obstruction symptom evaluation

NR: Nasal resistance

NPSG: Nocturnal polysomnography

Pm: Expiratory pressure swing in the mask

Ps: expiratory pressure swing in the supraglottis

PAP: Positive airway pressure

Pcrit: Critical closing pressure

ΔPm: change in expiratory mask pressure swings (C-Flex 3 minus CPAP)

ΔPs: change in expiratory pressure swings in the supraglottis (C-Flex 3 minus CPAP)

RM: Rhinomanometry

REM: Rapid eye movement sleep

SAHS: Sleep apnea-hypopnea syndrome

SDB: Sleep disordered breathing

SGP: Supraglottic pressure

UA: Upper airway

Ws: estimated expiratory work (integrated supraglottic pressure during expiration).

INDEX

1. INTRODUCTION 1

1.1 Sleep apnea-hypopnea syndrome 1

1.2 Historical background 2

1.3 Epidemiology 4

1.4 Risk factors 5

1.5 Anatomy and physiology of the upper airway 10

1.6 Upper airway resistance 27

1.7 Pathogenesis of SAHS 29

1.8 Clinical assessment and consequences 32

1.9 Treatment 36

1.10 The role of the nose in sleep disordered breathing 41

2. JUSTIFICATION OF THE RESEARCH 49

3. HYPOTHESIS 51

4. OBJECTIVES 53

5. METHODS 57

5.1 Protocol 57

5.2 Daytime evaluation 59

5.2.1 Clinical assessment 59

5.2.2 Subjective questionnaires of nasal symptoms 60

5.2.3 Measurements of nasal resistance during wakefulness 61

5.3 Nighttime evaluation 66

5.3.1 Diagnostic nocturnal polysomnography 66

5.3.2 CPAP titration polysomnography 67

5.3.3 Measurements of supraglottic pressure during sleep 67

5.3.4 Application of C-Flex settings 69

5.4 Mechanical model of the upper airway 70

5.5 Analysis 72

5.6 Statistics 73

6. RESULTS 75

6.1 Relationship between noninvasive measures of nasal resistance and directly assessed supraglottic resistance 75

6.1.1 Wake measurement predictive of sleep upper airway physiology 75

6.1.1.1 Nasal resistance during wakefulness by acoustic rhinometry 75

6.1.1.2 Nasal resistance during wakefulness by active anterior rhinomanometry 78

6.1.1.3 Correlation between measurements of nasal resistance by acoustic rhinometry and active anterior rhinomanometry 82

6.1.1.4 Evaluation of upper airway resistance (supraglottis) on optimal CPAP application during sleep 84

6.1.1.5 Correlation between measures of nasal resistance during wakefulness and supraglottic resistance during sleep 89

6.1.1.6 Correlation between upper airway and nasal resistances and clinical variables 89

6.2 Influence of upstream resistance on upper airway pressure during expiration on fixed optimal CPAP and with the application of C-Flex settings 91

6.2.1 Assessment of the expiratory pressure profile at the mask and at the upper airway on fixed CPAP with and without C-Flex 91

6.2.1.1 In patients with SAHS 91

6.2.1.2 In a mechanical model of the upper airway 98

7. DISCUSSION 109

8. CONCLUSIONS 117

9. REFERENCES 119

10. APPENDIX 1. PUBLICATION 1 143

11. APPENDIX 2. PUBLICATION 2 145

1. INTRODUCTION

1.1 SLEEP APNEA-HYPOPNEA SYNDROME

Obstructive sleep disordered breathing is a continuum of breathing disorders ranging from occasional snoring to habitual snoring, upper airway resistance syndrome and sleep apnea-hypopnea syndrome (SAHS). This spectrum of disease has a multiple etiology with the final common pathway of upper airway (UA) collapse.

SAHS is characterized by recurrent episodes of partial (*hypopnea*) or complete (*apnea*) upper airway collapse during sleep as a consequence of UA instability.[1,2] The perception of the increasing intensity of inspiratory effort and the increase in pharyngeal pressure lead to arousal or awakening which increases UA muscle dilator activity and breaks the apnea.[3] This sequence of events recurs hundreds of times in a night.

The most widely used severity criteria use ‘‘cutoffs’’ based on the frequency of apnea and hypopnea events. By consensus, mild sleep apnea has been defined as a number of apneas and hypopneas per hour of sleep of 5 to 15 events (AHI), moderate as greater than 15 to 30 events per hour, and severe as greater than 30 events per hour.[4] A similar measure called respiratory disturbance index (RDI) not only is based on airflow, desaturations, and arousals but also uses arousals related to respiratory effort. Most epidemiologic studies have used the AHI or RDI almost interchangeably. Unfortunately, the current severity criteria based on AHI or RDI correlates only loosely with symptoms or clinical severity.[5] Although this is a very practical definition, it is not particularly useful when it comes to “phenotyping” SAHS. Thus, it has been postulated that SAHS should be broken down into intermediate phenotypes that could then be assessed in terms of their relative contribution to the overall phenotype. These include the craniofacial morphology, obesity and susceptibility to sleepiness, as well as ventilatory and UA control. Difficulty arises in distinguishing those variables within the SAHS phenotype that are central to the disease process and those that are epiphenomena.[6]

The disorder is recognized as an important cause of medical morbidity and mortality and the signs, symptoms and consequences of SAHS are a direct result of the derangements that occur due the repetitive obstruction of the UA such as sleep fragmentation, hypoxemia, hypercapnia, marked swings in thoracic pressure and increased sympathetic activity.[7] Significant clinical consequences of the disorder cover a wide spectrum including daytime hypersomnolence,[8,9] neurocognitive dysfunction,[10] cardiovascular disease,[11-13] metabolic dysfunction,[14-16] respiratory failure and cor pulmonale.[17]

The gold standard treatment consists of 'splinting' the UA by applying a continuous positive airway pressure (CPAP)[18,19] that preserves its patency throughout the night. CPAP treatment normalizes sleep architecture,[20] reduces daytime sleepiness,[21] enhances daily function,[22] reduces automobile accidents[23] and decreases blood hypertension[24] and cardiovascular events.[25,26]

1.2 HISTORICAL BACKGROUND[27,28]

There were strong hints of the widespread existence of SAHS as early the 19th Century. Observations of periodic breathing in sleep were first reported in the mid 1850s and in the 1870s. British physicians reported on several cases of obstructed apneas as *"fruitless contractions of the inspiratory and expiratory muscles against glottis obstruction with accompanying cyanosis during sleep".* During the last half of the 19th Century, several cases of obese persons with extreme daytime sleepiness were described and labeled as *"Pickwickian Syndrome"* because of the resemblance of these patients and Dicken's character Joe as described in the Pickwick Papers in 1837.[29] The first physician to describe the clinical features of SAHS was Broadbent in 1877. Wells reported in 1898 curing several patients of sleepiness by treating their UA obstruction.[30] In 1950s a link

between obesity and control of breathing was appreciated. Daytime retention of CO_2 was observed in obese subjects with daytime sleepiness and without significant lung disease. Burwell et al[17] in 1956 published *"Extreme obesity associated with alveolar hypoventilation: A pickwikian syndrome"*. This report attributed the somnolence to hypercapnia and coined the term *"pickwikian"*. Despite that, no association with sleep disorders was considered, and the daytime sleepiness was ascribed to *"CO_2 poisoning"*. Descriptions of sleep effects on ventilation and ventilatory stability in health were reported by Bulow in the early 1960s.[31] In 1965 Jung and Kuhlo[32] in Germany, and Gastaut in France[33] described SAHS as such, and recognized the disorder in obese subjects as intermittent airway obstruction with frequent arousals providing the first comprehensive links between obesity, sleep-induced airway obstruction, sleep fragmentation and daytime sleepiness. In 1972, in Italy, Lugaresi and Saoul organized the first international symposium on *"Hypersomnia with Periodic Breathing"*. In the 1973 Guilleminault characterized sleep apnea and insomnia as a new syndrome,[34] and in 1976 same author coined the term *"obstructive sleep apnea syndrome"* to emphasize the occurrence of this syndrome in nonobese patients.[1] Extending the spectrum of sleep apnea syndromes, in 1982 Guilleminault et al reported the presence of abnormal respiratory efforts during sleep without apneas in children and gave the name of *"upper airway resistance syndrome"* in 1993 after a similar description in adults.[35,36] Treatment of SAHS advanced when some publications reported the occasional use of chronic tracheotomy for treatment of the disease.[37,38] In 1981 Fujita performed the first uvulopalotopharyngoplasty[39] and Sullivan[18] devised the first CPAP machine as an effective treatment for SAHS. In the 1980s Riley developed the maxillomandibular procedures.[40] From the mid 1990s to the present there have been an explosion of population, clinical and basic research directed toward the prevalence, causes, consequences and treatment of SAHS. The relatively high prevalence

of this sleep-specific problem with potential carryover to daytime pathology has provided great impetus to the growth of Sleep Medicine as a clinical and research specialty.

1.3 EPIDEMIOLOGY[41-43]

Population data sets to estimate SAHS prevalence did not exist until 20 years ago. Currently, a number of studies using large samples representative of the general population are available and provide prevalence estimates for SAHS in countries like United States,[44,45] Spain,[46] Australia,[47] China[48] and India.[49] Synthesis of the available data has been a difficult process as a consequence of methodological limitations such as differences in sampling schemes, disparities in techniques used for monitoring sleep and breathing, and variability in definitions. Despite that, based on available population-based studies the prevalence of SAHS with daytime sleepiness is approximately 3 to 7% for adult men and 2 to 5% for adult women in the general population. Studies evaluating the occurrence of sleep disordered breathing, independently of symptoms, show a much higher prevalence (6-24%) among adults and snoring affects up to 45% of adult population. Prevalence is similar in Europe, North America, Australia and Asia. Disease prevalence is higher in different population subsets, including overweight or obese people and older individuals. Despite all the clinical and scientific advancements regarding SAHS in the last two decades, a great majority (70-80%) of those affected remain undiagnosed. The lack of an appropriate level of case identification is partially driven by the fact that patients are frequently unaware of the associated symptoms that are often identified either by a bed partner or family member.[50,51]

Whereas there are considerable prevalence data, little is known about incidence or progression (i.e., worsening over time) of SAHS. Night-to-night variability in AHI and measurement error lead to difficulties in valid classification of SAHS status that can cause

systematic biases in estimating incidence. Accordingly, the few studies that have prospectively examined SAHS in defined populations have focused on SAHS progression, usually measured as changes in AHI over time, rather than on incidence. Data from baseline and 8-year follow-up studies of 282 participants in the *Wisconsin Sleep Cohort* showed a significant increase in SAHS severity over this interval. AHI progression was significantly greater in obese, older and habitually snoring subjects.[45] Preliminary data from the *Cleveland Family Study*[52,53] demonstrate trends similar to the Wisconsin data, reporting as significant predictors of higher AHI at follow-up excess body weight, central obesity, cardiovascular disease, and diabetes. The *San Diego Older Adult cohort*, a 18-year follow-up data, showed little change in AHI with aging.[54] The available data from both, population and clinic studies suggest that change in severity, mostly toward progression, does occur in individuals with mild or moderate SAHS,[55,56] and epidemiological evidence suggests that substantial progression of SAHS can occur over relatively short time periods. An efficient method of recognizing individuals likely to develop severe SAHS would allow interventions to reduce or reverse SAHS progression before the development of significant morbidity. It appears that habitual snoring and obesity may be useful markers of risk for SAHS progression.

1.4 RISK FACTORS

The major risk factors for SAHS include obesity, age, male gender and postmenopausal status.

Excess body weight - It is a common clinical finding and is present in more than 60% of the patients referred for a diagnostic sleep evaluation.[57] Epidemiologic studies from around the world have consistently identified body weight as the strongest risk factor for SAHS.[44-49] Moreover, longitudinal data from The Wisconsin Sleep Cohort Study,[11] The Cleveland Family Study[53] and The Sleep Heart Health Study[58] showed that an increase in

body weight over time can accelerate the progression of SAHS or lead to development of moderate to severe disease. Despite the unquestionable link between obesity and SAHS, controversy remains as to whether specific measures of body habitus (e.g. neck circumference, waist circumference) that reflect a central versus peripheral distribution of fat are associated with an increased risk for SAHS after controlling for body mass index. Mechanisms by which, increases in body weight can alter normal UA mechanics during sleep are 1) increasing parapharyngeal fat deposition resulting in a smaller UA; 2) modifying neural compensatory mechanisms to maintain UA patency; 3) promoting respiratory control system instability and 4) reducing lung volumes (functional residual capacity with a resultant decrease in the stabilizing caudal traction on the UA). The pathophysiology of SAHS is intimately linked with obesity with an estimated 58% of the moderate to severe cases attributable to a body mass index greater than or equal to 25 kg/m^2.

Age - In one of the earliest studies, Ancoli-Israel and colleagues[59] reported that 70% of men and 56% of women between 65 and 99 years of age had SAHS defined as an AHI of at least 10 events per hour. Subsequent several population-based cohorts confirm a progressively increase of SAHS prevalence with age and a plateau after the sixth decade of life.[41,46,60] In Spain, Duran et al[46] estimated the prevalence among a representative sample of the general population of men and women 30 to 70 years old from Vitoria-Gasteiz, Basque Country. This study showed the largest prevalence difference between middle and older age. For ages 71-100 years, the prevalence of AHI 5 was 80% for women and 81% for men. The prevalence for an AHI of 15 was 49% for women and 57% for men. When compared with the prevalence estimates for the middle-aged participants in this cohort, the prevalence in older age appears to be nearly three times higher for an AHI 5 and more than four times higher for an AHI 15.

Gender - SAHS is more common in males than females with a ratio of 2:1. Clinic based studies have shown that in patients referred for clinical evaluation, the ratio of men to women is in the range from 5 to 8:1.[57] Epidemiologic studies have confirmed the higher prevalence of SAHS in men but report a lower male to female ratio in the range of 2 to 3:1.[61] Several explanations exist for the disparity between clinic and population-based studies. First, men and women with SAHS have distinct symptom profiles, with women possibly not reporting the classical symptoms. Second, differential response of the bed partner to the symptoms of SAHS, with female bed partners of male patients appear to have a lower threshold for symptoms perception and reporting than male bed partners of female patients. Finally, it is also possible that health care providers have a lower index of suspicion for considering SAHS in women than men given the general expectation that the disorder affects men. The male predisposition for the disorder has been attributed to sex differences in anatomical (e.g. UA fat deposition might be greater in men than in women, as men have predominantly upper body fat distribution) and functional (airway muscle dilator activity seems to be increased in women) properties of the UA and in the ventilatory response to arousal in sleep.[62] Sex hormones also have an important role in pathogenesis of SAHS, as disease prevalence is higher in post versus pre-menopausal women[45] and hormone replacement therapy in post-menopausal women has been associated with a lower prevalence of the disease.[63]

Race - Until recently, most of the population-based studies on the prevalence of SAHS were focused on characterizing disease prevalence in Europe, North America or Australia. With the increasing appreciation that SAHS can lead to serious medial sequelae, several studies have been undertaken to characterize the disease prevalence in other countries.

Studies showed that the prevalence of SAHS in Asian[48] samples are comparable to that documented in European and North American samples. Asians are less obese than

Caucasians but disease prevalence in the East is not less than in the West. Moreover, for a given age, sex, and body mass index, Asians have greater disease severity than caucasians.[64-65] Differences in craniofacial features between Asians and Caucasians have been demonstrated and are considered as the etiologic factors for the increased risk and greater severity of SAHS in Asians despite lesser degrees of obesity.[66]

In African-Americans samples the prevalence of SAHS in middle-aged adults, is comparable to that documented in North American and European caucasians samples.[67] However, African-Americans that are at least 65 years of age[68] or those less than 25 years of age[67] have been found to have a higher prevalence of SAHS than middle-aged African Americans and those of other racial groups.

Craniofacial anatomy - Static cephalometric analysis using radiography, computerized tomography and magnetic resonance imaging have revealed a number of skeletal and soft tissue differences between individuals with and without SAHS during wakefulness. Features such as retrognathia, tonsillar hypertrophy, enlarged tongue or soft palate, inferiorly positioned hyoid bone, maxillary and mandible retroposition and decreased posterior airway space can narrow UA dimensions and promote the collapse of UA during sleep.[69] A meta-analysis showed that the mandible body length is the craniofacial measure with the strongest association with increased risk for SAHS.[70]

Familial and genetic predisposition - Several large-scale studies have confirmed a role for inheritance and familial factors in the genesis of SAHS.[71] First degree relatives of those with the disorder are more likely to develop the disease and familial susceptibility to SAHS increases directly with the number of affected relatives.[72] Analysis of the Cleveland Family Study showed that independent of the body mass index, up to 35% of the variance in disease severity can be attributed to genetic factors with possible racial differences in the mode of inheritance.[73] The epsilon 4 allele of the apolipoprotein E (gene mapped at

chromosome 19) has been associated with SAHS in some studies.[74-76] However the mechanism by which this polymorphism might cause SAHS has not been yet defined.

Smoking - Epidemiologic investigations showed that current smoking is associated with a higher prevalence of snoring and SAHS.[77-79] Data from the Wisconsin cohort[77] showed that current smokers were three times more likely to have SAHS than never-smokers, however former smokers were not more likely to have the disease than never smokers. Same study reported that heavy smokers (ie. more than 40 cigarettes a day) had the greatest risk for all the ranges of severity of SAHS. Kashyap et al[78] showed a higher prevalence of smoking in patients with SAHS (35% vs. 18% in non SAHS patients) and current smokers were 2.5 more likely to have SAHS than former smokers and nonsmokers combined, and 2.8 times more likely to have SAHS than former smokers alone.

Airway inflammation and damage due to the cigarette smoke could alter the mechanical and neural properties of the UA and increase its risk of collapsibility during sleep.

Alcohol consumption - Alcohol intake can induce apneic activity in normal or asymptomatic subjects[80] and can prolong apnea duration and worsen the severity of associated hypoxemia in patients with SAHS.[81] Experimental studies showed that alcohol reduces motor output to the UA resulting in hypotonic oropharyngeal muscles.[82]

Other risk factors - These conditions include polycystic ovary syndrome, hypothyroidism and pregnancy.

In polycystic ovary syndrome visceral adiposity and higher androgen levels may predispose to SAHS by altering UA passive mechanical properties and neural control during sleep.[83]

Patients with hypothyroidism may have increased susceptibility for SAHS due to combined mechanical abnormalities as a consequence of the mixedematous status and/or suppressed central respiratory control output.[84]

Gestational weight gain, decrease in pharyngeal luminal size as a consequence of diffuse edema, the effect of sleep deprivation on pharyngeal dilator muscle activity and alterations in pulmonary physiology increase the tendency for SAHS in pregnant women.[85]

1.5 ANATOMY AND PHYSIOLOGY OF THE UPPER AIRWAY

The UA extends from the nares to the larynx and is continuous with the lower airway which begins at the trachea and extends to the alveoli. The UA is the primary conduit for passage of air into the lungs and also participates in other physiological functions such as phonation and deglution. The UA has two well differentiate areas, the *nasal airway* (rigid part of the system) and the *pharyngeal airway (*elastic part of the system). Although most mammals have rigid skeletal support of the pharyngeal airway, patency of the human UA is maintained mostly by muscle activation and soft tissue structures.[86,87] Evolution of speech is thought to have needed substantial laryngeal motility, leading to a hyoid bone without rigid support and a vulnerable airway. Passive mechanical and active neural influences contribute to its patency and collapsibility and as a result, dilating forces (muscle activation) will have a complex interaction with collapsing forces (anatomy, airway negative pressure).

1.5.1 Nasal airway[88,89]

1.5.1.1 Nasal airway anatomy

The nose and paranasal sinuses form a complex rigid unit of different cavities at the entrance of the UA. This system has highly specific functions that include air conditioning, filtering, and warming of inspired air and potentially forming an immunologic response for allergens, and pollutants to protect the delicate structures of the lower airway.

Nasal Pyramid - The external nose is composed of bones and cartilage. Its strong structure protects the internal structures of the nasal cavities and its sensitive mucosa. The external aspect of the nose can be compared with a three-sided pyramid. The top of this

pyramid is implanted on the forehead and the base contains the two *nares o nostrils* with, between them, a septum called *membranous columella* that extents from the nasal apex or tip to the center of the upper lip. The *nasal vestibule* is a slight dilatation within the nares and corresponds to the entrance to the nose. The upper third of the nose is formed by nasal bones, the middle third is made up of the upper lateral cartilages, forming bilateral triangular flat expansions of the septal cartilage, and the lower third is supported by the lower lateral or alar cartilage. The caudal margins of the upper lateral cartilages usually overlie the upper margins of the lower lateral cartilages. This junction is called the *limen nasi* and in this area is situated the narrowest site in the nasal cavity, the *internal nasal valve* which is formed by this limen nasi, the head of the inferior turbinate, and the septum. The internal nasal valve will be the most important factor to determine nasal airflow resistance. The bony-cartilaginous external nose is covered by muscle and skin, and these muscles influence continuously the global airflow entering the nasal cavity.

Nasal septum - The midline structure divides the nasal cavity in two halves and is composed of bony and cartilaginous components. Its major importance consists, in association to the inferior nasal turbinates, of the regulation of the airflow and resistance. As a part of the internal nasal valve in case of deviation or malposition (eg, congenital or post-traumatic) of this structure, it can narrow the valve and cause nasal obstruction.[90]

Nasal cavity - It consists of a 5 cm high and 10 cm long dual chamber. The total surface area of both nasal cavities is about 150 cm^2 and the total volume is about 15 ml. Opens anteriorly in the nostrils and communicates posteriorly with the rhinopharynx by the way of the choanae. The *choanae* are formed by the horizontal plate of the palatine bone inferiorly, the vomer medially, the vaginal process of the sphenoid bone superiorly, and the medial pterygoid plate laterally. The floor of the nasal cavity consists of the palatal processes of the maxilla and the horizontal processes of the palate bones. The alar or lower lateral cartilages, nasal bones, nasal processes of the frontal bones, and bodies of

the ethmoid and sphenoid bones form the roof of the nose. The lateral wall is formed by the inner surfaces of the maxilla and lacrimal bones and supports the three turbinates, the inferior, middle, and superior turbinate. The head of the inferior turbinate interferes directly with the entering airflow, and its tail, in case of hypertrophy, can significantly reduce the choanal size. The inferior turbinate also forms an important part of the internal nasal valve. Any anatomic or physiologic disorders of this turbinate or the surrounding structures can significantly influence the nasal resistance.[91] Under and lateral to each of the turbinates are passages called the inferior, medium and superior *meatus*.

Nasal Valve - It is situated approximately 1.5 cm from the nares and has a cross-sectional area of 2 about 30 mm on each side. It is the narrowest point of the nasal airway. It is composed by the overlapping of the caudal margins of the upper lateral cartilages and the upper margins of the lower lateral cartilages, the head of the inferior turbinate, and the septum. Four distinct components of the nasal valve establish the cross-sectional dimensions of the nasal airways and their resistance to respiratory airflow.[92] 1) *The cartilaginous termination of the nasal vestibule* (structural component*)*. This constriction provides an airflow resistor of major importance. It is situated between the caudal end of the upper lateral cartilage and the septum. Its cross-sectional area is unaffected by topical decongestant signifying that erectile tissues that can alter nasal airway dimensions elsewhere in the nasal airway are absent at this site. Furthermore, dimensions of this airway cross-section are little affected by transmural pressures generated by inspiration because of the stabilizing activity of alar dilator muscles. 2) T*he bony entrance to the cavum* (structural component*).* The air enters the cavity of the bony nasal cavum via the vertical piriform aperture. Within the relatively capacious cavity the decelerated and disturbed (nonlaminar) airstream meets little resistance. Indeed, the cavum can accommodate sizable intrusions into its lumen with negligible effect on airflow resistance. 3) T*he mucosa of the inferior turbinate* (dynamic component) is an erectile tissue. It

contains abundant capacitance vessels (venous sinusoids) in which blood content determine turbinate volume. The cross-section of the ventral portion of the airway in the vicinity of the piriform aperture therefore is modulated by the degree of vasodilatation of the inferior turbinate. The “head” of the congested turbinate extends proximally, and its distal portion extends into the capacious body of the cavum where it has proportionately little effect on cross-sectional area and airflow resistance. 4) T*he septal mucosa* (dynamic component) also supports a substantial erectile body. Its major portion is situated dorsal to the inferior turbinate and proximal to the middle turbinate, and the septal body intrudes increasingly on the piriform airway in its dorsal portion as it congests.

Paranasal sinuses - The paranasal sinuses consist of four paired cavities located in the facial mass. They are called maxillary, ethmoid, sphenoid, and frontal according to their location in the facial structures. The paranasal sinuses are filled with air and are connected with the nasal cavity by way of an ostium. The functions of the sinuses are controversial. They may assure harmony in facial growth and make the skull lighter. They also can be seen as a protector of the brain. Other functions given to the sinuses, like air conditioning, speech resonance chamber, or smell perception, probably are less well founded.

Vascular - Blood supply for the nasal cavity comes from the external and internal carotid systems, external and internal ethmoidal arteries and sphenopalatine artery. The veins accompany the arteries and drain into the facial vein and ophthalmic veins. All of these vessels form a complex network in the mucosa and specifically contribute to *Kiesselbach’s plexus*, localized on the anterior septum. The direction of the arterial blood flow in the nasal mucosa runs anteriorly in the opposite direction than the inspired air, increasing the warming of the inspired air. Blood flow through the nasal blood vessels is controlled by autonomic innervations of the nasal mucosa. Sympathetic stimulation causes

a reduction in nasal blood flow and a pronounced decongestion of nasal venous erectile tissue.

Mucosa - The anterior part of the nasal cavity, is lined with a squamous epithelium with vibrissae or coarse hairs, sebaceous glands, and sweat glands. Inside the nasal cavity, three different types of epithelium can be observed. The first third of the nasal cavity is covered with *squamous and transitional epithelium*. This epithelium contains cuboidal cells with microvilli. In the posterior two thirds of the nasal cavity, a *pseudostratified columnar epithelium* (respiratory epithelium) is found, which is composed of four major types of cells: ciliated (columnar) cells, nonciliated (columnar) cells, goblet cells, and basal cells. This epithelium protects the upper and lower airways with the mucociliary clearance activity. Both of these epithelium lie on a basement membrane and a lamina propia. The basement membrane is penetrated by capillaries so that fluids can pass directly through these vessels onto the mucosal surface. The third epithelium is the *olfactory epithelium*, which covers the superior turbinate and adjacent septum. It is a pseudostratified epithelium containing olfactory cells, basal cells, and Bowman's glands (small serous tubulo-alveolar glands).

1.5.1.2 Nasal airway physiology

The nose has important roles in respiration and olfaction. In healthy individuals, inspired air is filtered, warmed, and humidified by the nasal mucosa before reaching the lung alveoli. These functions of the nose assure the protection for the lower airways.

Respiratory function - Most adults (85%) are nose breathers and only in certain situations, such as exercise, are the oral or oronasal routes used. Inspired air penetrates into the nostrils, splits into different flows, and follows the meatus. The speed at the entrance of the nasal cavity is about 2 to 3 m/s, but rises to about 12 to 18 m/s at the point of the internal nasal valve, which forms the narrowest point of the airway and diminishes to 2 to 3 m/s in the region of the turbinates.[93] At the entrance of the nose, the airflow

becomes turbulent, which is an important factor in the nasal function of warming and humidifying the inspired air and when entering the rhinopharynx, the airflow changes direction, becoming laminar and increasing in velocity to 3 to 4 m/s. In expiration, the airflow is more turbulent than in inspiration. The nose is normally a compliant part of the UA, and the nasal alae demonstrate inspiratory bursts of activity resulting in nasal flaring and stiffening which are precisely timed to precede diaphragm activity.[94]

Filtering function - One of the major functions of the nose is the filtering of inspired air from the high concentration of particles, because these particles could damage the fragile structures of the lower airways and slow the clearance of the alveoli.

Air conditioning - The nose has an important role in the ‘‘air conditioning’’ (heating and humidification) of the inspired air. Air is heated by conduction, convection, and radiation. When the venous sinusoids of nasal mucosa are filled, they form a vascular cushion and act as a sort of radiator, which warms up the inspired air. The heat exchange is efficient, because the blood flow is in the opposite direction to the incoming airflow. The air is heated up to a temperature near to the body temperature. The inspired air is humidified up to a humidity of more than 80% before it enters the lungs.

Immunologic function - There are two specific mechanisms that protect the system against several irritants, microorganisms, and allergens. The primary line of defense in humans includes the filtering function of the nose with the mucociliary transport system. Inspired microorganisms, irritants, and allergens are trapped in the nasal mucous blanket covering the ciliated mucosa and are transported to the rhinopharynx, are swallowed, and are destroyed by the gastric enzymes. Another specific system, forming the second line of defense, is the inflammatory reaction mediated by monocytes and macrophages.

Olfaction - It has a primary role in the regulation of food intake and in the perception of flavor. Olfaction has an important protective function in the detection of irritating and toxic substances.

Nasal cycle - It consists of a cyclic change in nasal congestion and decongestion and it is found in about 80% of the population. It is controlled by the respiratory areas in the brain stem (hypothalamus) and modulated by the sympathetic system producing a cyclic variation of nasal resistance. The duration of the cycle varies between 2 to 7 hours, and the amplitude is greatest in people who are lying down and is lower in people who are standing up. The cyclic variation is more active in adolescence and is less active in adulthood, probably caused by atrophy of the mucosa. Physiologic congestion under the control of the autonomic nervous system causes the nasal mucosa to shrink or swells in response to changes in posture, temperature, humidity and sleep.[95,96] Exercise induces an increase in sympathetic tone and a decrease in nasal resistance. Posture can influence the thickness of the nasal mucosa, most likely associated with a change in venous pressure in combination with the alteration of sympathetic tone, with an increase of nasal resistance when lying down, and when lying on one side on the dependent side. Emotional factors also have an effect on the nasal mucosa by way of the sympathetic system. Stress stimulates the system and induces a decrease in resistance to anticipate the fight reflex, and emotional instability can lead to an increase of nasal secretion and congestion.

Normal individuals are not usually aware of this phenomenon because the total nasal resistance usually remains fairly constant and is less than the resistance of either one of the individual nasal passages. It is unclear why this cycle exists but it has been proposed that the nasal cycle may have a role in respiratory defense by alternating the work of air conditioning between the two nasal passages, generating of plasma exudates, which physically clean the epithelium and provide a source of antibodies and inflammatory mediators, and maintaining the patency of the airway during the inflammatory response to

infection.[97] The nasal cycle may become synchronized to the sleep cycle and the switch in patency from one nostril to the other may occur during rapid eye movement sleep.

1.5.2 Pharyngeal Airway[98-103]

1.5.2.1 Pharynx anatomy

The UA is a complex structure whose functions include respiration, speech and swallowing. The human UA is divided into four sections. *Nasopharynx*: between the nares and the hard palate. *Velopharynx*: between the hard palate and the soft palate. *Oropharynx*: from the soft palate to the epiglottis. *Hypopharynx*: from the base of the tongue to the larynx. There are more than 20 UA muscles surrounding the airway that actively constrict and dilate the UA lumen. They can be classified into four groups: 1) muscles regulating the position of the soft palate (alai nasi, tensor palatini, levator palatini); 2) tongue (genioglossus, geniohyoid, hyoglossus styloglossus); 3) hyoid apparatus (hyoglossus, genioglossus, digastric, geniohyoid, sternohyoid) and 4) the posterolateral pharyngeal walls (palato glossus, pharyngeal constrictors).

Soft tissue structures form the walls of the UA and include the tonsils, soft palate, uvula, tongue and lateral pharyngeal walls. The main craniofacial bony structures that determine the airway size are the mandible and the hyoid bone, providing the anchoring structures to which muscles and soft tissue attach.

In normal non-obese subjects, the mean minimum cross-sectional area across multiple segments of the UA has been measured using several techniques (acoustic rhinometry, fast and conventional tomography) showing a wide range in size due to the individual variability but also due to differing locations of measurement, positional change (sitting/supine), and differences imposed by the choice of imaging modality. The minimum caliber of the UA in the wake state (it combines truly anatomical properties - bone structure, fat deposition - and activation of the UA dilator muscles.) is primarily in the

retropalatal oropharynx, which makes it a site as the potential location of collapse during sleep.

1.5.2.2 Pharynx physiology and mechanics

In humans, the UA, from the posterior end of the nasal septum to the epiglottis constitutes the pharyngeal airway and, has relatively little bony or rigid support. There are anatomic and physiologic influences that tend to collapse this part of the UA that must be offset by dilating forces. The two primary forces tending to collapse the pharyngeal airway are the intraluminal negative pressure generated by the diaphragm during inspiration and the extraluminal tissue pressure (pressure resulting from tissue and bony structures surrounding the UA). These influences must be offset primarily by the action of pharyngeal dilator muscles, although longitudinal traction on the airway resulting from lung inflation likely contributes as well.[104,105] The force generated by UA dilator contraction represents the only adaptive dilating force that counterbalances the collapsing forces and stabilizes the UA. Any alteration in UA function and/or activation pattern and/or ability to produce force will interact with UA stability and therefore promote UA instability.

1.5.2.2.1 Collapsing forces of the pharyngeal airway

Intraluminal negative pressure - During each inspiration, the diaphragmatically generated negative pressure would diminish airway size depending on the compliance of the airway walls and opposing dilating forces. The airway pressure required to collapse the pharyngeal airway has been best described by the critical closing pressure (Pcrit), a concept developed and evolved by Schwartz and colleagues.[106,107] This closing pressure is dependent on many variables and Pcrit is not a product of hypopharyngeal pressure but rather the pressure upstream to the collapsing segment. Thus, the negative pressure generated by respiratory pump muscles can reduce airway size, but will generally not collapse the airway by its only action.

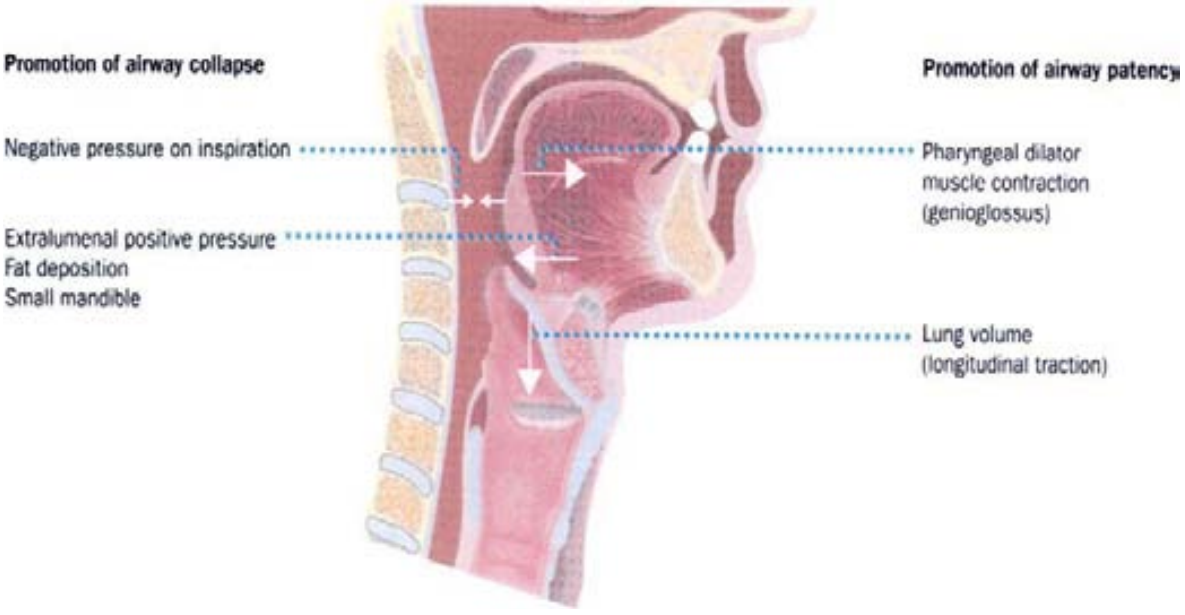
Airway anatomy - In normal, non-obese individuals, when muscle activity is completely inhibited (passive condition), the pharyngeal airway generally remains patent and requires about –5 cm H_2O to collapse.[108] As a result, the extraluminal tissue pressure (the pressure in the soft tissue surrounding the pharynx) in these individuals must be 0 cm H_2O, negative, or not sufficiently positive to overcome the elastance of the pharynx wall. Thus, the quantity of soft tissue located in the bony compartment created by the mandible and spinal column relative to the size of the compartment is sufficiently small that it does not apply a collapsing pressure on the pharyngeal airway (Figure 1).[109] In patients with SAHS, when total muscle paralysis is induced (passive condition), the pharyngeal airway collapses and positive pressure is required to open the airway. As a result, the extraluminal tissue pressure must be positive and sufficiently high to overcome the elastance of the airway walls. Thus, in the patient with sleep apnea, the quantity of tissue in the bony compartment relative to the size of the compartment is sufficient to generate a positive pressure on the airway, which partially or completely collapses it in the passive condition. There is a continuum in humans from the completely open passive airway (0 or negative tissue pressure) to the firmly collapsed one (positive tissue pressure). Increasing tissue pressure (Figure 1) is likely a product of either fat deposition (extra soft tissue in a normal-sized bony compartment) or a crowding of normal pharyngeal structures into a smaller bony compartment. Physical structures that fill (partially or completely) the airway lumen (tonsils or adenoids) can also increase collapsibility. Several additional factors may also affect anatomy or airway size, like vascular perfusion, the posture of the individual (supine vs. lateral), airway secretions, and tissue microstructure.

1.5.2.2.2 Dilating forces of the pharyngeal airway

Pharyngeal dilator muscle activation - Pharyngeal dilator muscle activation is the primary process that counteracts the collapsing forces. These muscles may activate during inspiration with less activity during expiration (inspiratory phasic pattern) or have a

similar level of activity across the respiratory cycle (tonic pattern).[98] The genioglossus is an inspiratory phasic muscle, and is the most important pharyngeal dilator muscle.[110-112] There are three primary neural inputs controlling the genioglossus. First, negative pressure in the airway reflexively activates mechanoreceptors located mainly in the larynx, leading to superior laryngeal nerve afferent activity and ultimately increased hypoglossal output to the genioglossal muscle. Second, the central respiratory pattern also influences genioglossal activation. Third, neurons that modulate arousal (active awake, less active, or inactive asleep), such as serotonergic or noradrenergic neurons, have a tonic excitatory influence on UA motoneurons. This has been called the “wakefulness stimulus” and generally increases muscle activity.[113]

Changes in lung volume - Lung inflation applies a caudal traction on the trachea and larynx, thereby inducing a longitudinal tension on the pharyngeal airway. This caudal force tends to stiffen the pharynx and reduces collapsibility.[105] Thus, decrements in lung volume, which can occur with changes in posture (upright to supine) or transitions from wakefulness to sleep, result in less tension on the pharynx walls.[114] As a result, the extraluminal tissue pressure required to collapse the pharyngeal airway is importantly reduced at lower lung volumes.



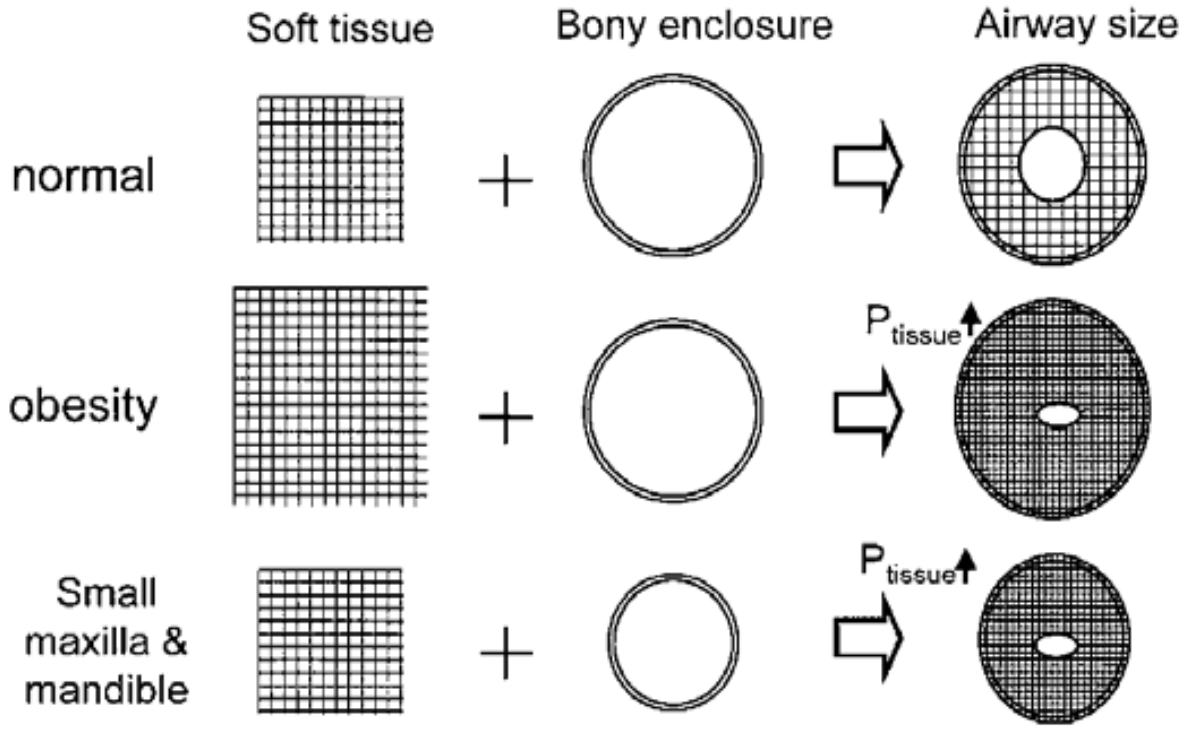


Figure 1 – Collapsing and dilating forces of the pharyngeal airway

1.5.2.2.3 Ventilatory control stability

The quantity and pattern of ventilation in humans is tightly regulated to both maintain oxygen and carbon dioxide levels within narrow limits and to minimize the work required to accomplish this. This is a product of multiple feedback loops, including the chemoreceptor (O_2 and CO_2), intrapulmonary receptors, and respiratory muscle afferents, and this is generally the case during both wakefulness and sleep.

Any mechanical system that is regulated by feedback loops, such as the respiratory system, has the potential to become unstable. This is best explained in the context of "loop gain", which is an engineering term.[103] A high-gain system responds quickly and vigorously to a perturbation, whereas a low-gain system responds more slowly and weakly. Loop gain is the ratio of a corrective response to a disturbance (ventilatory perturbation that instigated the response) [loop gain=(response to disturbance/the disturbance itself)]. For a system to become unstable (waxing and waning ventilation), two conditions must be met. First, there must be a phase delay between the effector portion of the system (the lungs) and the sensor for the system (CO_2 detection in the carotid body and brainstem). This is always the case for the respiratory system as there is an inherent delay between blood gas changes in the lung and the detection of these changes at the sensor. A prolonged circulation time (as occurs in congestive heart failure), which amplifies this delay, may further destabilize ventilation. Second, loop gain must be greater than one. If loop gain is less than 1, a respiratory disturbance will lead to a response, but it will be sufficiently small such that ventilation relatively quickly returns to a stable pattern. If loop gain is greater than 1, a respiratory disturbance will lead to such a large response that ventilation will wax and wane indefinitely. Thus, a high loop gain is destabilizing to ventilation both awake and asleep. However, the presence of ventilatory instability is generally more obvious during sleep because respiration during wakefulness is heavily influenced by behavior (e.g.,

talking, eating), making cycling patterns less obvious. A tonic “wakeful” drive to respiration also tends to stabilize respiration.

1.5.2.2.4 Effects of sleep on pharyngeal patency

Radiographic measurements have shown that during wakefulness patency of the UA is well maintained in different postures. However, with the onset of sleep there are several modifications that may occur.

Effect of sleep on UA mechanics - Sleep is associated with significant increase in UA resistance. Supraglottic resistance has been shown to increase from low values 1±2 cm H_2O/ L/s to values as high as 5±10 cm H_2O/L/s and to 50 cm H_2O/L/s in heavy snorers. Most studies suggest that airway caliber decreases during sleep, with the lateral pharyngeal walls playing an important role in this narrowing.

Effect of sleep UA on muscle tone - The phasic inspiratory activity of the genioglossus and geniohyoid are maintained during sleep in normals. Conversely, tonic and phasic tone decrease in the genioglossus, geniohyoid, tensor palatine and other respiratory muscles at the onset of sleep. These have been shown to be associated with transient decreases in ventilation and increased UA resistance.

Effect of sleep on load response - During wakefulness application of a resistive load to the airway results in increased respiratory drive, this response may be lost or greatly attenuated during sleep.

Effect of CO_2 on muscle activity during sleep - In the wake state, elevation of CO_2 is a powerful respiratory stimulant and this may be only minimally affected by sleep, at least in non-REM stages.

1.5.2.2.5 Models of behavior of the upper airway

The most basic approach to the dynamic behavior of the UA during cyclic respiration is to treat the airway as a rigid tube and analyze its resistance (i.e. assume a fixed or average relationship between driving pressure and flow). An extension of this

model is to consider resistance as varying during the inspiratory cycle composed of a dynamic interaction between flow and pressure. The need for this more complex model is related to the effect of the negative intrathoracic pressure transmitted to the passive UA during inspiration which promotes a reduction in pharyngeal cross-sectional area. According to the *"balance of pressures"* concept, the size (and thus resistance) of the UA depends on the balance between collapsing intraluminal pressures generated during inspiration by subatmospheric pressures in the thorax and, outward contracting forces of the UA dilator muscles. Description of the UA as a collapsible tube is a model to better describe this "dynamic collapse" of the airway. Factors that influence collapse of the susceptible airway include: 1) respiratory driving pressure across the region susceptible to collapse, determined by the negative intra-thoracic inspiratory pressure and any fixed resistances of anatomic structures such as the nose; 2) intrinsic properties of the airway wall, called the "tube law" and is determined by the size, collapsibility and longitudinal tension on the tube; 3) neural input to the UA which dictates the behavior of the dilating/stabilizing musculature.

Passive static properties of the airway - Static properties of a tube can be inferred from its behavior during steady state flow. Resistance describes pressure/flow relationship through a conduit. Because of collapsibility and the influence of dilator muscles, the UA does not have a fixed cross-sectional area, which is a minimum requirement for having the linear pressure/flow relationship necessary to define "a resistance". To overcome this limitation of the "resistance" concept, pharyngeal behavior has been described using either the resistance calculated at a single fixed flow rate or resistance at the peak flow rate during a maneuver. Static properties of the UA have also been evaluated by direct measurement of the compliance of the pharyngeal wall (slope of the volume to pressure or cross-sectional area to pressure relationship).

Passive dynamic properties of the airway (independent of tone) - Whereas the UA in normal adult man generally remains patent in the absence of all muscle tone when intraluminal pressure is zero, application of intraluminal negative pressure (as during inspiration) or flexion may result in complete collapse. The pressure at which this occurs has been referred to as critical closing pressure (Pcrit). This same collapse can also occur due to increased extra-luminal pressure. An example of this is loss of airway patency in the supine position from passive collapse due to gravitational forces generated by craniofacial structures or adipose tissue surrounding the UA. Mass loading of the anterior neck may also increase the collapse of the passive airway.

Active properties of the UA (i.e. muscle dilator) - The UA is rich in neural receptors, which play a part in controlling baseline tone of genioglossus. Any loss of this tone, as occurs at sleep onset, probably contributes to raising pharyngeal resistance. During inspiration there is a phasic inspiratory activity of the muscles of the nose, pharynx and larynx that occurs before the diaphragm and intercostals muscle activity suggesting pre-activation of the UA muscles in preparation for the development of negative pressure. It remains unclear whether the activity of “dilator” muscles is in fact to dilate the airway, or whether these increases in muscle tone act to stabilize the airway and maintain patency against the collapsing forces present during inspiratory airflow.

1.5.2.2.6 Measurements of pharyngeal collapsibility: pharyngeal critical closing pressure (Pcrit)[103,116]

Quantitative measurements of mechanical and neuromuscular contributions to pharyngeal collapsibility have been difficult to derive during sleep. One approach has been to model the UA as a collapsible tube (*ie*, a Starling resistor). This model is based on a pattern of dependence of flow on the driving pressure, and flow increases as driving pressure increases; however, above a critical driving pressure, there is a progressive plateau of flow at some maximal level despite continued increase in driving pressure (flow

limitation). In the Starling resistor model (Figure 2),[106] the collapsible segment of the tube is bound by an upstream and downstream segment with corresponding upstream pressure, downstream pressure, upstream resistance and downstream resistance. Occlusion occurs when the surrounding pressure (Pcrit), becomes greater than the intraluminal pressure, resulting in a transmural pressure of zero. In this model of the UA, upstream pressure is atmospheric at the airway opening and downstream pressure is the tracheal pressure. When the Pcrit is significantly lower than upstream pressure and downstream pressure (upstream pressure > downstream pressure > Pcrit) flow through the tube follows the principles of an Ohmic resistor. When downstream pressure falls during inspiration below Pcrit (upstream pressure > Pcrit > downstream pressure), inspiratory flow limitation occurs and is independent of further decreases in downstream pressure. Under this condition the pharynx is in a state of partial collapse and maximal inspiratory flow varies linearly as a function of the difference between the upstream pressure and Pcrit. When the upstream pressure falls below Pcrit (Pcrit > upstream pressure > downstream pressure) the UA is occluded. Measures of Pcrit have been shown to define an spectrum of UA obstruction from normal breathing (Pcrit < -10 cm H_2O), to snoring (Pcrit range -10 to -5 cm H_2O), to obstructive hypopneas (Pcrit range -5 to 0 cm H_2O) and finally obstructive apneas (Pcrit > 0 cm H_2O) during sleep.[106] Measurement of Pcrit reflects either the contributions of anatomically imposed mechanical loads on the UA (passive Pcrit) or dynamic neuromuscular responses to maintain UA patency (active Pcrit)[116].

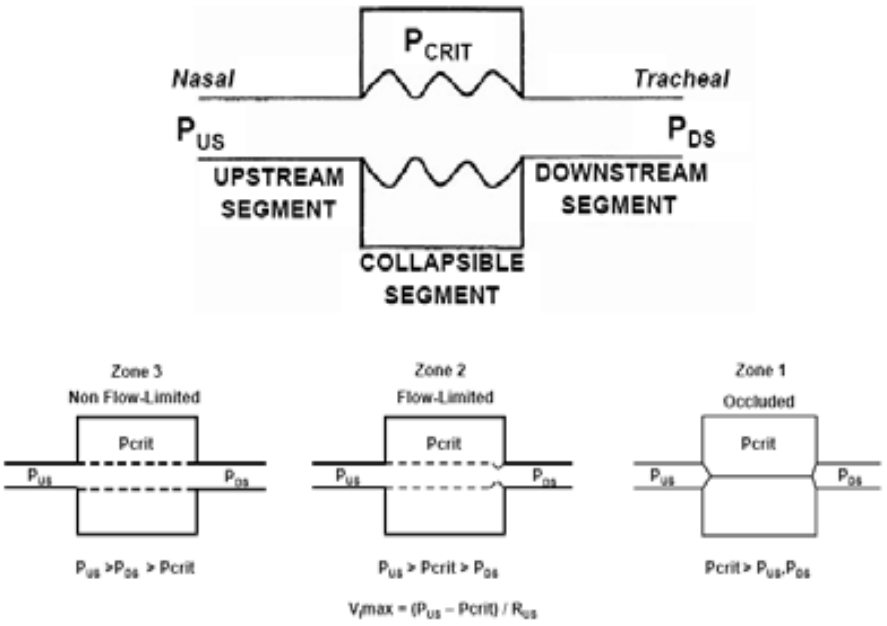


Figure 2 – Starling resistor model

1.6 UPPER AIRWAY RESISTANCE

1.6.1 Nasal Resistance[117]

Nasal patency is predominantly controlled by changes in the capacitance vessels and primary sites of nasal obstruction to airflow include the nasal vestibule, the nasal valves, and the nasal turbinates. Nasal resistance to respiratory airflow accounts for about 50% of the total airway resistance[93] and in the healthy nose it is confined to the nasal valve. This segment induces disruption of the laminar flow pattern with which inspiratory air enters the nasal vestibule. Resistance to airflow is inversely related to the cross-sectional area of the nasal airway (Poiseuille's law) which, in the nose, have a skeletal (static or structural) and mucosal (dynamic or mucovascular) components. A stable resistance of the combined nasal airways is maintained with remarkable consistency in healthy subjects at rest in a comfortable environment due to resistive changes reciprocate

between sides. In subjects free from signs of nasal disease, mean total resistance has been reported to be around 0.23 Pa cm^3/s, ranging between 0.15 and 0.39 Pa cm^3/s.[118] A total nasal resistance to airflow of 0.3 Pa cm^3/s can be considered the upper limit of the normal range in healthy peopole.[119] Many different local and remote, physiologic and pathologic stimuli modify resistance to airflow of the combined nasal cavities such as, the direction of the nostrils, shape and size of the nasal cavities and flow velocity, nasal cycle, age, exercise, posture, vasomotor response to hormones, environment, and pharmacotherapy, emotional, and psychological responses. During sleep the nasal resistance remains constant.

1.6.2 Pharyngeal resistance

Hyatt and Wilcox stated in 1960 that in normal subjects, approximately 50% of the total resistance to airflow occurs in the UA.[120] The nasal and the hypopharyngeal segments are supported by bony and cartilaginous structures, and thus are relatively stiff while the pharyngeal tissues are not supported by such rigid structures. These characteristics account for the fact that resistance of the nasal and laryngeal segments is roughly linear,[121] in spite of the pharyngeal segment which is a collapsible structure.

The airway above the glottis presents greater impedance to airflow in awake patients with SAHS than in awake normal subjects, and the most likely explanation for this is the narrowing of UA in patients. Airflow resistance of the supraglottic airway is greater in supine awake than sitting awake in normal subjects and patients with SAHS.[115]

Wiegand D et al[122] showed that in healthy subjects, inspiratory supraglottic resistance increases during NREM sleep and REM sleep compared to wakfulness. The increase in resistance from wakefulness to sleep varied considerably between subjects and the UA resistance during wakefulness did not predict UA resistance during sleep.

Some studies[123-125] reported that inspiratory and expiratory UA resistance (total or segmental resistance) was higher in patients with SAHS than in snorers or normal

subjects, during wakefulness and sleep. The major site of increased resistance within the UA during sleep was in that portion of airway between the nasopharynx and retroepiglottal airspace.[126] This, during sleep, the pharyngeal resistance increases while the nasal resistance remains constant.

1.7 PATHOGENESIS OF SAHS

1.7.1 Anatomic factors

Structural or mechanical alterations are a primary determinant of UA obstruction during sleep[108,127] and may predispose to UA obstruction when protective neuromuscular mechanisms decrease at sleep onset.[128]

Patients with SAHS have anatomical differences in the craniofacial structures as reduction in the length of the mandible, inferiorly positioned hyoid bone and a retro position of the maxilla,[129] increase in the volume of the tongue and uvula,[130] soft palate, tonsils, parapharyngeal fat pads and the lateral walls surrounding the pharynx.[87] Imaging studies have shown that patients with SAHS have a smaller airway lumen than controls, and a difference in airway shape, with its long axis directed anterior-posterior rather than laterally[131] which may place pharyngeal dilator muscles at a relative mechanical disadvantage. An increased airway length from the top of the hard palate, to the base of the epiglottis reflects an increased proportion of collapsible airway exposed to collapsing pressures.[132]

Obesity affects pharyngeal size by direct deposition of fat around the airway (thickness of the lateral pharyngeal walls[133] or by altering muscle orientation and function.[134] Another consequence of obesity is the reduction of lung volumes (functional residual capacity) by a combination of increased abdominal fat mass and the recumbent posture that reduces tracheal traction on the pharyngeal segment promoting an UA less stable during inspiration.[105,135]

Thickened lateral pharyngeal walls for increased fat deposition, pharyngeal inflammation and/or edema, increased vascular volume and increased muscle volume are anatomic alterations that can predispose to UA collapse.[131,136]

1.7.2 Neuromuscular factors

Loss of wakefulness stimulus - SAHS patients during wakefulness showed elevated UA muscle activity which was significantly lowered with the application of positive nasal pressure,[137] suggesting that increased UA dilator muscle activity compensates for a more anatomically narrow UA in these patients in wake state. Reductions in UA muscle activity with sleep onset through serotonergic, cholinergic, noradrenergic, and histaminergic pathways may lead to UA obstruction and have been hypothesized to be due to the loss of a *"wakefulness stimulus"* that may be greater in SAHS patients than healthy control subjects.[2,128]

Insufficient reflex activation of UA dilator muscles and impaired sensory function - The activation of UA dilator muscle during wakefulness and sleep is mainly due to reflex activation provoked by negative intra-pharyngeal pressures that are more pronounced in SAHS patients due to the smaller airway. This reflex is quite active during wakefulness, but significantly declines during sleep.[138,139] One explanation could be that UA sensory pathways may be impaired in SAHS patients.[140,141]

1.7.3 Neuroventilatory factors

Preactivation of the pharyngeal dilator muscles stabilizes the UA prior to the inflow of air and suggests central nervous system coordination between the UA and the diaphragm. The central nervous system is influenced by central and peripheral chemoreceptors with conditions of hypercapnia and hypoxemia increasing central drive to the UA and decreasing pharingeal collapsibility.[142] Increased hypercapnic ventilatory responses, prolonged circulatory times or low oxygen stores within the body can result in ventilatory instability that leads to the development of periodic breathing.[143] Sleep also

unmask a highly sensitive apneic threshold (the PCO_2 level below which apnea occurs) that remains within 1 to 2 mmHg of the normal waking level and, SAHS patients have an increased loop gain and thus more unstable respiratory control system.[144,145]

One of the main mechanisms of sleep-related UA closure is an asynchrony between UA dilator muscles and inspiratory muscles.[3] Indeed, UA dilator muscles normally contract before the inspiratory muscles, to open and stabilizes the UA during inspiration. During sleep, the decrease in the neural drive to the UA dilator muscles delays their action and decreases their efficiency. The UA is therefore functionally passive or quasi so when the contraction of the diaphragm begins. The loss of the counterforce that normally opposes the negative inspiratory pressure explains why the airways tend to close.

1.7.4 Interaction of anatomic and neuromuscular factors on pharyngeal collapsibility

It has been shown that patients with SAHS during sleep have both an increased mechanical load on the UA (passive Pcrit) and impaired neuromuscular responses to UA obstruction (active Pcrit). A Pcrit -5 cm H_2O represents the disease threshold above which hyponeas and apneas occurred. When mechanical loads on the UA are below the disease threshold, SAHS is not present regardless of whether neuromuscular responses are recruited. When mechanical loads on the UA are above the disease threshold recruitment of neuromuscular compensatory responses are necessary to maintain the UA patency. Under this paradigm the development of SAHS requires a “two-hit” defect, with defects in both UA mechanical and neuromuscular responses.[102,146]

1.7.5 Other factors involved in the pathogenesis of SAHS

Lung volume - The UA size increases at higher lung volumes. This effect is probably due to increased tracheal tug leading to an increase in UA size and decreased airflow resistance. Patients with SAHS have a greater change in UA dimensions with change in lung volume.[147]

Pharyngeal Nerve/Muscle Damage - Several studies suggested that there may be inflammation and trauma to the UA due to snoring, vibration, extrinsic contraction, or fatigue.[141,148] This may lead to a reduction in sensory mechanisms in the pharyngeal airway (ability to detect negative pressure), denervation of pharyngeal dilator muscles, or actual damage to the muscles themselves.

1.8 CLINICAL ASSESSMENT AND CONSEQUENCES OF SAHS

1.8.1 Symptoms and Signs

The classic signs and symptoms for SAHS include signs of UA obstruction during sleep (snoring, snorting, gasping, choking, and witnessed apneic episodes), insomnia, and daytime hypersomnolence in the setting of obesity.[149] Generally, these symptoms develop over years and progress in association with increases in weight, aging, or transition to menopause. A detailed longitudinal sleep history and physical examination are essential in identifying at risk individuals because as many as 90% of cases in men and 98% of cases in women may go undiagnosed for many years.[50] The typical presentation of obesity, snoring, and witnessed apneas are less predictive of SAHS with age, suggesting that the diagnosis may be missed in an “atypical patient”.[41,150] Following the history and physical examination, patients can be stratified according to their SAHS disease risk which will determine the manner of objective testing to confirm the diagnosis.

1.8.2 Diagnosis

An objective measure of sleep respiratory disturbance is generally required to confirm the diagnosis of SAHS and to establish the severity, in order to make an appropriate treatment decision. Accepted methods of objective testing are in-laboratory polysomnography (gold standard) and home testing with portable monitors.[151-153]

The frequency of obstructive events is reported as an apnea + hypopnea index (AHI) or respiratory disturbance index (RDI) (apneas, hypopneas + respiratory event

related arousals). The diagnosis of SAHS is confirmed if the RDI is greater than 15 events/hour or greater than 5events/hour in a patient who reports associated symptoms. SAHS severity is defined as mild for RDI ≥ 5 and < 15, moderate for RDI ≥ 15 and ≤ 30, and severe for RDI > 30/hour.

1.8.3 Consequences or comorbidity

1.8.3.1 Mechanisms of Disease and Associated Cardiovascular Risk[154]

Obstructive sleep apneas initiate a range of pathophysiological mechanisms which may act to promote cardiac and vascular disease.

Sympathetic Activation - Heightened sympathetic drive elicited by recurrent apneas during sleep persists into normoxic daytime wakefulness.[155]

Cardiovascular Variability - Compared with similarly obese control subjects, resting awake SAHS patients have diminished heart rate variability and increased blood pressure variability.[156,157]

Vasoactive Substances - Recurrent hypoxemic stress induces increased release of vasoactive and trophic substances that may elicit vasoconstriction persisting for hours.[158]

Inflammation - The combination of repetitive hypoxemia and sleep deprivation in SAHS patients may be associated with increased levels of plasma cytokines, adhesion molecules, serum amyloid A, and C-reactive protein. There also is evidence for enhanced leukocyte activation and increased circulating tumor necrosis factor-α levels in SAHS.[159]

Oxidative Stress - The repetitive hypoxemia and reoxygenation that characterize sleep in SAHS patients may be implicated in the triggering of oxidative stress mechanisms.[160,161]

Endothelial Dysfunction - Recent data suggest not only that conduit vessel endothelial function[158] may be impaired in SAHS but also that the impairment may be

related to endothelial cell apoptosis and that treatment with CPAP may improve endothelial function.[162,163]

Insulin Resistance - Increased catecholamine and sleep deprivation may be associated with insulin resistance in SAHS.[164]

Thrombosis - SAHS has also been associated with increased platelet activation, increased fibrinogen, and other potential markers of thrombotic risk.[165]

Intrathoracic Pressure Changes - Obstructive apnea causes repetitive forced inspiration against a closed UA (Mueller maneuver), which generates very substantial negative pressures in the chest cavity. This negative intrathoracic pressure increases transmural gradients across the atria, ventricles, and aorta, and disrupts ventricular function and autonomic and hemodynamic stability. Consequences may include increased wall stress, increased afterload, increased atrial size, impaired diastolic function, thoracic aortic dilation, and propensity toward dissection.[166,167]

1.8.3.2 Cardiovascular Diseases and SAHS

1.8.3.2.1 Hypertension

About 50% of SAHS patients are hypertensive, and an estimated 30% of hypertensive patients also have SAHS, often undiagnosed.[168] SAHS is an independent risk factor for the development of essential hypertension because it can precede and predict the onset of hypertension.[169,170] Logan et al[171] noted that the prevalence of SAHS in patients with drug-resistant hypertension was 83%. Studies to assess the effect of SAHS treatment by CPAP on blood pressure showed moderate and variable effects of CPAP on blood pressure.[24,172-175] Patients with more severe SAHS, difficult-to-control hypertension, and better CPAP compliance may have more substantial blood pressure reduction with CPAP.

1.8.3.2.2 Heart Failure

In 2 large case series SAHS was detected in 37% and 11% of patients with heart failure resulting from systolic dysfunction who were referred for polysomnography.[176,177] SAHS also has been noted in ≥50% of heart failure patients with preserved systolic function.[178] Three months of CPAP was reported to attenuate abnormalities in diastolic function.[179] Indeed, there is evidence to suggest that SAHS is associated with altered cardiac structure and function[180,181] and that some of these changes may be reversible with effective CPAP treatment.

1.8.3.2.3 Stroke

Several studies have noted a high prevalence of SAHS in subjects studied shortly after stroke,[182] with an increased risk of death[183,184] and beneficial effects of CPAP treatment of those patients.[185]

1.8.3.2.4 Arrhythmias

Nocturnal arrhythmias have been shown to occur in up to 50% of SAHS patients[186] and the most common include non-sustained ventricular tachycardia, sinus arrest and second-degree atrioventricular conduction block. Recent data from the Sleep Heart Health Study, suggested that those patients with severe SAHS had higher risk of nocturnal complex arrhythmias, even after adjustment for age, sex and BMI.

1.8.3.2.5 Myocardial Ischemia and Infarction

The prevalence of SAHS in coronary artery disease patients has been shown to be up to 2-fold greater than in non–coronary artery disease subjects.[187] In longer-term studies, SAHS in patients with coronary artery disease was associated with a significant increase in the composite end point of death, myocardial infarction, and cerebrovascular events at a 5 year median follow-up interval.[188] Treatment of SAHS was associated with a decrease in the occurrence of new cardiovascular events. [25,189]

1.8.3.2.6 Pulmonary Arterial Hypertension

The pulmonary arterial hypertension seen in association with SAHS is generally mild[190] and treatment of SAHS with CPAP may lower daytime pulmonary artery pressure.[191]

1.8.3.3 Other consequences of SAHS

Untreated SAHS can contribute to the development or progression of other disorders. Patients with SAHS and moderate to severe coexistent lung disease are more likely to develop type II respiratory failure that will improve with treatment of the obstructive apneas.[192] SAHS leads to neuropsychological impairment. [193] Perhaps the most important complication of SAHS, and the one that has the greatest impact from the public health perspective, is driving accidents. More than one third of patients with SAHS report having had an accident or near accident on account of falling asleep while driving.[194] There is also evidence that SAHS patients have a 50% increased risk of workplace accidents.[195]

1.9 TREATMENT OF SAHS

SAHS should be approached as a chronic disease requiring long term, multidisciplinary management. Positive airway pressure (PAP) is the treatment of choice for mild, moderate, and severe SAHS and should be offered as an option to all patients. Alternative therapies may be offered depending on the severity of the SAHS and the patient's anatomy, risk factors, and preferences.

1.9.1 Non PAP treatments

1.9.1.1 Medical therapy[196,197]

Weight reduction - Dietary weight loss should be combined with the primary treatment for SASH. Bariatric surgery may be an adjunctive treatment.

Pharmacologic agents - Selective serotonergic uptake inhibitors, protriptyline, estrogen therapy and methylxanthine derivatives have not show consistent or significant

improvement in the AHI of SAHS patients and cannot be recommended for the treatment of SAHS. Modafinil is recommended for the treatment of residual excessive daytime sleepiness in SAHS patients who have sleepiness despite effective PAP treatment and who are lacking any other identifiable cause for their sleepiness.

Medical therapies to improve nasal patency - Short-acting nasal decongestants and topical nasal corticosteroids may improve AHI and concurrent rhinitis.

Positional therapies - Methods that keep the patient in a non-supine position can be a supplement to primary therapies for SAHS in patients who have a positional SAHS.

1.9.1.2 Oral appliances[198,199]

Oral appliances are indicated for use in patients with primary snoring and patients with mild to moderate SAHS who prefer oral appliance to CPAP, or who do not respond to CPAP, are not appropriate candidates for CPAP, or who fail treatment attempts with CPAP or behavioral measures.

1.9.1.3 Surgical options[200,201]

Techniques such as tracheotomy, maxillary-mandible advancement, uvulopalatopharyngoplasty, radiofrequency ablation and multilevel surgery should be considered according the severity of the SASH.

1.9.2 PAP treatment[150, 202-205]

CPAP is the primary treatment for SAHS and provides a “pneumatic splint” of the UA by delivering an intraluminal pressure that is positive with reference to the atmospheric pressure, preventing negative inspiratory pressures from inducing airway collapse by continuously delivering positive pressure via tightly sealed nasal prongs or nasal mask. CPAP use normalizes sleep architecture, reduces daytime sleepiness, enhances daily function, reduces automobile accidents and decreases blood hypertension and cardiovascular events.

CPAP is indicated for the treatment of moderate to severe SAHS and can be recommended for the treatment of mild disease. Patients with AHI $\geq$ 5 and symptoms (daytime sleepiness and non restorative sleep) are candidates for treatment with CPAP. In patients with AHI $\geq$ 30 with no symptoms, CPAP treatment should be recommended.

1.9.2.1 Mechanisms by which PAP stabilizes upper airway during sleep[206,207]

The most widely accepted view is that the positive pressure provides a mechanical stent of the UA. Imaging studies demonstrate that PAP increases UA cross-sectional area and volume in awake normal subjects and SAHS patients with the largest change in the lateral dimensions. A second mechanism by which PAP may affect UA size is by increasing lung volume. The increased lung volume provides a downward traction on the trachea (tracheal tug) and this action is believed to stretch UA structures and increase UA size.

1.9.2.2 PAP modes (Figure 3)

1.9.2.2.1 Continuous positive airway pressure

CPAP delivers a predetermined constant pressure during both inspiration and exhalation.

1.9.2.2.2 Bilevel positive airway pressure

Bilevel PAP delivers a separately adjustable lower expiratory positive airway pressure and higher inspiratory positive airway pressure.

1.9.2.2.3 Autotitrating positive airway pressure

Autotitrating-PAP devices were developed with two potential uses: 1) autotitrating PAP to select an effective level of CPAP without the need for an attended titration; and 2) autoadjusting PAP for long-term treatment with the advantage of delivering the lowest effective pressure in any circumstance.

1.9.2.2.4 Expiratory pressure relief or flexible positive airway pressure

These are recent variants of PAP developed to improve patient comfort by allowing the airway pressure to fall below the prescribed PAP in early expiration with a return to the prescribed level at end exhalation. Currently, there are two available forms: C-Flex (Respironics; Murrysville, PA) and EPR (ResMed Corporation; Poway, CA). With the C-Flex device,[208] the pressure drop is progressively greater on settings 1, 2, and 3, and proportionally to expiratory flow. With the EPR device, settings of 1, 2, or 3 correspond to pressure drops of 1, 2, or 3 cm H_2O, respectively.

C-Flex showed same efficacy (AHI reduction) that treatment with fixed CPAP[209-211] and no difference in inspiratory flow limitation, but flexible pressure may lead to a decrease in expiratory time compared with CPAP.[212] Patient outcomes analysis reported a mean improvement of Epworth sleepiness scale scores non-significantly favoring C-Flex over CPAP.[211,213,214] A recent meta-analysis identified 10 randomized clinical trials comparing C-Flex to standard CPAP.[215] Four parallel studies[211,213,216,217] and three crossover studies[216,218,219] indicated that C-Flex was not used significantly more than standard CPAP.

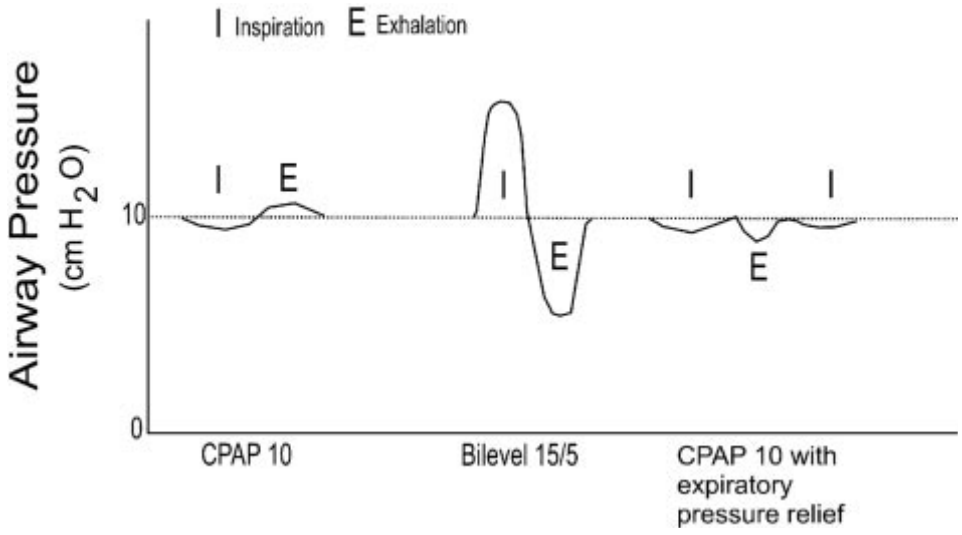


Figure 3 – Positive pressure modes

1.9.2.3 Outcomes of treatment with PAP[220,221]

Benefits from PAP treatment can be classified into four categories: 1) improvement of symptoms such as daytime sleepiness, disturbed sleep, impaired quality of life, or cognition; 2) reduced bed partner sleep disturbance or quality of life; 3) reduction of risk for cardiovascular disease, neurocognitive degeneration, or increased mortality associated with sleep apnea; and 4) reduction in the risk for motor vehicle accidents.

1.9.2.4 Acceptance and adherence to PAP[222]

Improvements of clinical outcomes occur with greater use of CPAP[173] and one study demonstrated a dose-response relationship between hours of use and sleepiness.[223] Despite the efficacy of CPAP treatment, studies defining adherence as use for at least 4 hours per night have reported that 29% to 83% of patients did not adhere to CPAP therapy.[203] The pattern of adherence is established within the first week of treatment and may predict long term use.[224] Factors that can influence or predict CPAP use can be

categorized as: 1) disease and patients characteristics; 2) treatment titration procedures; 3) technological device factors and side effects; and 4) psychological and social factors. However, only 4 to 25% of the variance in CPAP use has been related to these factors. The most common complaint of patients relates to problems with the mask.[207] Nasal symptoms and side effects are also common and may account for 30-50% of cases of CPAP intolerance, and increased nasal resistance (NR) results in a 50% greater chance of rejecting CPAP as a treatment.[225,226] Finally, pressure intolerance and "difficulty exhaling" are frequently cited by patients as limiting the acceptance of CPAP therapy.

1.9.2.5 Side effects and adverse effects

Side effects and adverse effects can be categorized as: 1) those related to nasopharyngeal symptoms; 2) those related to the interface or nasal route of delivery; and 3) those specifically related to the magnitude of pressure.

1.10 THE ROLE OF THE NOSE IN SLEEP DISORDERED BREATHING[227-229]

The continuum of sleep disordered breathing (SDB) has a multifactor etiology, with the final common pathway of UA collapse. Much research has focused on obstruction at the level of the oropharynx and hypopharynx. However, the precise role played by the nasal airway in SDB and its contribution to airway collapse is unclear. Some studies have sought to answer this question have identified a relationship between the nasal airway and SDB, but others have found no relationship. The initial management approach for many patients with SAHS is CPAP. If indeed the nose contributes to airway collapse, one would expect patients with more obstructed noses to require higher CPAP pressures. According that, the role of the nose on SDB is related to its contribution to UA collapse and to CPAP tolerance. The understanding of this could potentially aid in identifying patients who would benefit from nasal surgery or to predict CPAP treatment failure.

There are four proposed mechanisms by which nasal obstruction may lead to SDB:

1. Nasal airway resistance leads to increased respiratory effort, which increases intrapharyngeal pressure gradients, overwhelming pharyngeal dilator muscles and leading to UA collapse.

2. Nasal obstruction predisposes the individual to mouth breathing, allowing the tongue and mandible to shift backward. Airway narrowing increases intraluminal negative pressure (Bernoulli's Principle) and increases airway resistance, causing collapse.

3. Obstruction may lead to persistent snoring, which increases respiratory effort, predisposing to UA collapse.

4. Nasal obstruction may activate the nasopulmonary reflex, wherein abnormal nasal trigeminal nerve stimulation decreases downstream pulmonary ventilation.

Although the role of the nose in SDB remains the subject of debate, presently, it is believed that changes in nasal function are only a cofactor in the physiopathology of SAHS.

1.10.1 Positive association between nasal obstruction and sleep disordered breathing

Previous studies of seasonal allergic rhinitis[230] and nasal packing[231] indicated that nasal obstruction increases SDB. Attempts to find a linear correlation between nasal obstruction and SDB have been less successful.[232,233] However a weak correlation between nasal resistance measured by posterior rhinomanometry and the severity of obstructive sleep apnea has been reported and nasal resistance was found to be an independent contributor to SAHS.[234]

Some investigations have shown that loud habitual snoring may be due to nasal obstruction,[235,236] a significant reduction of cross-sectional area in a group of snorers[237]

and nasal resistance that tended to be higher in snorers[238] specially in supine position suggesting a role in the pathogenesis of SDB.

Some studies evaluated the role of dimensions on nasal cavity on SDB. Liu et al[239] showed that patients with severe SAHS tended to have smaller cross-sectional area. The airway measurements using acoustic rhinometry in children with SAHS, demonstrated larger nasal airway volume and area during upright position with a significant decline in nasal cavity volume from upright to supine. The magnitude of the decline in nasal cavity volume was predictive of the diagnosis of SAHS in the entire sample.[240]

Assuming a causal role for the nose in the development of snoring and SAHS, it would be predicted that the mean RDI in higher nasal resistance patients would be greater than that in patients with lower nasal resistance. Besides, as nasal resistance increases, apneic events should become more severe. A study in adults evaluating NR with active anterior RM[241] showed that snoring index was higher in the group with high nasal resistance and unilateral higher nasal resistance correlated significantly but weakly in the expected direction with RDI. Lofaso et al[234] using posterior RM found a statistically significant higher nasal resistance in patients suffering from SAHS in comparison with the control healthy group. Similarly, in children a value of nasal resistance of 0.59 Pa/cm3/s had high sensitivity and specificity to identify children with adenotonsillar hypertrophy affected by SAHS.[242]

1.10.2 Negative association between nasal obstruction and sleep disordered breathing

Some studies reported that, nasal resistance has no impact on the pathogenesis of SAHS. Thus, both snoring and sleep apnea are probably caused by other factors, such as restrictive processes in the pharyngeal area, rather than increased nasal resistance.[232,236,243]

Although it would seem that increased nasal obstruction is associated with the severity of SAHS and difficulty with the use of nasal continuous positive air pressure, some studies showed that nasal patency (CSA) does not correlate with the severity of SAHS or the effective CPAP level.[244]

1.10.3 Impact of postural change on nasal physiology in healthy subjects and in sleep disordered breathing

In healthy individuals, it has been shown that the intranasal minimal cross-sectional area decreases and the nasal airway resistance increases in the supine posture.[245,246] It has been postulated that this increase in respiratory load supine is a passive process resulting from increased venous pressure in the head when supine, decreasing the venous drainage from the nasal erectile tissue. However, other data, suggest that the regulation of nasal patency supine is an active process mediated via pressure sensitive receptors in the skin.[247]

Limited data indicate that the nasal reaction to a change in body position from sitting to supine is altered in patients with SAHS and the mechanisms are not well defined. In a study evaluating the relationship between AHI and nasal resistance, 20 of 36 SAHS patients had normal NR, both in sitting and supine, and only nine had a pathological increase in airway resistance supine, measured with rhinomanometry.[248] In a study using acoustic rhinometry, comparing snorers with controls, the nasal volume decreased less in the snorers between sitting and supine than in the controls.[249] Hellgren et al[250] studied patients with well-defined moderate SAHS without any nasal disease and CPAP naïve, compared to a group of healthy controls. Results showed that there was no difference in mean minimum CSA in the sitting position between the SAHS patients and the controls, and changing to supine position did not alter the mean minimum CSA in the SAHS patients, but did decreased significantly in the controls.

1.10.4 Role of the obesity on nasal physiology

Obesity may compromise nasal airflow and several factors have been proposed of which the most important ones suggested are excess fat around the neck, fat deposits in the cheeks and venous stasis with subsequent edema of nasal mucosa. The consequence would be nasal obstruction and high nasal resistance predisposing to SAHS.

In non-obese SAHS patients nasal measurements correlated with AHI and oxygen desaturation index.[249] In a group of obese SAHS despite the significant weight loss, total nasal inspiratory resistance and total nasal volume remained practically unchanged.[251] Morris et al[252] investigated the relationship between nasal obstruction and SDB while stratifying patients by body mass index and the data indicated that the group of patients most likely to experience increased RDI in response to nighttime nasal occlusion tended to have significantly lower BMI than those patients who were not affected by nasal occlusion.

These studies suggest that nasal resistance may have a more important role in non-obese patients with SAHS, whereas other factors that increase collapsibility, such as deposition of fat around the neck, reduced functional residual capacity and inability of the lungs to dilate and distract the UA and may conceal the effect of nasal resistance in obese patients.

1.10.5 Relationship between nasal resistance and CPAP treatment

The complaints voiced by patients unable to tolerate CPAP mostly refer to the nose. These include dry nose, recurrent sinusitis, nasal stuffiness, nasal crusting, rhinorrhea, nose bleeding, sneezing, air leaks into the mouth, air swallowing, and sensation of suffocation. Nasal side effects are believed to account for 30–50% of cases of inability to tolerate CPAP and probably represent the plurality of complaints, outweighing factors related to the mask, machine, and stress or anxiety.[253]

Some studies evaluated the impact of CPAP treatment on nasal physiology. The effect of an acute exposure to nasal CPAP for 6 h in awake normal subjects (no SAHS, no

nasal pathology) was a reduction of NR compared with the control (no CPAP exposure). One possible explanation would be an acute mechanical splinting effect of CPAP on the nasal soft tissues, as occurs in the oropharynx and that the more positive intraluminal nasal pressure resulted in reduced turbinate mucosal vascularity and/or edema.[254] Otherwise, after 6 months of CPAP treatment a group of SASH didn't show any changes in nasal resistance and volume.[255]

Increased nasal resistance has been shown to predict intolerance of CPAP treatment,[226] with a lower CSA in non-tolerant CPAP patients.[256] Having a CSA of <0.6 cm^2 at the head of the inferior turbinate predicted CPAP intolerance with good sensitivity and excellent specificity.[256]

1.10.6 Impact of nasal surgery on nasal physiology

Interpreting outcomes of nasal surgery for SAHS in the literature has been problematic because of the lack of a control group, limited case numbers, confounding concomitant uvulopalatopharyngoplasty, limitation to only subjective or objective evaluation, or lack of valid quality of life assessment and NR measures. Despite these limitations some studies showed that surgical correction of an obstructive nasal airway in SAHS patients with nasal obstruction improves their daytime spirit, as well as disease specific and generic quality of life.[257,258] Significantly decreased NR and CPAP level have been observed after nasal surgery in SDB patients,[225,259] however, improved NR did not show a parallel improvement in AHI[258] suggesting that decreased daytime NR does not necessarily improve adverse respiratory events during sleep.

The discrepancy occurring in the postoperative patients may stem from two competing effects. One is the relief of nasal obstruction allows the patients to sleep more comfortably and, consequently, improves sleep quality and reduces daytime sleepiness. The other is the improved nasal breathing leads to a deeper sleep that may result in more

collapse of the UA. Another explanation could be the shift from apnea to hypopnea after nasal surgery, but without changes in total amount of AHI.

2. JUSTIFICATION OF THE RESEARCH

The proposed research wants to understand the relationship between nasal resistance and actual delivered pressure during positive airway pressure treatment in patients with SAHS and, the potential impact this may have on therapy compliance.

2.1 JUSTIFICATION STUDY 1 – Awake measures of nasal resistance and upper airway resistance on CPAP during sleep. J Clin Sleep Med 2011. (Appendix 1)

Despite the efficacy of CPAP treatment, some studies reported variable adherence to CPAP and, the complaints voiced by patients unable to tolerate CPAP mostly refer to the nose. On CPAP treatment, upper airway resistance is dictated primarily by nasal resistance which produces an increase of the pressure experienced by patients during expiration as a consequence of interaction with expiratory flow. This could explain the difficulty exhaling reported by patient and a low compliance of therapy.

To date, no reliable parameters have been identified that predict tolerance or intolerance of CPAP. There has been no comparison of awake *noninvasive* measures of nasal resistance and total upper airway resistance on CPAP (which, as pointed out above, is assumed to reflect primarily nasal factors) during sleep. We designed the present study to obtain a daytime/wake noninvasive measurement predictive of nighttime/sleep physiology that might have clinical implications for patients with SAHS on CPAP.

2.2 JUSTIFICATION STUDY 2 – The supraglottic effect of a reduction in expiratory mask pressure during continuous positive airway pressure. Sleep 2012 (Appendix 2)

Difficulty exhaling is a frequent complaint reported by patients on CPAP treatment. The present thesis proposes to investigate the relationship between “measured” nasal resistance and pressure deviations from constant CPAP caused by the interaction between the resistance and exhalation. This is motivated by the belief that these pressure

swings at the upper airway may impact on patient comfort and therefore influence on CPAP compliance and adherence.

New approaches of CPAP treatment (C-Flex) have been designed to decrease the pressure during expiration as an attempt to improve comfort during exhalation. But there are no studies focused on understanding the underlying physiology and effects of C-Flex neither the way in which these pressure changes at the upper airway experienced by patients can be modified by applying flexible CPAP (C-Flex^{TM}) to the mask providing a mechanism for improved comfort.

HYPOTHESIS

Rationale

On optimal CPAP, collapsibility of the upper airway is abolished. Thus, behavior of the upper airway on CPAP during sleep should be similar to the awake condition, where there is rigidity at the collapsible area (supraglottis) of the upper airway. In this condition (on CPAP during sleep), total upper airway resistance is dictated primarily by nasal resistance, which at constant CPAP necessarily produces flow-related effects on supraglottic pressure.

Using this logic, we predicted that high nasal resistance should be perceived by the patient even on CPAP, providing a mechanism that might contribute to intolerance and non-adherence to treatment.

3.1 Hypothesis Study 1

- In patients with SAHS, there is a correlation between nasal resistance during wakefulness and upper airway (supraglottis) resistance on CPAP during sleep. Thus, measurements of nasal resistance during wakefulness could predict upper airway resistance on CPAP during sleep.

  [High nasal resistance during wakefulness $\Rightarrow$ High supraglottic resistance during sleep on CPAP]

3.2 Hypothesis Study 2

- Increased upstream upper airway resistance (nasal resistance) during wakefulness would result in greater expiratory pressure swings in the supraglottis on CPAP, as a consequence of the interaction between nasal resistance and exhalation (Figure 4A).

  [High nasal resistance ⇒ High expiratory supraglottic pressure swings]

- The expiratory pressure swings at the supraglottis on CPAP could be mitigated with the application of C-Flex, a reduction of the pressure at the mask during early expiration. (Figure 4B).

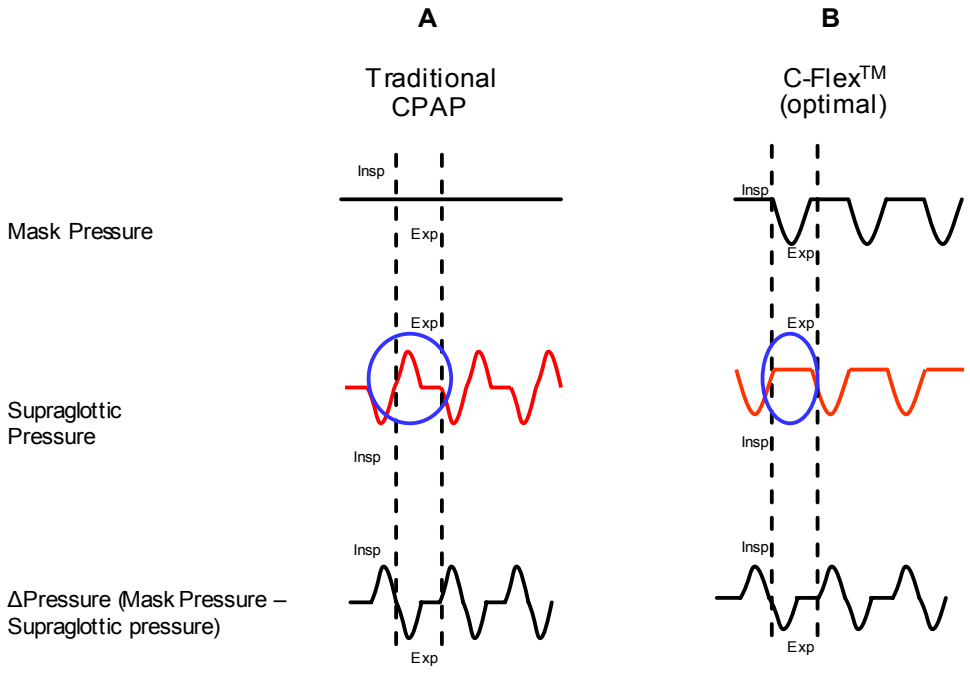


Figure 4 - Mask pressure and supraglottic pressure on CPAP (A) and on C-Flex (B).

4. OBJECTIVES

Rationale

The main goal of this research is to explore the impact of nasal resistance on the pressure that SAHS patients experience at the upper airway when fixed CPAP is applied at the mask (which increases during exhalation because of the directional effect of airflow through the nasal resistance) and also, the way in which these pressure changes at the upper airway experienced by patients can be modified by applying flexible CPAP (C-Flex) to the mask.

In addition to testing the application of C-Flex in SAHS patients, we also used a mechanical model of the upper airway to control respiratory flow and pattern and to eliminate reflex changes seen in patients. This study did not examine comfort, treatment adherence, or clinical outcomes per se; our goal was to define the underlying physiology and effects of C-Flex to better address the role it has in the clinical setting (eg, defining its relevance to patients with high nasal resistance).

Overall obejectives

- The relationship between noninvasive measures of nasal resistance during wakefulness and directly assessed upper airway resistance in asleep patients with SAHS on CPAP treatment.
- The impact of upstream (nasal) resistance on upper airway (supraglottis) pressure during expiration while on fixed optimal CPAP and with the application of flexible CPAP (C-Flex settings).

Specific objectives Study 1

4.1 To examine the relationship between noninvasive daytime/wake measures of nasal resistance and directly assessed upper airway resistance on CPAP, at the most collapsible part (supraglottis) during sleep in patients with SAHS.

4.1.1 To obtain a noninvasive daytime/wake measurement predictive of nighttime/sleep upper airway physiology in patients with SAHS.

4.1.1.1 Evaluation of nasal resistance during wakefulness by acoustic rhinometry.

4.1.1.2 Evaluation of nasal resistance during wakefulness by active anterior rhinomanometry.

4.1.1.3 Correlation between measurements of nasal resistance by acoustic rhinometry and active anterior rhinomanometry.

4.1.1.4 Evaluation of upper airway resistance (supraglottis) during optimal CPAP application during sleep.

4.1.1.5 Correlation between daytime/wake measures of nasal resistance by acoustic rhinometry and active anterior rhinomanometry and directly assessed upper airway resistance (supraglottis) on CPAP during sleep.

4.1.1.6 Correlation between upper airway resistance, nasal resistance, and clinical variables.

Specific objectives Study 2

4.2 To assess the influence of upstream (nasal) resistance on upper airway (supraglottis) pressure during expiration while on fixed optimal CPAP and with the application of flexible CPAP (C-Flex settings).

4.2.1 To examine the expiratory pressure profile at the mask and at the upper airway (supraglottis) on fixed CPAP with and without C-Flex in a group of patients with SAHS and in a mechanical model of the upper airway by:

4.2.1.1 Analyzing respiratory variables during expiratory phase: pressure swings in the mask and supraglottis; delta pressures defined as the change in mask and supraglottis pressure swings with the application of C-Flex.

4.2.1.2 Calculating the integrated supraglottic pressure during expiration as a surrogate for expiratory work.

4.2.1.3 Calculating upper airway resistance as the difference between mask pressure and supraglottic pressure at peak airflow divided by peak airflow.

4.2.1.4 Comparing measurements on fixed optimal CPAP and on C-Flex

5. METHODS

5.1 PROTOCOL

The target population for this study was adult subjects with complaints of snoring and excessive daytime sleepiness presenting to the New York University Sleep Disorders Center for evaluation of SAHS. All patients underwent full in-laboratory overnight polysomnography (NPSG) to confirm the diagnosis of SAHS (AHI >5 events/hour). If patients were eligible and willing to participate *daytime evaluation* was done including demographic and clinical variables, questionnaires to assess subjective nasal symptoms and evaluation of nasal resistance with acoustic rhinometry and anterior rhinomanometry in the sitting and supine positions. *Nighttime test* performed was, in-laboratory CPAP titration polysomnography with additional measurements of supraglottic pressure on optimal fixed CPAP and during the same CPAP level with expiratory pressure reduction (C-Flex). Patients were excluded if they had a medically unstable condition (i.e. recent myocardial infarction, congestive heart failure) and if they were unable to sleep with CPAP. Subjects signed a consent form approved by the Institutional Review Board at the New York University School of Medicine.

The flowchart of the study is represented on Figure 5.

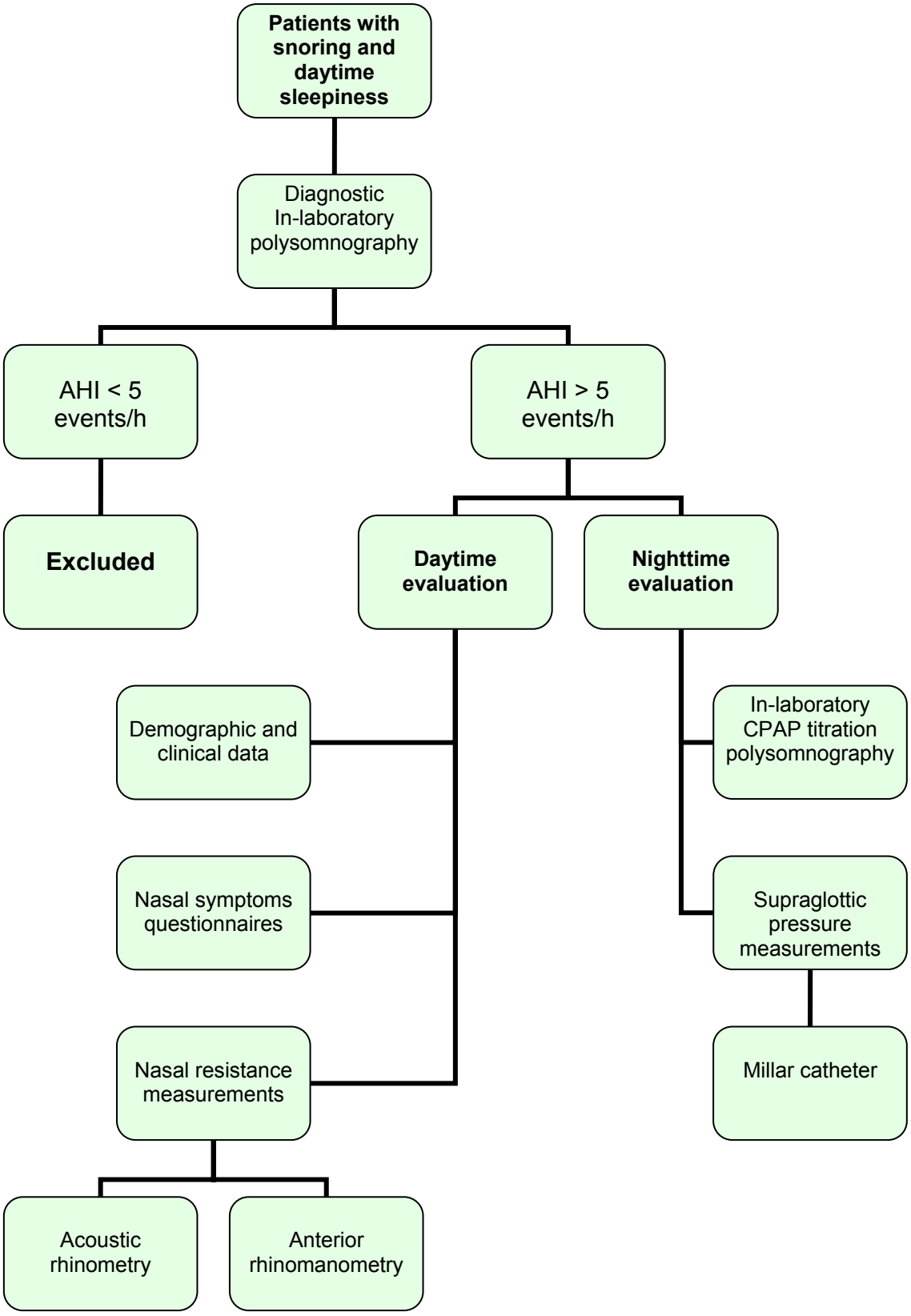


Figure 5 - Flowchart of the study

5.2 DAYTIME EVALUATION

5.2.1 Clinical assessment

We documented demographic and clinical variables: age, gender, body mass index, medical history and physical examination. Subjective daytime sleepiness was measured using Epworth Sleepiness Scale.[260]

5.2.2 Subjective questionnaires of nasal symptoms

The assessment of subjective nasal symptoms was made with nasal obstruction symptom evaluation (NOSE) instrument. The NOSE questionnaire is a validated tool in the subjective assessment of nasal obstruction.[261,262] It consists of 5 assessments of nasal obstruction-related symptoms scored using a 5-point Likert scale (not a problem, very mild problem, moderate problem, fairly bad problem, severe problem). Patients are asked to rate their symptoms as perceived over the past month. Higher scoring on the test implies more severe nasal obstruction. Figure 6 shows the questionnaires used to assess subjective nasal obstruction.

Nasal Obstruction Symptom Evaluation (NOSE) Instrument

→ **To the Patient:** Please help us to better understand the impact of nasal obstruction on your quality of life by **completing the following survey**. Thank You!

Over the past 1 month, how much of a problem were the following conditions for you?

	Please circle the most correct response				
	Not a problem	*very mild problem*	*moderate problem*	*fairly bad problem*	*severe problem*
1. Nasal congestion or stuffiness	0	1	2	3	4
2. Nasal blockage or obstruction	0	1	2	3	4
3. Trouble breathing through my nose	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Unable to get enough air through my nose during exercise or exertion	0	1	2	3	4

Rating Scale for Subjective Nasal Obstruction

Right now, how well can you breath through your nose?

1. No obstruction at all; completely free air passage.
2. Slight obstruction to flow.
3. Moderate obstruction to flow; mouth breathing is easier.
4. Considerable obstruction to airflow.
5. Complete obstruction to airflow; I can only mouth breathe.

Figure 6 - Questionnaires to assess nasal obstruction

5.2.3 Evaluation of nasal resistance during wakefulness

5.2.3.1 Acoustic rhinometry

Technique. Acoustic rhinometry (AR) provides a structural picture of nasal airway and was introduced in 1989 using the analysis of audible sound waves reflected from the nasal cavity.[263] It is an objective and noninvasive technique that allows the determination of nasal cross-sectional area (CSA) as a function of the distance into the nasal cavity using acoustic reflections. The method is based on the analysis of the amplitude (representative for the area) of sound waves as reflections by the nasal cavity of an incident sound as a function of time (representative for the distance into the nasal cavity). Variations in the size and contour of the nasal airway cause distortions in the reflected sound wave. The time at which these reflected changes occur gives an estimate of the distance in the nasal cavity that causes the distortion, and the magnitude of distortions is a measure of the change in CSA. The acoustic rhinometer consists of a sound source, wave tube, microphone, filter, amplifier, digital convertor, and a computer. The sound source generates an acoustic pulse that is conducted to the nasal cavity by means of a hollow plastic tube. The nasal end of this tube has a nose-piece which fits snugly against the nostril without deformation. A sound wave is transmitted into the nasal cavity which is then reflected back from the nasal passages and converted into digital impulses, which are then constructed on a rhinogram. This rhinogram provides a two-dimensional anatomic assessment of the nasal airway and the CSA of the nose can be illustrated graphically as a function of the distance from the nostril (Figure 7). The equipment is calibrated using a test acoustic impulse. An important property of AR is the ability to localize and quantify reversible (mucosal) blockage, in addition to irreversible (structural anatomic) blockage. It has been validated as a reproducible, accurate and reliable noninvasive technique to assess nasal airway patency.[264,265] Some studies have correlated findings of AR with those

of CT scan,[266] MRI[267] and endoscopy.[268] There are significant databases of comparative normal and abnormal values in the literature.[269,270]

With this technique three areas of constriction are identified: CSA1 represents the internal nasal valve at the junction of the upper lateral cartilage and septum (relatively constant in a given patients, independent of congestion); CSA2 represents the head of the inferior turbinate; and CSA3 is bounded by the head of the middle turbinate and the anterior portion of the inferior turbinate. CSA2 and CSA3 are highly variable due to erectile mucovascular tissue. Rhinometric data beyond 5.5 - 6 cm from the nostril are not useful because acoustic losses presumed to be related to the maxillary and frontal sinus ostia.[271]

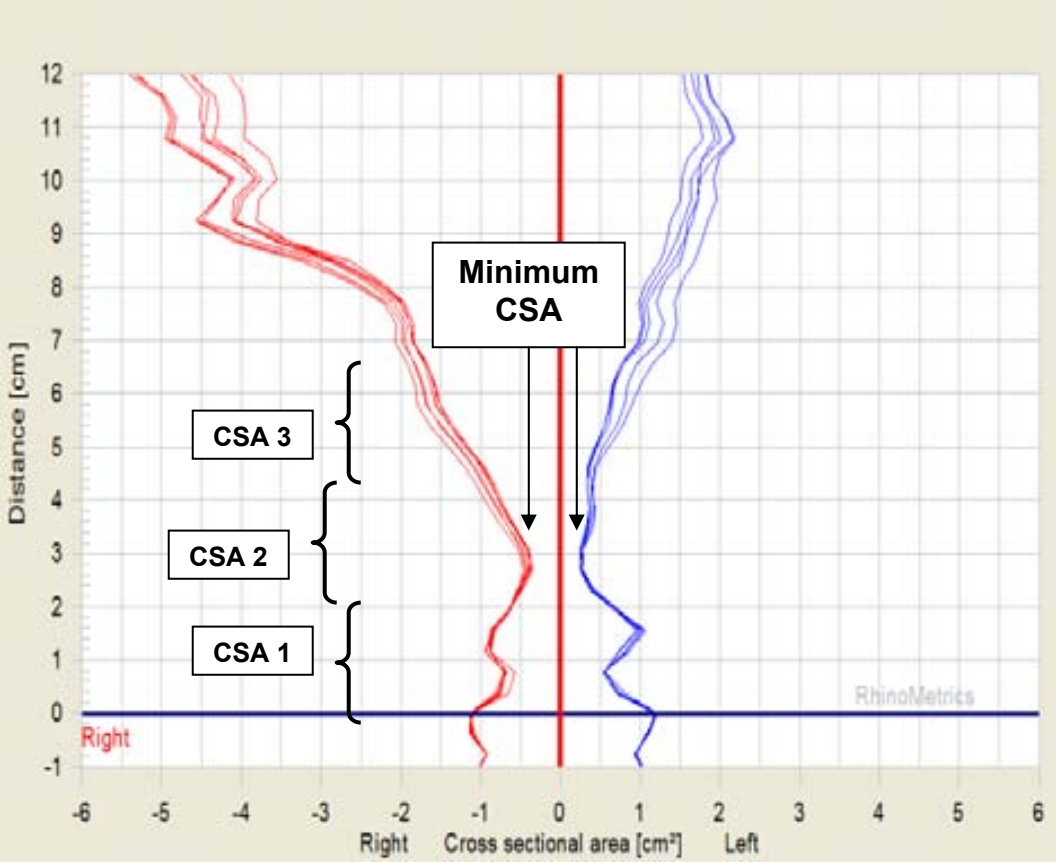


Figure 7 – Rhinogram. Each line represents one breath through right nostril (red) and left nostril (blue).

Proceedings. Measurements were performed using the RhinoScan instrument (Rhinometrics A/S, Lynge, Denmark) using standard techniques.[272-274] This AR device displays the minimal CSA in two sections of the nose. CSA1 with distance range 0 - 2.20 cm and CSA2 with distance range 2.20 - 5.40 cm. Before each use the AR device was calibrated using a standardized probe. Sterile surgical lubricant was applied to the nosepiece to create an acoustic seal. The wand was held to each nostril without causing any distortion of the anatomy and the patient was asked to hold his breath until a stable reading emerged. Three measurements were obtained at each nostril and accepted as normal when they had a coefficient of variation less than 2%. We collected daytime data in the sitting position after 30 minutes of acclimatization to the laboratory environment and in supine position after 15 minutes of recumbency. Measurements were repeated in a separate session on the CPAP titration polysomnography night prior to sleep. No topical decongestants were used. From the awake daytime and night measurements, mean CSA1 and CSA2 were calculated for each visit and position by pooling the data from left and right nostrils. Minimal CSA for each patient was defined as the lowest of CSA1 and CSA2. In order to obtain a value proportional to nasal resistance (NR) and to use this as a "resistance" analog, we made the assumption that flow was turbulent and proportional to $1/R^4$ or $1/(\text{cross sectional area})^2$, expecting at least a monotonic relationship. Thus, we assumed resistance (NR) was proportional to $1/CSA^2$ where CSA was the minimum of CSA1 and CSA2 for each nostril, and that the two resistances acted in parallel during normal breathing $1/\text{total NR} = 1/NR_{left} + 1/NR_{right}$

5.2.3.2 Rhinomanometry

Technique. Rhinomanometry (RM) provides a dynamic assessment of the nasal airway and involves the simultaneous measurement of nasal airflow and the pressure required to achieve that flow, from which nasal airway resistance can be calculated.[275,276]

It's a simultaneous recording of transnasal pressure and airflow during occlusion of one nostril. Classically is divided into passive or active and anterior or posterior.[227] Active RM requires the subject to generate the flow through the nose by their own effort. Passive RM uses external generation of a constant flow of air at a given pressure and requires no respiratory effort. Active RM is a quick test and the International Committee on Standardization of Rhinomanometry recommends it for most studies.[277-279] Anterior and posterior RM primarily differs in the location of the transducer used to measure posterior pharyngeal pressure. The rhinomanometer consists of a pressure transducer for measuring posterior nasal pressure, a pneumotachometer for measurement of flow and a computer for converting these measurements into digital signals.

Active anterior RM is the measurement of the pressure encountered by air passing through the nasal cavity. Patient is actively breathing through one nasal cavity while the narinochoanal pressure difference is assessed in the contralateral cavity. It involves placement of a pressure transducer in the nostril not being tested thus providing a measure of transnasal pressure on the contralateral side. Because there is no flow in the nostril with the pressure transducer, the pressure at the anterior end of this nostril is equal to the pressure in the posterior end of this nostril and this pressure is generated by the open nostril. Nasal airflow resistances are computed form the ratio between transnasal pressure and airflow. It has been validated as a reproducible and reliable method to assess nasal airway patency[280] and reference values have been suggested in some studies.[281] Figure 8 shows rhinomanometry data from one patient.

Proceedings. Measurements were performed using a commercialized rhinomanometer instrument (RhinoStream, Rhinometrics A/S, Lynge, Denmark). We obtained direct measurement of NR by the active anterior technique in accordance with the standard set by the International Committee on Standardization of rhinomanometry.[274] The RM was performed during wakefulness in both sitting and supine positions on 2

occasions, on the day of the recruitment and again at night just prior to the CPAP titration NPSG. For each nostril, flow resistance for inspiration and expiration was separately measured at 75 Pa of pressure using the average of three measurements with a maximum deviation between measurements of 10%. Total NR was calculated separately in inspiration and expiration by combining the parallel NR from the two nostrils using the formula: $1/\text{total NR} = 1/NR_{left} + 1/NR_{right}$.

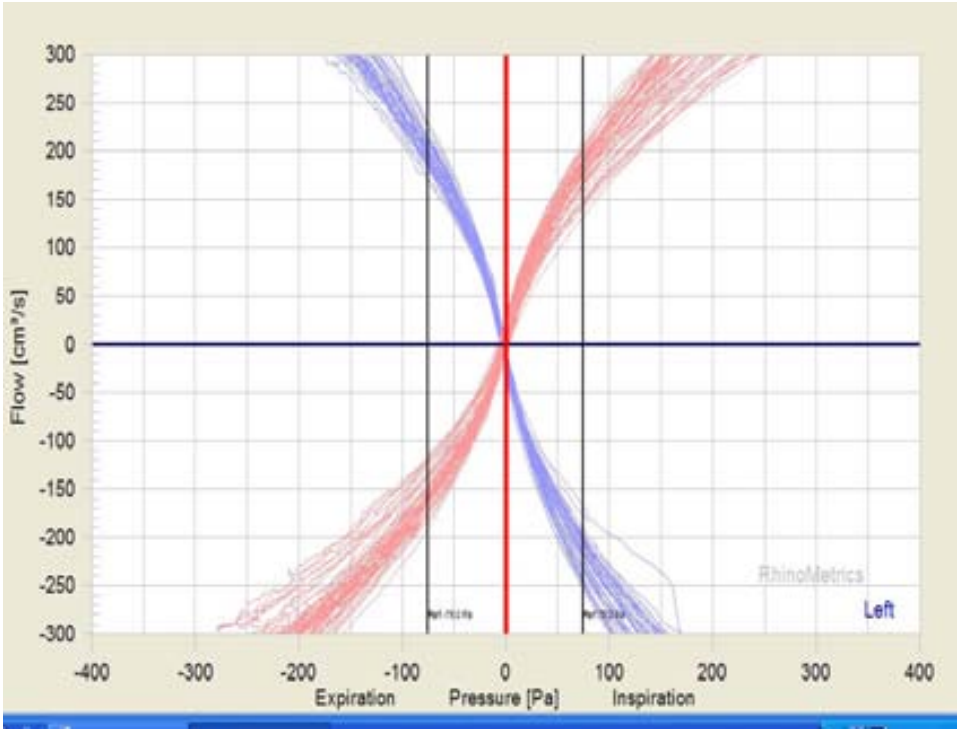


Figure 8 - Rhinomanometry. Each line represents one breath through right nostril (red) and left nostril (blue).

5.3 NIGHTTIME EVALUATION

The diagnostic and CPAP titration NPSGs were performed in the New York University Sleep Disorders Center as per American Academy of Sleep Medicine recommended clinical guidelines.[153,282]

5.3.1 Diagnostic nocturnal polysomnography

Technique and proceedings. The diagnostic NPSG (Sandman Elite, Nellcor Puritan Bennett, Boulder CO, USA) included frontal, central and occipital electroencephalogram, electrooculogram, submental electromyogram to monitor sleep; an anterior tibialis electromyogram to monitor leg movements; a unipolar electrocardiogram for cardiac monitoring; pulse oximeter for oxygen saturation; piezoelectric strain gauges for chest and abdominal movements; and a multiposition switch for determining sleep position. A nasal cannula pressure transducer system (Protech PTAF2, Woodinville WA, USA) was used to measure airflow and an oral thermistor to detect mouth breathing. For the NPSG data, sleep, arousals and leg movements were scored by American Academy of Sleep Medicine standards.[153]

Sleep Scoring of NPSG. Sleep stages were scored and the following measures were extracted: absolute and relative amounts of each sleep stage, latency to each stage, total sleep time, sleep efficiency and wake after sleep onset. An arousal index was calculated as number of arousals per hour of sleep.

Respiratory Event Scoring of NPSG. Respiratory events lasting 10-120 seconds were scored by American Academy of Sleep Medicine standards[153] using the airflow channel and defined as follows: a decrease in airflow >90% relative to baseline for >10 seconds for *apnea*, a decrease in airflow >50% relative to baseline for >10 seconds or any visible reduction (20-50%) relative to baseline for >10 seconds with a 4% desaturation or arousal for *hypopnea*. AHI was defined as the sum of apneas and hypopnea divided by total sleep time.

5.3.2 CPAP Titration nocturnal polysomnography

Technique and proceedings. If CPAP treatment was clinically indicated the patients were referred for in-laboratory CPAP titration NPSG.[202] Pressure was directly measured at the CPAP mask using a pressure transducer (Ultima Dual Airflow Pressure Sensor™, Braebon 0585, Ontario, Canada). Airflow was recorded from the output of a Respironics BiPAP® Auto M Series device in CPAP mode. CPAP was titrated manually during the first hour of the study to a level that eliminated all sleep disordered breathing events including obstructive apneas, hypopneas and runs of flow limitation. The optimal pressure was defined as the minimum pressure at which flow limitation disappeared. This pressure was determined by performing step-down dropping the pressure every two minutes by 1 cmH_2O until the appearance of flow limitation. The pressure prior the appearance of flow limitation established the minimum therapeutic pressure.

5.3.3 Measurements of supraglottic pressure during sleep

During CPAP titration NPSG, in addition to standard monitoring, supraglottic pressure was obtained using a pressure transducer-tipped catheter (Millar MPC 500, Millar Instruments, Houston, TX, USA). The nose was anesthetized using atomized lidocaine 5% and lidocaine 2% jelly for the throat. The Millar catheter was introduced transnasally and the tip of the catheter was located just below the uvula. The catheter position was confirmed visually through the mouth. The catheter was taped to the nose to secure its position throughout the study. The nasal CPAP mask was then applied and leak at the exit site of the catheter was minimized. The output of the Millar catheter was amplified and recorded at 64Hz. To verify that the supraglottic catheter was just below the collapsible segment of the upper airway, the behavior of difference between the supraglottic and CPAP inspiratory pressures after the patient fell asleep was inspected during a brief “step-down” of CPAP pressure. Correct positioning of the catheter tip required that the delta pressure between the mask and the supraglottic area increases substantially during

inspiration simultaneously with the appearance of inspiratory flow limitation. If this increase in delta pressure was not observed as CPAP was reduced, it was assumed the catheter position was too high and the catheter was advanced. Figure 9 shows the sites were we obtained mask pressure and supraglottic pressure measurements.

Supraglottic pressure measurements were obtained during optimal fixed CPAP and during the same CPAP level with expiratory pressure reduction (C-Flex). C-Flex produces a constant inhalation pressure but reduces airway pressure during exhalation in proportion to the patient's expiratory airflow (thus a drop in pressure occurs primarily during early expiration). C-Flex allows for three setting, C-Flex 1, C-Flex 2, C-Flex 3 which corresponds to an increasing proportionality constant between expiratory flow and pressure reduction (Figure 10).

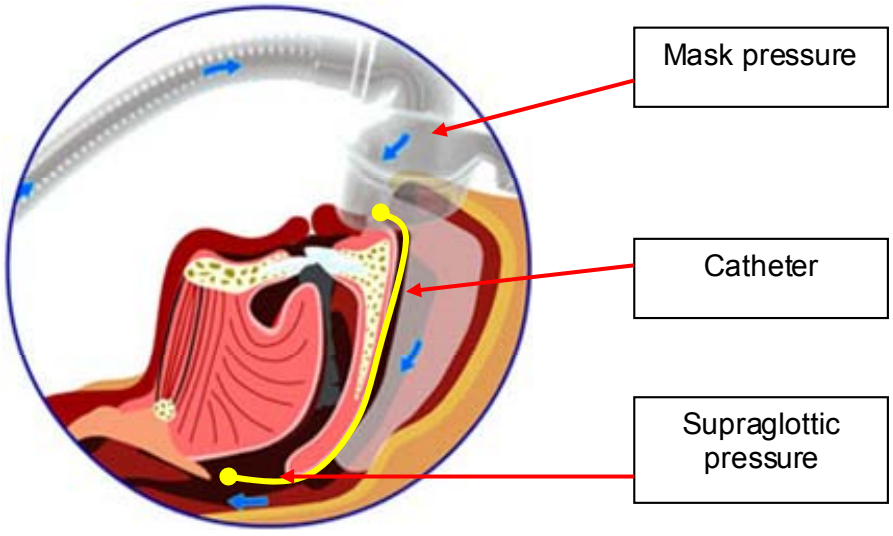


Figure 9 - Sites of pressure measurements

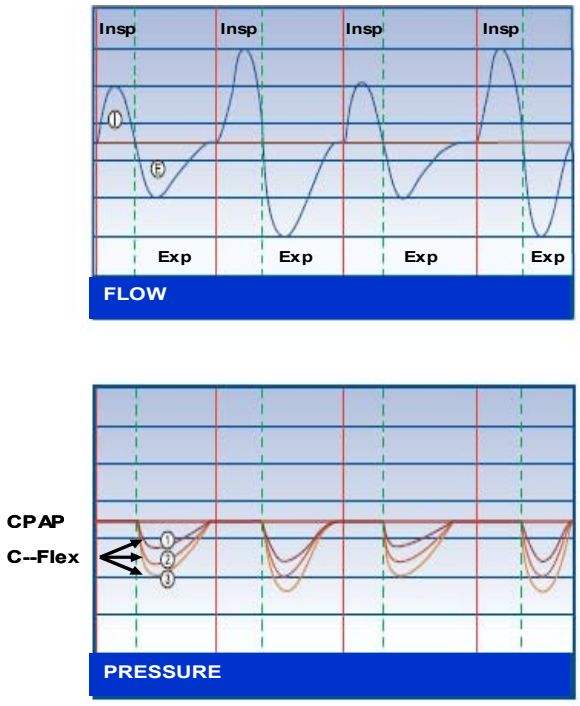


Figure 10 - Mask pressure during fixed CPAP and during C-Flex application

5.3.4 Intervention during CPAP titration nocturnal polysomnography: application of C-Flex settings

Interventions were performed after 5 minutes of stable N2 sleep with the patient on optimal CPAP. The data were discarded if an arousal occurred. Three different levels of C-Flex were applied cyclically multiple times throughout the night. The order of application of C-Flex level was not randomized. Each level was maintained for 1 minute, and fixed CPAP was restored at the end of the sequence, which was repeated at least twice, up to 10 times, across the night. Changes in pressure were accomplished with a single machine while patients were asleep, and, thus, patients were effectively blinded to the intervention.

5.4 MECHANICAL MODEL OF THE UPPER AIRWAY

To create a bench test for some of our observations in patients, we designed a mechanical model of the upper airway in patients on CPAP (ie, without a collapsible airway). This model (Figure 11) consisted of a rigid resistive tube, the resistance of which could be varied by changing the aperture size. A pure sinusoidal respiratory pattern was generated using a mechanical pump (Respiration Pump 607, Harvard Apparatus Co, INC. Dover, MA). In a separate data collection, a healthy volunteer breathing through the system generated a “normal” breathing pattern (exponential expiration with pause). Airflow was measured from the output of a Respironics BiPAP Auto M Series device in CPAP mode. Simulated mask pressure was measured with a pressure transducer (Ultima Dual Airflow Pressure Sensor). Simulated supraglottic pressure was obtained using the Millar catheter. Measurements were obtained using these 2 respiratory patterns (sinusoidal and normal-exponential) at 2 respiratory rates and 2 tidal volumes. All measurements were performed with 2 different resistances during fixed CPAP treatment and during the application of C-Flex settings. Three different levels of C-Flex were applied and maintained for 1 minute each, and fixed CPAP was restored at the end of the sequence, which was repeated.

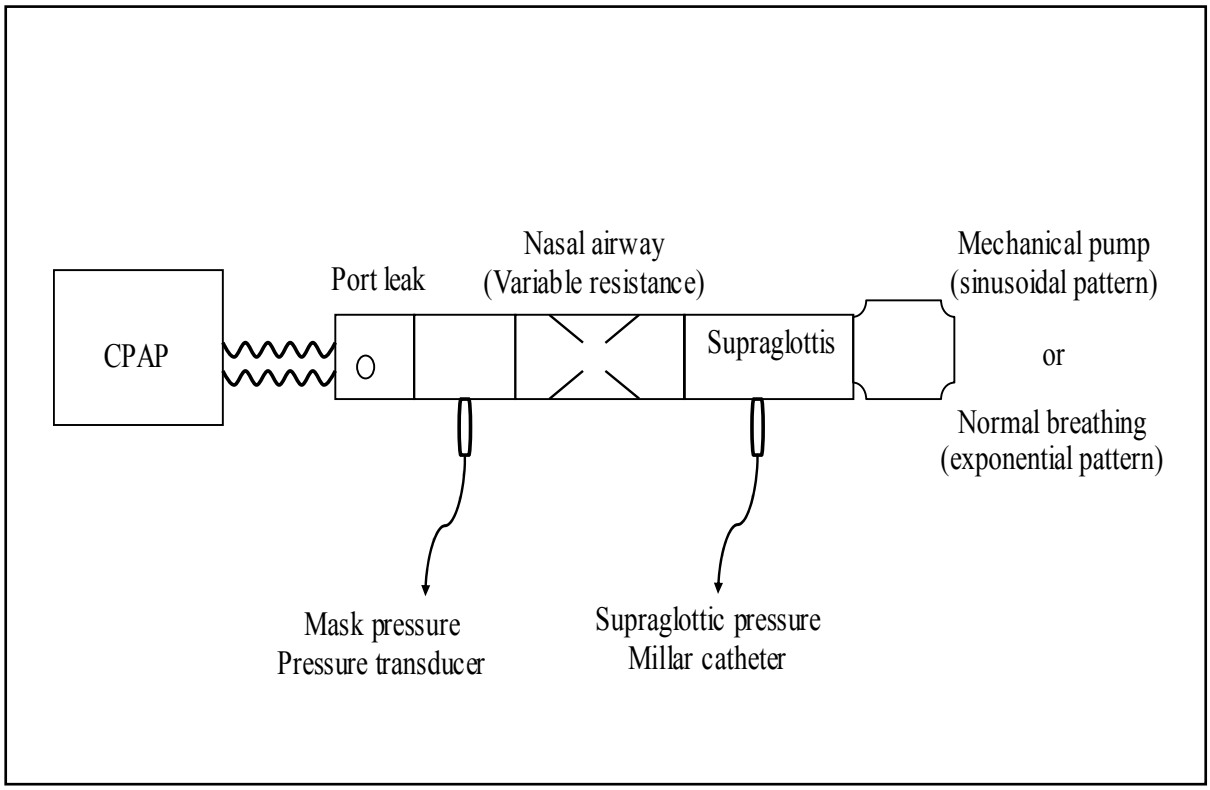


Figure 11 - Mechanical model of the upper airway. The model consists of a rigid resistive tube with a variable "upstream" upper airway resistance controlled by changing the aperture size to mimic a patient using nasal continuous positive airway pressure (CPAP). A rigid tube was used to model the upper airway because dynamic collapse does not occur in patients on CPAP. The pressure taps are placed within the model to obtain measurements that simulate nasal and supraglottic pressures in a patient. Patterns of breathing were applied by a mechanical pump (sinusoidal) or a healthy volunteer breathing on a mouthpiece ("normal" pattern).

5.5 Analysis

5.5.1 Analysis of the upper airway pressures

Figure 12 shows a drawing of airflow, mask pressure, and supraglottic pressure signals and the derived variables. Respiratory variables were analyzed only during the expiratory phase. We assessed values of variables on CPAP and on different C-Flex settings. Mask pressure (Pm in Figure 12) is the expiratory pressure swing in the mask (the difference between mask pressure at peak expiratory airflow and mask pressure at the end of expiration, which is the set CPAP). Supraglottic pressure (Ps) is the expiratory pressure swing in the supraglottis (the difference between the supraglottic pressure at peak expiratory airflow and the supraglottic pressure at the end of expiration). Delta Pm (ΔPm) is the change in mask-pressure swings with application of C-Flex (Pm on C-Flex minus Pm on CPAP). Delta Ps (ΔPs) is the change in supraglottic pressure swings with application of C-Flex (Ps on C-Flex minus Ps on CPAP). We calculated the integrated supraglottic pressure during expiration (Ws) as a surrogate for expiratory work.

In patients (during stage N2 sleep and in the same position) and in the UA model, we identified 2 separate periods suitable for data collection during which stable respiration was present. In each of these periods, data from 3 consecutive breaths were averaged to obtain the value for each variable on C-Flex 1, C-Flex 2, C-Flex 3, and fixed CPAP. The average value from 2 segments is reported as a single value for each variable on C-Flex 1, C-Flex 2, C-Flex 3, and fixed CPAP. Analysis of the supraglottic pressure signal was done without hiding the mask pressure signal, and the investigator was, thus, not blinded as to the presence of C-Flex.

5.5.2 Analysis of the upper airway resistance

UA resistance was calculated for each inspiration and expiration as the difference between mask pressure and supraglottic pressure at peak airflow divided by peak airflow. We assessed reproducibility/stability of the UA resistance measurement in three different

situations: short term-sleep (in stage N2 sleep and within 10 minutes), long term-sleep and long term-awake (measurements in the same position in stage N2 sleep or wake but at least one hour apart). In each of these situations we compared 3 measurements of UA resistance for inspiration and expiration.

5.6 STATISTICS

Statistical analysis was made using SPSS for Windows (version 17; SPSS, Chicago IL). Significance was assumed at a p value of less than 0.05. Values are shown as mean ± SD.

5.6.1 Data from acoustic rhinometry and rhinomanometry

For each variable, comparisons between positions (sitting versus supine) and between daytime, nighttime wake and sleep were made using paired *t*-test. Correlations between variables were evaluated using Pearson correlation coefficient.

5.6.1 Data from upper airway pressure measurements

An independent samples t-test was used for comparisons between low and high resistance. Comparisons of ΔPm and ΔPs were made using paired-samples *t*-tests comparing CPAP with C-Flex 3.

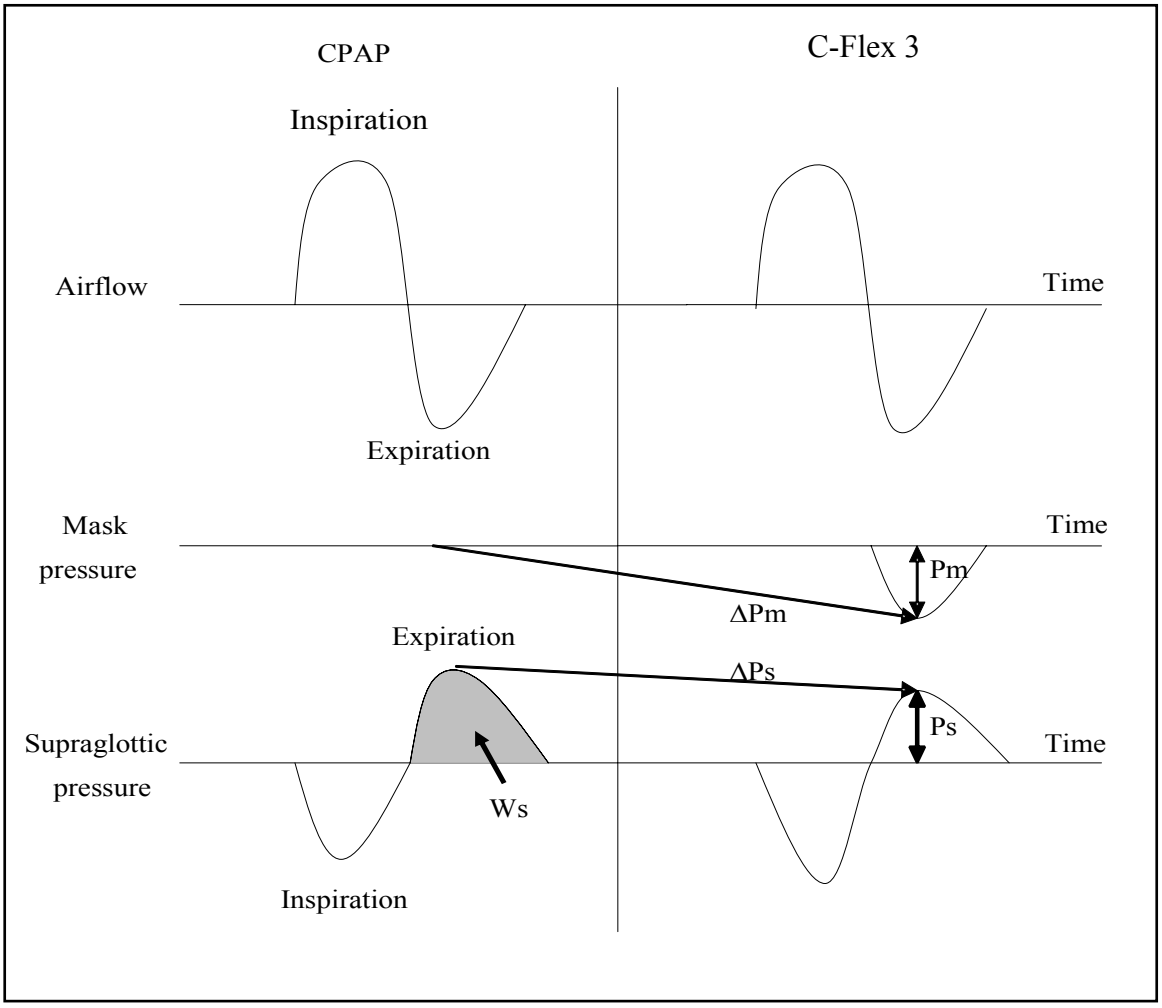


Figure 12- Drawing of airflow, mask pressure, and supraglottic pressure signals and the derived variables. This drawing shows data collected and variables analyzed for a single breath. The left panel shows continuous positive airway pressure (CPAP) and the right shows C-Flex 3. The top tracing shows airflow (inspiration up). The middle tracing is pressure at the mask, and the bottom tracing is supraglottic pressure (inspiration down). Pm refers to the expiratory pressure swing in the mask; Ps, expiratory pressure swing in the supraglottis; ΔPm, change in expiratory mask pressure swings (C-Flex 3 minus CPAP); ΔPs, change in expiratory pressure swings in the supraglottis (C-Flex 3 minus CPAP);Ws, estimated expiratory work by calculating integrated pressure (grey area).

6. RESULTS

Of 22 subjects recruited, 17 patients (13 male/4 female) completed the study: five were excluded due to insufficient sleep (2), excessive mask leak (2) and poor supraglottic catheter signal quality (1). The mean age was 49.2 ± 11.1 years, mean body mass index 35.1 ± 9.8 Kg/m^2, mean apnea-hypopnea index 61.2 ± 35.1/hr, mean respiratory index disturbance 64.8 ± 35.1/hr, mean Epworth Sleepiness Scale 12.7 ± 5.4, mean CPAP level 10.11 ± 3.5 cm H_2O.

On the NOSE questionnaire, 9 subjects showed no or mild symptoms of nasal obstruction (NOSE scores <8 out of 20) and 5 subjects showed moderate-severe symptoms (NOSE score 11-18). No subject had a NOSE score >18.

STUDY 1-Awake measures of nasal resistance and upper airway resistance on CPAP during sleep. J Clin Sleep Med 2011. (Appendix 1)

6.1 ASSESSMENT OF A DAYTIME/WAKE MEASUREMENT PREDICTIVE OF NIGHTTIME/SLEEP UPPER AIRWAY PHYSIOLOGY

6.1.1 Relationship between noninvasive measures of nasal resistance during wakefulness and directly assessed supraglottic resistance on CPAP during sleep in SAHS patients

6.1.1.1 Evaluation of nasal resistance during wakefulness by acoustic rhinometry

6.1.1.1.1 Nasal cross-sectional area across sessions (daytime vs. nighttime) and positions (sitting vs. supine)

Within each subject and for each position, CSA1 (awake day vs. awake night, p= 0.15 [sitting], p= 0.07 [supine]) and CSA2 (awake day vs. awake night, p= 0.37 [sitting], 0.16 [supine]) were reproducible across sessions. CSA1 and CSA2 showed changes from

sitting to supine position that tended to stay constant across sessions in each individual. However both increases and decreases in CSA occurred with equal frequency and averaged to zero for the group (Figure 13A, B). Of note, decreases/increases did not always occur in the same subjects for CSA1 and CSA2. Table 1 shows the group mean data for CSA1 and CSA2 by position. In each patient, a single value of CSA1 or CSA2 was calculated using the average of daytime and nighttime awake data.

6.1.1.1.2 Nasal resistance analog by acoustic rhynometry across sessions (daytime vs. nighttime) and positions (sitting vs. supine)

Similar to the results for CSA itself, NR as calculated from CSA did not show any change across sessions or a consistent position effect for the group (Table 1).

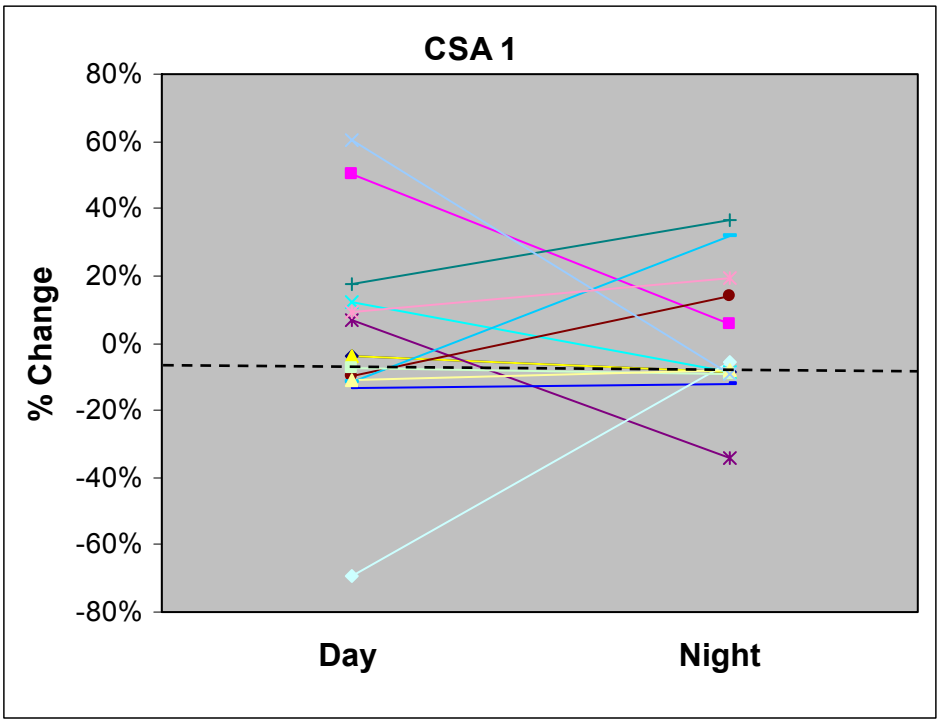


Figure 13A - Positional change of CSA1 from sitting to supine position during wakefulness in both sessions, daytime and nighttime. The Y axis shows the percentage of change of CSA1 from sitting to supine position. Each line represents a subject (n= 14) and the first

point of the line shows the change of CSA1 from sitting to supine position during the daytime session. Second point of the line represents the change of CSA1 from sitting to supine position during the nighttime session.

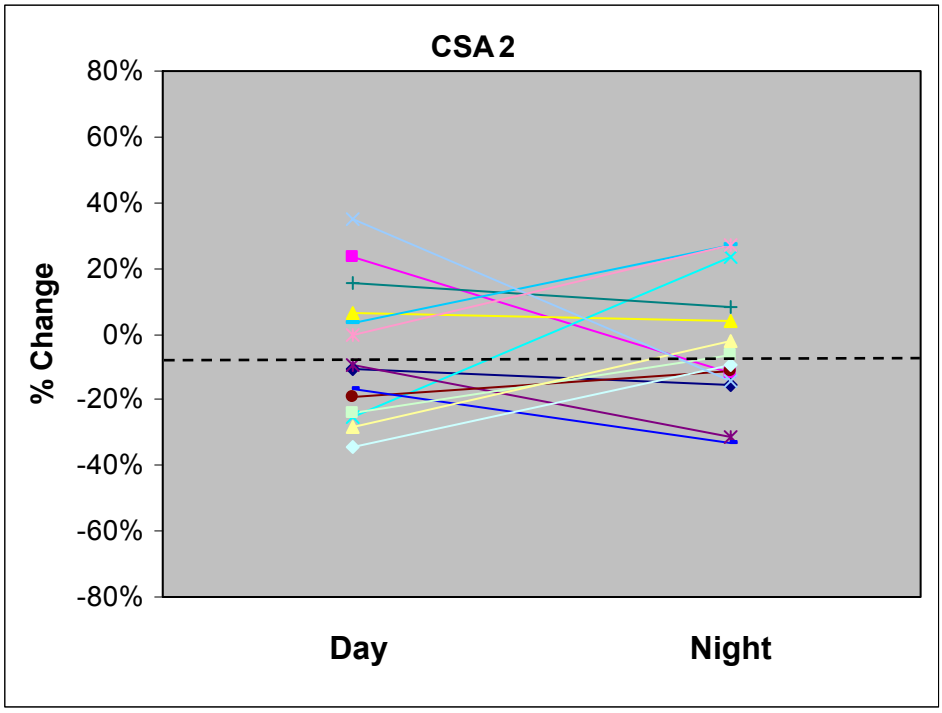


Figure 13B - Positional change of CSA2 from sitting to supine position during wakefulness in both sessions, daytime and nighttime. The Y axis shows the percentage of change of CSA2 from sitting to supine position. Each line represents a subject (n= 14) and the first point of the line shows the change of CSA2 from sitting to supine position during the daytime session. Second point of the line represents the change of CSA2 from sitting to supine position during the nighttime session.

Table 1 - Awake acoustic rhinometry - Values of CSA and nasal resistance (n=14)*

	Mean (SD)	Range
CSA1 (cm^2)		
Sitting	0.58 ± 0.10	0.40 – 0.77
Supine	0.56 ± 0.09	0.38 – 0.76
CSA2 (cm^2)		
Sitting	0.53 ± 0.12	0.29 – 0.72
Supine	0.50 ± 0.15	0.31 – 0.83
Minimal CSA (cm^2)^T		
Sitting	0.50 ± 0.11	0.29 – 0.70
Supine	0.47 ± 0.12	0.31 – 0.76
Nasal resistance (arbitrary units)		
Sitting	2.46 ± 1.32	1.1 – 6.27
Supine	2.66 ± 1.31	0.87 – 5.21

CSA refers to cross-sectional area; ^{T}Minimal CSA, minimal cross-sectional area between CSA1 and CSA2; SD, standard deviation. * Values for CSA1, CSA2 and nasal resistance were obtained for each patient by averaging daytime and nighttime measurements. Values in the table are the mean values for all subjects.

6.1.1.2 Evaluation of nasal resistance during wakefulness by active anterior rhinomanometry

6.1.1.2.1 Nasal resistance by rhinomanometry across sessions (daytime vs. nighttime) and positions (sitting vs. supine)

Similar to the data for CSA, measurements of NR by anterior RM did not vary across sessions (day vs. night). Changes of NR from sitting to supine during inspiration and expiration also did not show a statistically significant variation across sessions (Figure

14A, B). In view of this, for each patient a single value of NR was calculated for each position from the average of daytime and nighttime awake measurements and is shown in Table 2.

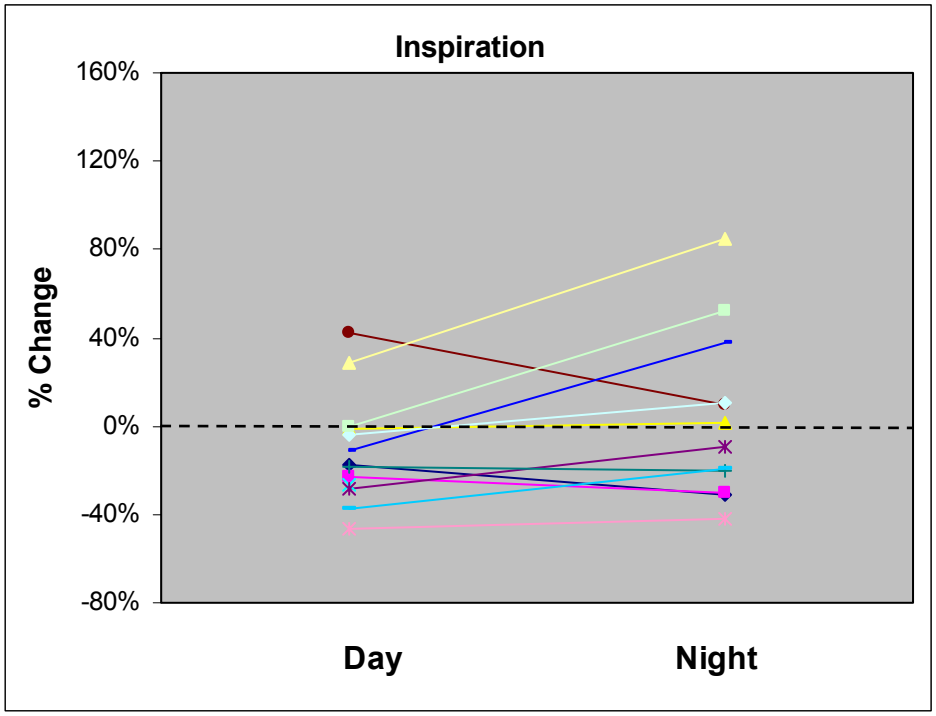


Figure 14A – Positional change of inspiratory nasal resistance by rhinomanometry from sitting to supine position during wakefulness in both sessions, daytime and nighttime. The Y axis shows the percentage of change of inspiratory nasal resistance from sitting to supine position. Each line represents a subject (n= 12) and the first point of the line shows the change of inspiratory nasal resistance from sitting to supine position during the daytime session. Second point of the line represents the change of inspiratory nasal resistance from sitting to supine position during the nighttime session.

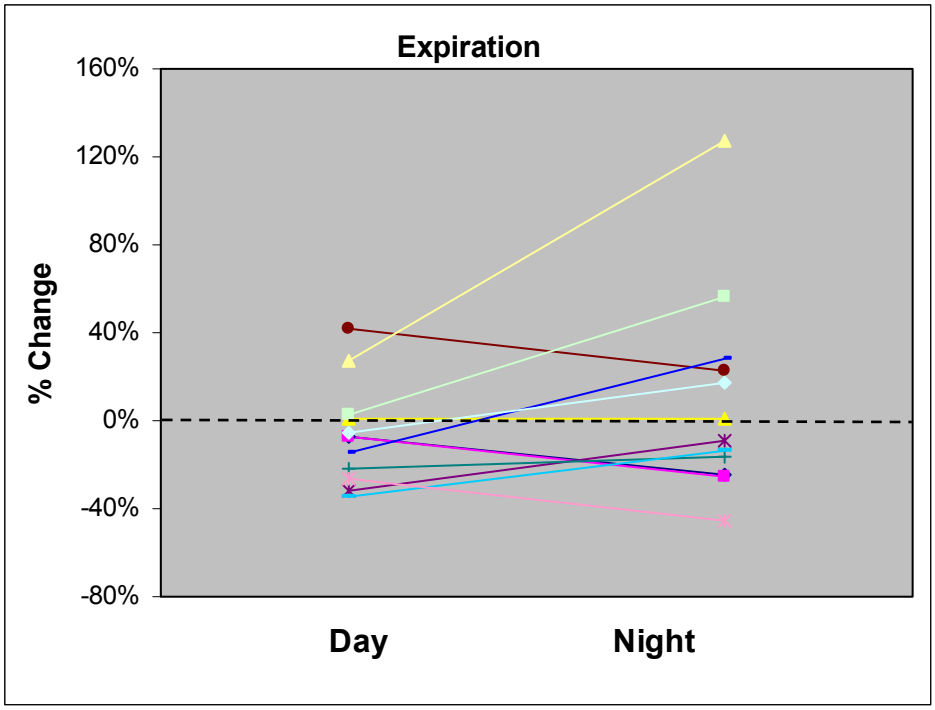


Figure 14B – Positional change of expiratory nasal resistance by rhinomanometry from sitting to supine position during wakefulness in both sessions, daytime and nighttime. The Y axis shows the percentage of change of expiratory nasal resistance from sitting to supine position. Each line represents a subject (n= 12) and the first point of the line shows the change of expiratory nasal resistance from sitting to supine position during the daytime session. Second point of the line represents the change of expiratory nasal resistance from sitting to supine position during the nighttime session.

Table 2 - Awake rhinomanometry - Values of nasal resistance (n=14)*

	Mean (SD) Pa s/cm^3	Range Pa s/cm^3
Inspiration		
Sitting	0.24 ± 0.08	0.15 – 0.44
Supine	0.24 ± 0.09	0.13 – 0.42
Expiration		
Sitting	0.23 ± 0.08	0.13 – 0.43
Supine	0.23 ± 0.07	0.14 – 0.43
Mean Nasal Resistance		
Sitting	0.23 ± 0.07	0.14 – 0.44
Supine	0.23 ± 0.08	0.14 – 0.43

SD refers to standard deviation. *Values for inspiratory and expiratory nasal resistance are the combined measurements for each patient from daytime and nighttime measurements. Values for mean nasal resistance are the combined data during inspiration and expiration for each position.

Our patients had a wide range of nasal resistance by rhinomanometry, with 8 having normal values and 6 having high values. This is similar to other published RM data in SAHS.[248] By anterior RM, 6/14 patients showed a sitting NR (average of inspiration and expiration) above 0.25 Pa s/cm^3 which has been suggested as the upper limit of normal by Cole et al.[281] In the group with high NR by anterior RM, 4 subjects showed a decrease of NR from sitting to supine position, but only one of these patients had a change greater than 30% suggested by Altissimi et al[283] as the cut-off of NR change with the change of position. In the group with low NR (8/14), six patients showed an increase of NR in supine position, and one of these patients had a change greater than 30%.

6.1.1.3 Correlation between measurements of nasal resistance by acoustic rhinometry and active anterior rhinomanometry

Table 3 shows the correlation coefficients between measurements from the AR and RM. No strong relationships could be shown between the two techniques in sitting position, but there was significant correlation in the supine position. Figure 15 shows the correlation between nasal resistance by AR and anterior RM.

Table 3 - Correlation coefficients between acoustic rhinometry and rhinomanometry (n=14)

		Acoustic rhinometry			
		CSA1 sitting	**CSA2 sitting**	**Minimal CSA sitting**	**Nasal resistance sitting**
Rhinomanometry	**Nasal resistance – sitting**				
	Inspiration	-0.16	-0.26	-0.27	0.18
	Expiration	-0.17	-0.34	-0.32	0.23
	Mean†	-0.17	-0.30	-0.29	0.20
		CSA1 supine	**CSA2 supine**	**Minimal CSA supine**	**Nasal resistance supine**
	Nasal resistance - supine				
	Inspiration	-0.13	-0.52	-0.52	0.59*
	Expiration	-0.08	-0.44	-0.41	0.47
	Mean†	-0.11	-0.51	-0.49	0.56*

CSA refers to cross-sectional area. †Values for mean nasal resistance are the combined data during inspiration and expiration for each position. *Statistically significant ($p<0.05$)

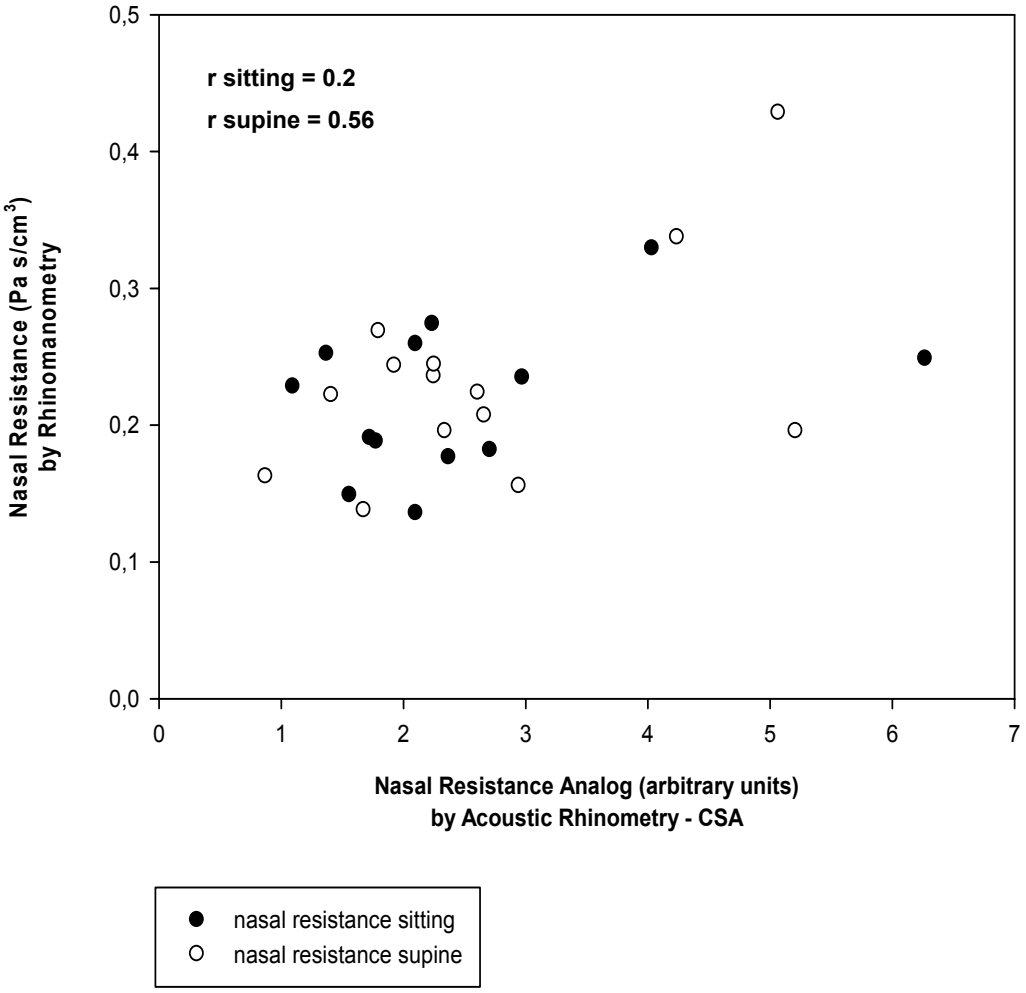


Figure 15 – Correlation between nasal resistance by acoustic rhinometry (X axis) and nasal resistance by rhinomanometry (Y axis). Each point represents a subject (n=14). Black dots represent measures of nasal resistance in sitting position and open dots are measures of nasal resistance in supine position. Values for mean nasal resistance by rhinomanometry are the combined data during inspiration and expiration for each position.

6.1.1.4 Evaluation of upper airway (supraglottis) resistance on CPAP during sleep in patients with SAHS

6.1.1.4.1 Pressure deviations at the mask and supraglottis from set CPAP

Pressure in the mask remained within 0.5 cm H_2O of set pressure at the machine. As expected from the UA resistive behaviour, mean supraglottic pressure fell during inspiration and rose during expiration from that set at the mask/machine. Overall, the absolute value of the difference between set pressure and supraglottic pressure during wakefulness across subjects was 2.63 $\pm$ 2.18 cm H_2O in inspiration (range from 0.6 to 7.7 cm H_2O) and 1.66 $\pm$ 1.42 cm H_2O in expiration (range from 0.3 to 6.1 cm H_2O). During sleep, the mean value of the difference between set pressure and supraglottic pressure across subjects was 3.02 $\pm$ 2.62 cm H_2O in inspiration (range from 0.6 to 9.2 cm H_2O) and 1.56 $\pm$ 1.27 cm H_2O in expiration (range from 0.4 to 2.8 cm H_2O).

6.1.1.4.2 Calculated resistances for the upper airway (supraglottis)

Table 4 shows the results of the resistances calculated for the UA, derived from peak flow and the peak pressure drop from mask to supraglottic area. In 11/14 subjects, inspiratory UA resistance was similar to expiratory UA resistance. However in 3 subjects inspiratory UA resistance was much higher than expiratory UA resistance, suggesting suboptimal CPAP may have been present. Inspiratory and expiratory resistances were larger during sleep than during wakefulness on CPAP, although the difference did not reach statistical significance.

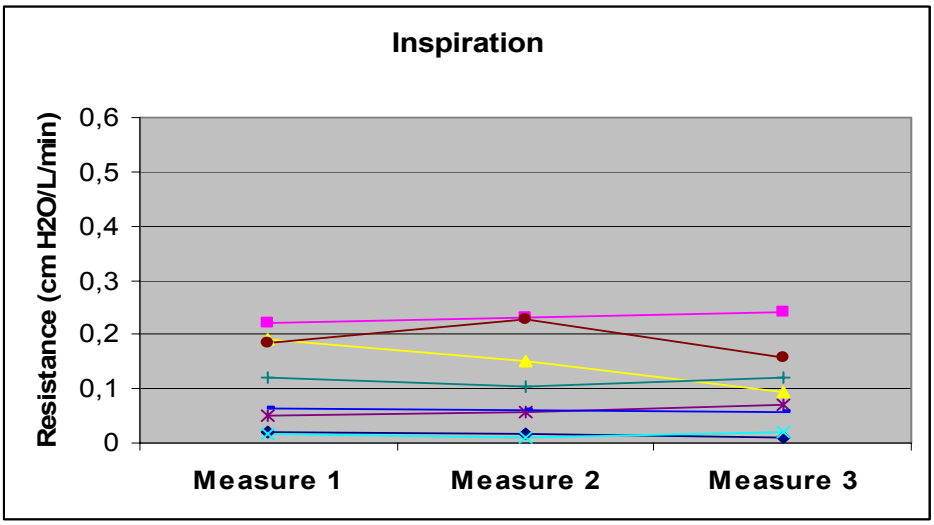
Measurement of UA resistances within a single patient remained stable between repeated measures both short term (within 10 minutes with multiple measures) and across the night (measurements one hour apart in the same position in stage 2 sleep or wake) at a statistical significance of 0.05 (Figure 16A,B,C,D,E,F).

Table 4 - Sleep upper airway resistance by supraglottic catheter (n=14)

	Mean (SD) cm H_2O/L/min	**Range cm H_2O/L/min**
Wakefulness		
Inspiration	0.09 ± 0.06	0.03 – 0.21
Expiration	0.09 ± 0.06	0.04 – 0.22
Sleep		
Inspiration	0.12 ± 0.08	0.02 – 0.27
Expiration	0.10 ± 0.09	0.01 – 0.26
Wakefulness (inspiration & expiration)	0.09 ± 0.06	0.03 – 0.22
Sleep (inspiration & expiration)	0.11 ± 0.08	0.01 – 0.26

SD refers to standard deviation

A



B

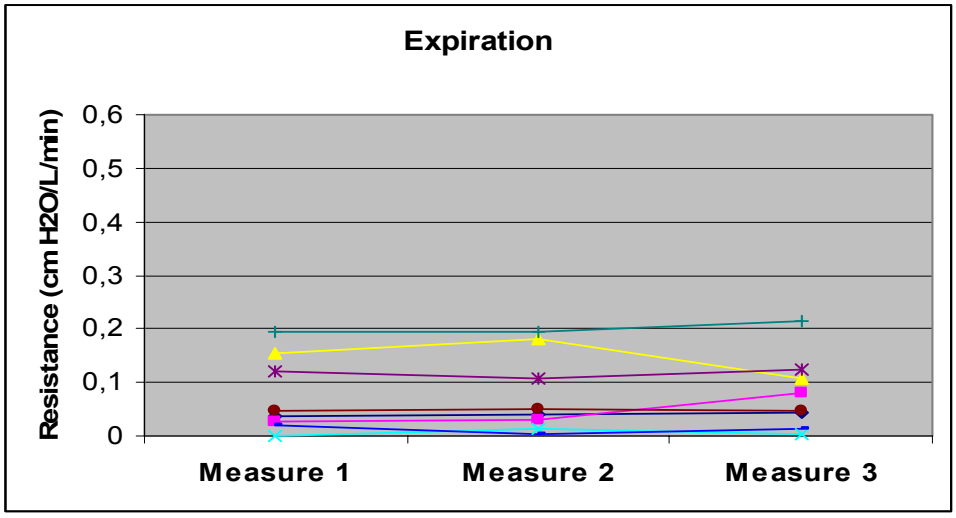
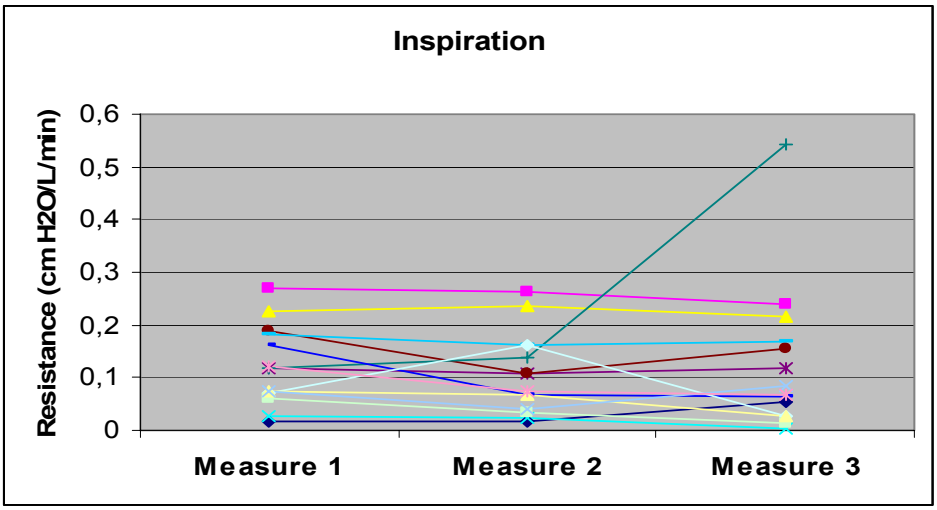


Figure 16A, B – Reproducibility of the upper airway resistance in short-term sleep (within 10 minutes of stage N2 sleep). X axis represents 3 points in time within a period of 10 minutes of stable stage N2 sleep. Y axis is the value of upper airway resistance measured by supraglottic catheter. Each line represents a subject (n= 8).

C



D

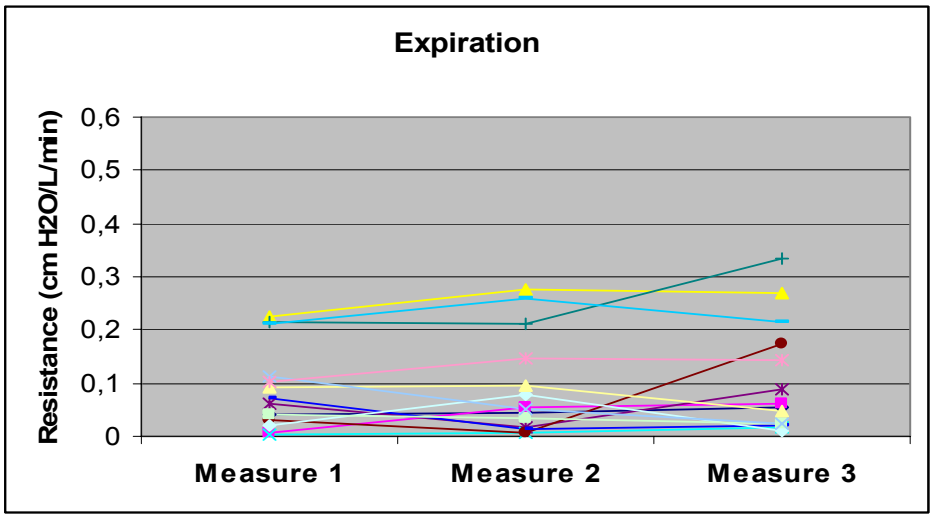
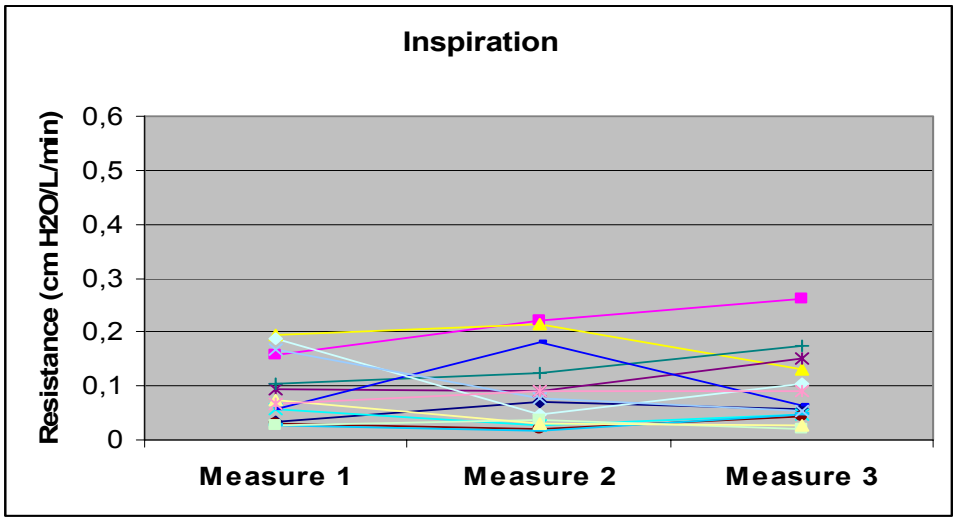


Figure 16C, D – Reproducibility of the upper airway resistance in long-term sleep (measurements at 1 hour apart in the same position in stage N2 sleep. X axis represents 3 points in time across the night of stable stage N2 sleep and separated at least by 1 hour. Y axis is the value of upper airway resistance measured by supraglottic catheter. Each line represents a subject (n= 14).

E



F

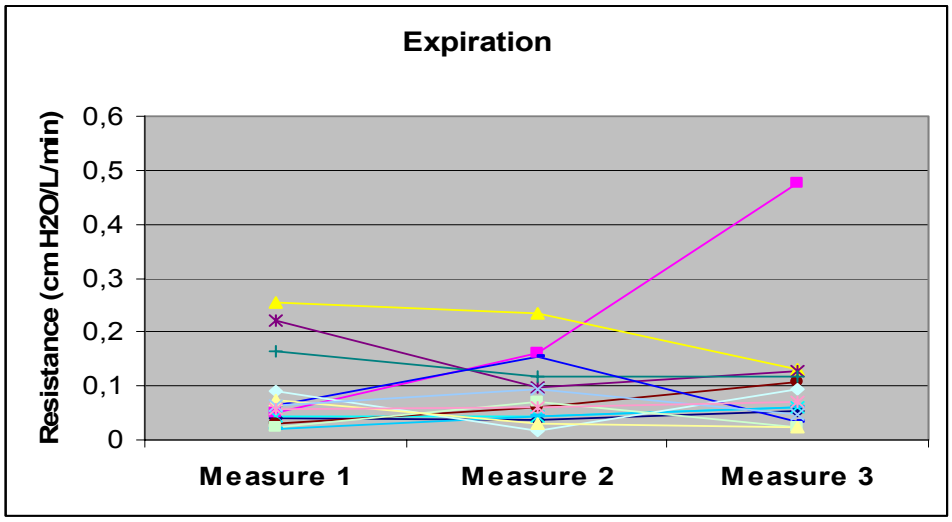


Figure 16E, F – Reproducibility of the upper airway resistance in long-term awake (measurements at 1 hour apart in the same position awake). X axis represents 3 points in time across the night of stable breathing during wakefulness and separated at least by 1 hour. Y axis is the value of upper airway resistance measured by supraglottic catheter. Each line represents a subject (n= 14).

6.1.1.5 Correlations between nasal resistance during wakefulness and supraglottic resistance during sleep

Table 5 shows the correlation coefficients between UA resistance and NR by AR and RM. Although correlation coefficients were statistically significant they do not seem physiologically plausible, as patients with *lower* CSA awake have *lower* UA resistance during sleep on CPAP. In addition, we found no relationship between direct measurement of UA resistance and awake RM.

6.1.1.6 Correlations between upper airway and nasal resistances and clinical variables

No significant relationships were found between measures of nasal resistance (AR and RM) or UA resistance and RDI, NOSE questionnaire and CPAP level. The correlation coefficients were all near zero (<0.12) and p values of these correlations were all >0.6.

We could not show any association between positional change in RDI from supine to *lateral* and supine to *sitting* measurement of resistance in the 7 patients with all measurements. Only three patients had positional changes in AHI>50%.

Table 5 - Correlation coefficients between directly assessed upper airway resistance and nasal resistance by acoustic rhinometry and rhinomanometry (n=14)

		Directly assessed upper airway resistance (sleep)		
		UA resistance Inspiration	**UA resistance Expiration**	**UA resistance Mean**
Acoustic rhinometry (awake)	**CSA1**			
	Sitting	-0.15	0.45	-0.54
	Supine	0.37	0.54*	0.50
	CSA2			
	Sitting	0.44	0.37	0.45
	Supine	0.64*	0.69*	0.73*
	Minimal CSA			
	Sitting	0.14	0.20	0.19
	Supine	0.59*	0.64*	0.68*
	Nasal resistance			
	Sitting	-0.21	-0.16	-0.20
	Supine	-0.51	-0.54*	-0.58
Rhinomanometry (awake)	**Nasal resistance inspiration**			
	Sitting	-0.12	---	---
	Supine	-0.47		
	Nasal resistance expiration			
	Sitting	---	0.22	---
	Supine		-0.03	
	Mean nasal resistance			
	Sitting	---	---	0.64
	Supine			-0.30

UA refers to upper airway; CSA, cross-sectional area. *Statistically significant ($p<0.05$)

STUDY 2-The supraglottic effect of a reduction in expiratory mask pressure during continuous positive airway pressure. Sleep 2012. (Appendix 2)

6.2 ASSESSMENT OF THE INFLUENCE OF UPSTREAM (NASAL) RESISTANCE ON UPPER AIRWAY (SUPRAGLOTTIS) PRESSURE DURING EXPIRATION ON FIXED OPTIMAL CPAP AND WITH THE APPLICATION OF C-FLEX.

6.2.1 Assessment of the expiratory pressure profile at the mask and at the upper airway (supraglottis) on fixed CPAP with and without C-Flex

6.2.1.1 Patients with SAHS

Seventeen patients completed the study. The mean apnea-hypopnea index was 61.2 ± 35.1 events /h, mean respiratory index disturbance 64.8 ± 35.1 events/h, mean Epworth Sleepiness Scale score, 12.7 ± 5.4; and the mean CPAP level, 10.11 ± 3.5 cm H_2O. Figure 17 shows all the signals collected during the CPAP titration NPSG.

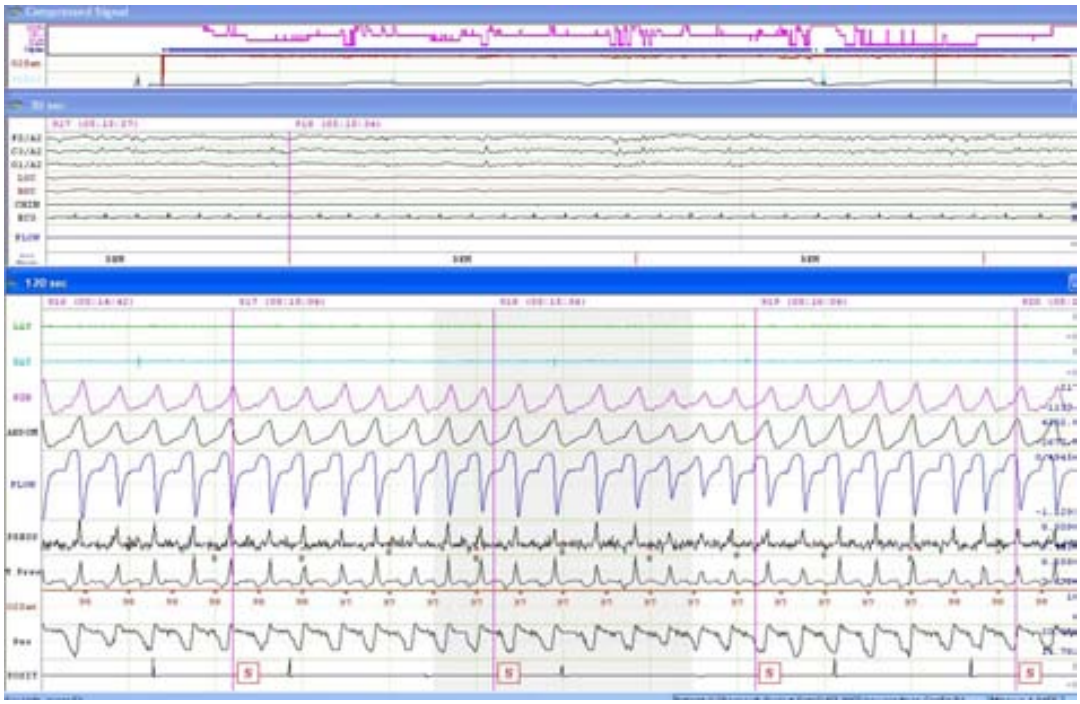


Figure 17 – Raw tracing data from one patient with SAHS

Figure 18 shows with detail respiratory tracings collected during the CPAP titration NPSG. Raw-tracing data of airflow, mask pressure, and supraglottic pressure from 1 patient with SAHS.

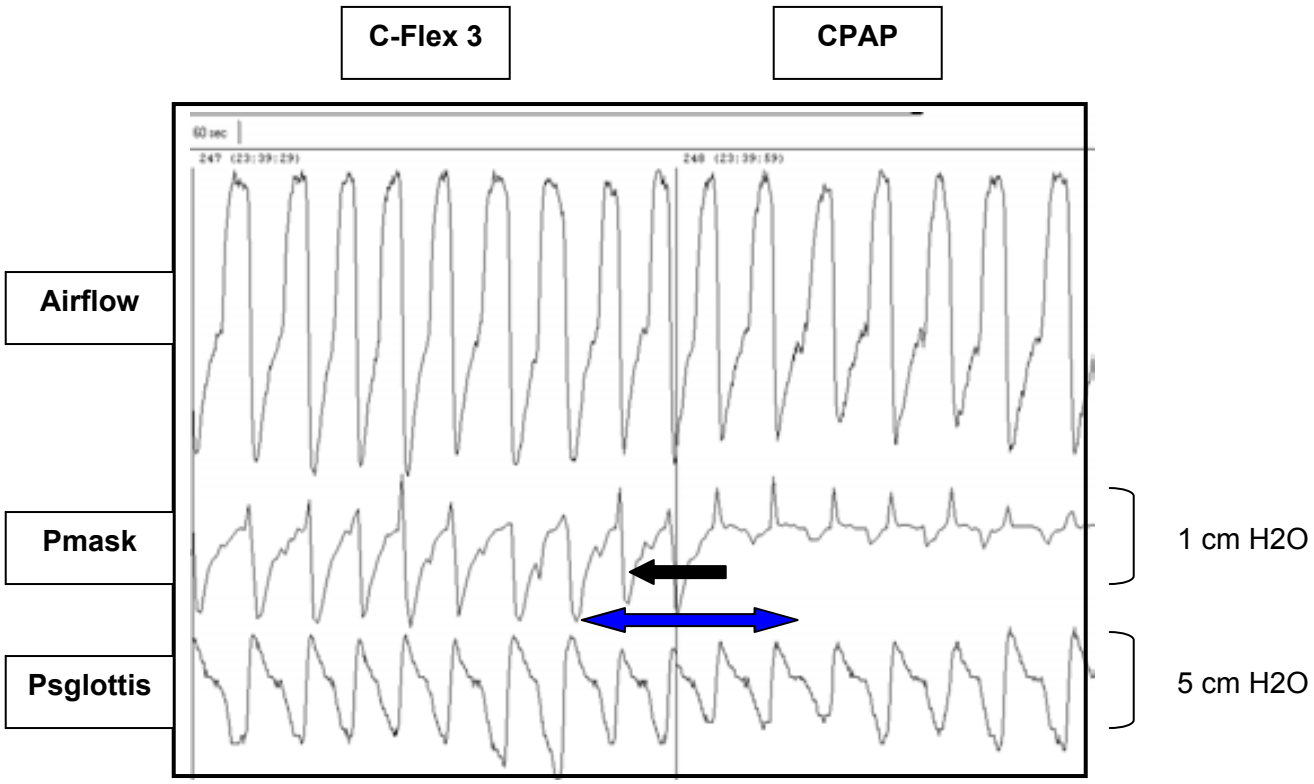


Figure 18 - The black arrow shows the reduction of mask pressure during expiration with the application of C-Flex 3. Blue arrow shows a similar expiratory peak of supraglottic pressure with and without C-Flex (visual analysis).

Swings in the expiratory mask pressure in the patients during CPAP were near 0 (Pm = +0.09 ± 0.08 cm H_2O) and, as expected, swings in the supraglottic expiratory pressure did occur (Ps = +1.87 ± 1.30 cm H_2O). During C-Flex 3, all patients developed expiratory mask pressure dips (Pm = -1.13 ± 0.48 cm H_2O), and the drop of Pm was

progressive as C-Flex went from setting 1 to setting 3 (Figure 19A). Concurrently, expiratory supraglottic pressure swings (Ps) were +1.75 ± 1.19 cm H_2O (Figure 19B). Thus, unexpectedly, there was no significant reduction in supraglottic expiratory pressure swings during C-Flex, compared with the swings present in Ps during CPAP alone (p = 0.46).

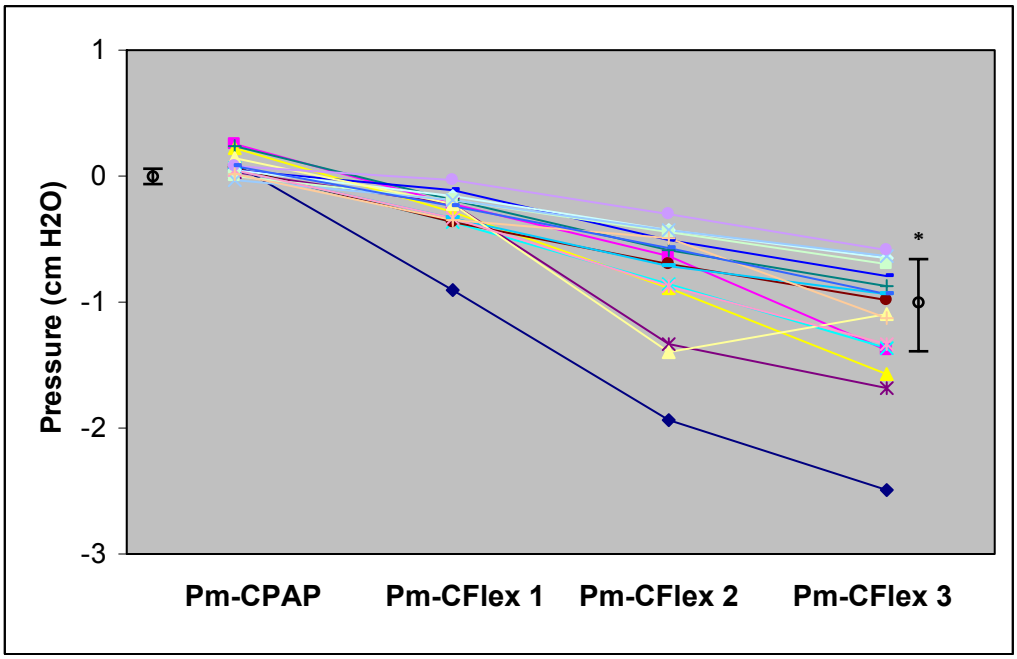


Figure 19A - Patients with obstructive sleep apnea-hypopnea syndrome—the effect of C-Flex compared with continuous positive airway pressure (CPAP) on mask pressure swings (Pm). Each line represents a patient (n = 17) with lines connecting the magnitude of the expiratory pressure swing within the mask when the patient was using CPAP to the expiratory pressure swing within the mask when the patient was using C-Flex 3. All patients developed expiratory dips, and the Pm showed progressive reduction on C-Flex 1, C-Flex 2, and C-Flex 3 compared with CPAP. The mean ± SD values of the CPAP and C-Flex 3 are shown, and the * indicates a significant difference in the mean (p < 0.0001).

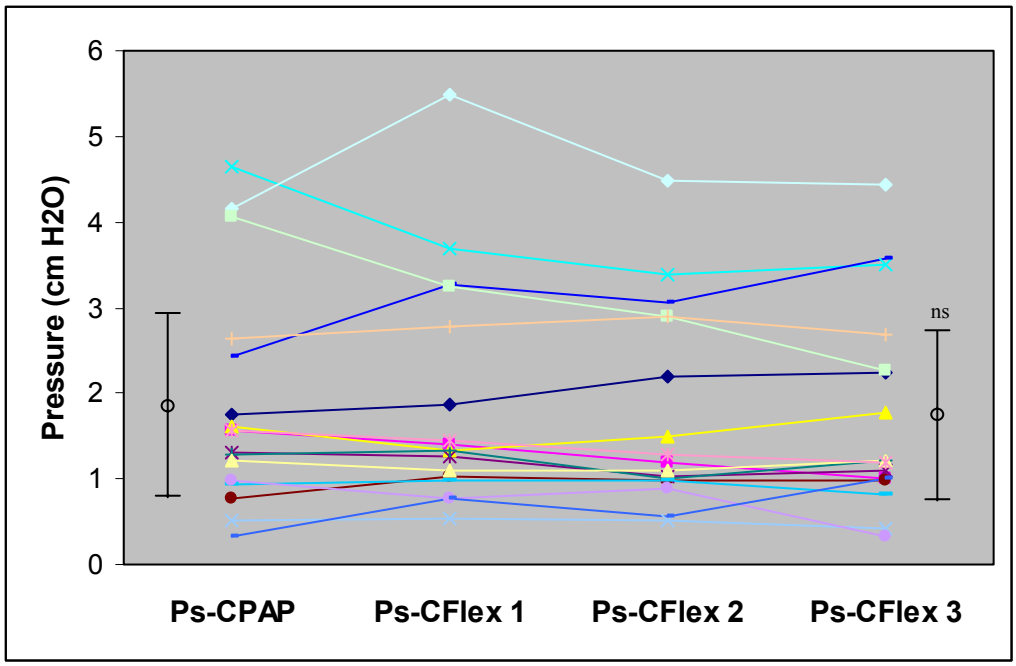


Figure 19B - Patients with obstructive sleep apnea-hypopnea syndrome—the effect of C-Flex compared with continuous positive airway pressure (CPAP) on supraglottic pressure swings (Ps). Each line represents a patient (n = 17) with lines connecting the magnitude of the expiratory pressure swing in the supraglottis when the patient was using CPAP to the expiratory pressure swing in the supraglottis when the patient was using C-Flex 3. Patients did not show a reduction in expiratory supraglottic pressure swings (Ps) with the application of various levels of C-Flex. The mean ± SD value of the CPAP and C-Flex 3 are shown, and ns indicates no significant difference in the means.

Figure 20A shows the effect of C-Flex compared with CPAP on Pm in the individual patients. The transmission of the expiratory mask pressure swings to the supraglottis did not occur in 15 of the 17 patients (eg ΔPm was -1.23 ± 0.53 cm H_2O and ΔPs was -0.06 ± 0.47 cm H_2O, p = 0.000, see figure 20B). This behavior was in contrast to the expectation that C-Flex would reduce or abolish changes in expiratory supraglottic pressures.

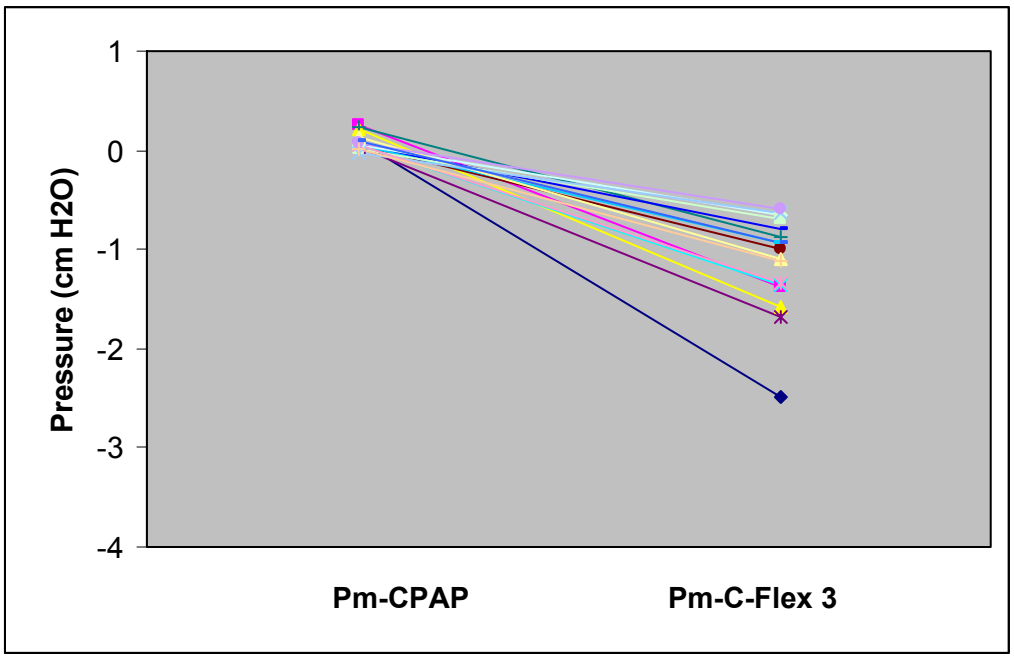


Figure 20A - Patients with obstructive sleep apnea-hypopnea syndrome—the effect of C-Flex compared with the effect of continuous positive airway pressure (CPAP) on mask pressure swings (Pm). Each line represents a patient (n = 17) with lines connecting the magnitude of expiratory pressure swing within the mask when the patient was using CPAP to the expiratory pressure swing within the mask when the patient was using C-Flex 3. All patients developed expiratory dips, and Pm showed reduction when patients were using C-Flex 3, compared with CPAP.

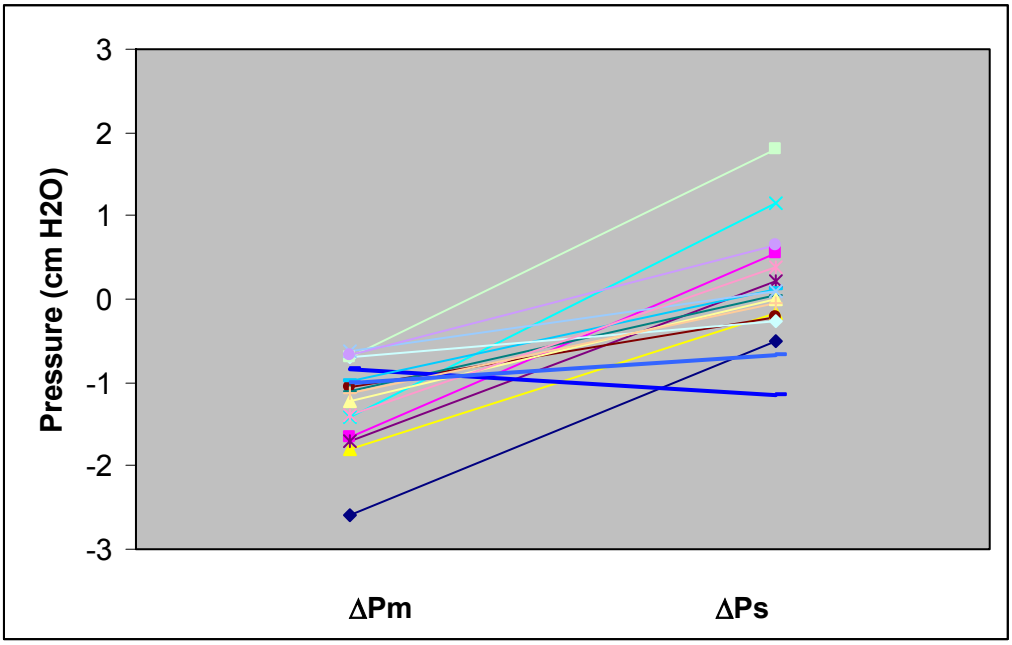


Figure 20B - Patients with obstructive sleep apnea-hypopnea syndrome—the change in expiratory pressure swings with C-Flex 3. Each line represents a patient with lines connecting the change of expiratory mask pressure (Pm) between continuous positive airway pressure and C-Flex 3 and the change in expiratory supraglottic pressure (Ps). There was no transmission of the mask pressure swings to the supraglottis in 15 of the 17 patients (eg, change in Pm [ΔPm] was more negative than change in Ps [ΔPs]). The 2 thick lines represent the 2 patients with a parallel drop in ΔPm and ΔPs.

When patients were using CPAP during sleep, no differences occurred between the mean inspiratory and mean expiratory instantaneous UA resistance (0.12 ± 0.08 cm $H_2O \cdot L^{-1} \cdot min^{-1}$ vs 0.10 ± 0.09 cm $H_2O \cdot L^{-1} \cdot min^{-1}$, p = 0.11). Table 6 examines the role of expiratory UA (upstream) resistance on our findings by separating our patients whose expiratory UA resistance was less than (n = 12) and greater than (n = 5) 0.1 cm $H_2O \cdot L^{-}$

$^{1}\cdot min^{-1}$, in accord with what has been shown in the literature on nasal resistance.[284-286] Patients with low UA resistance during CPAP use (constant mask pressure) showed expiratory pressure swings at the supraglottis (Ps) of +1.15 ± 0.45 cm H_2O. As expected, Ps was significantly greater (p = 0.001) in patients with high levels of UA resistance (+3.59 ± 0.99 cm H_2O). On C-Flex 3, there were no discernable differences between groups for ∆Pm and ∆Ps.

Table 6 - Expiratory mask and supraglottic pressure swings and effect of C-Flex compared to CPAP in SAHS patients

SAHS Patients	**Low UA resistance** (n=12) (<0.1 cm H_2O/L/min)		**High UA resistance** (n=5) (>0.1 cm H_2O/L/min)	
	CPAP	**C-Flex 3**	**CPAP**	**C-Flex 3**
Pm (cm H_2O)	0.11 ± 0.09	-1.21 ± 0.53	0.03 ± 0.02	-0.93 ± 0.31
Ps (cm H_2O)	+1.15 ± 0.45	+1.11 ± 0.52	+3.59 ± 0.99	+3.29 ± 0.84
∆Pm (cm H_2O)	-1.32 ± 0.55		-0.96 ± 0.31	
∆Ps (cm H_2O)	-0.04 ± 0.39		-0.29 ± 1.18	

Pm: Expiratory pressure swing in the mask

Ps: Expiratory pressure swing in the supraglottis

∆Pm: Change in mask pressure swings (C-Flex 3 minus CPAP)

∆Ps: Change in supraglottic pressure swings (C-Flex 3 minus CPAP)

Values are means ± standard deviation

6.2.1.2 Mechanical model of the upper airway

To examine this unexpected lack of change in supraglottic pressure—despite a drop in expiratory pressure at the mask—we used a mechanical model in which the pattern of airflow could be controlled.

6.2.1.2.1 Mechanical model with sinusoidal respiratory pattern

Figure 21 shows raw-tracing data of airflow, mask pressure, and supraglottic pressure from the mechanical model of the UA with a pure sinusoidal respiratory pattern generated using a mechanical pump.

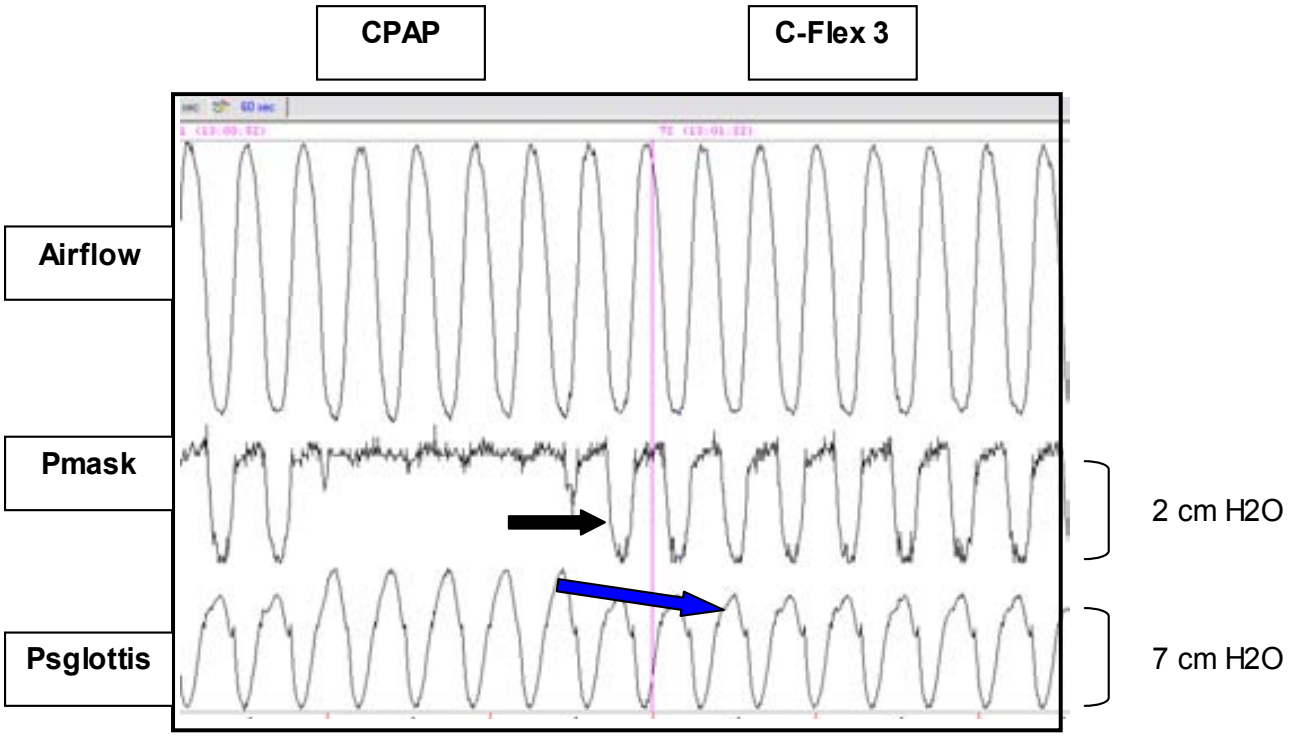


Figure 21 - The black arrow shows the reduction of mask pressure during expiration with the application of C-Flex 3. Blue arrow shows a lower (visual analysis) expiratory peak of supraglottic pressure with the application of C-Flex 3 compared to CPAP.

When we implemented our mechanical model of the upper airway with a sinusoidal respiratory pattern and a low simulated UA resistance during CPAP (constant mask pressure), expiratory pressure swings at the simulated supraglottis (Ps) were +1.94 ± 1.47 cm H_2O. As expected, with a high simulated UA resistance, Ps increased to +4.40 ± 3.03 cm H_2O.

During the highest level of C-Flex (C-Flex 3), mask pressure developed expiratory dips and Pm was -1.45 ± 0.74 cm H_2O on low simulated UA resistance and -1.57 ± 0.66 cm H_2O on high simulated UA resistance. Concurrently, expiratory Ps was +0.51 ± 1.11 cm H_2O on low simulated UA resistance and +2.87 ± 2.41 cm H_2O on high simulated UA resistance.

Table 7 shows the effect of C-Flex compared with CPAP on Pm and Ps in our mechanical-model data. The data across a range of imposed tidal volumes and frequencies are grouped according to whether there was a low or high simulated upstream "UA" resistance. The change in Ps (ΔPs) when going from CPAP to C-Flex 3 was similar to the change in Pm (ΔPm) (eg, there was no statistically significant difference in the magnitude of the swings between Ps and Pm). Furthermore, in the model, expiratory pressure swings were transmitted similarly from mask to supraglottis for all patterns of breathing and for low and high UA resistance.

Table 7 - Effect of C-Flex compared with CPAP on mask and supraglottic expiratory pressure swings in the mechanical model with sinusoidal breathing

Upper Airway Model	**Change** (C-Flex 3 minus CPAP)	
Sinusoidal respiratory pattern	**ΔPm** (cm H_2O)	**ΔPs** (cm H_2O)
Low upper airway resistance *(0.028 ± 0.018 cm H_2O/L/min)*		
RR 10 bpm, TV 450 ml	-0.80	-0.81
RR 16 bpm, TV 450 ml	-1.34	-1.25
RR 24 bpm, TV 450 ml	-1.26	-1.37
RR 12 bpm, TV 800 ml	-1.25	-1.44
RR 24 bpm, TV 800 ml	-2.5	-2.25
Total group	-1.43 ± 0.64	-1.42 ± 0.52
High upper airway resistance *(0.059 ± 0.022 cm H_2O/L/min)*		
RR 12 bpm, TV 450 ml	-0.89	-0.80
RR 16 bpm, TV 450 ml	-1.22	-1.02
RR 24 bpm, TV 450 ml	-1.35	-1.60
RR 12 bpm, TV 800 ml	-1.95	-2.04
RR 24 bpm, TV 800 ml	-2.13	-2.29
Total group	-1.51 ± 0.52	-1.55 ± 0.64

RR: Respiratory rate TV: Tidal volume Bpm: Breath per minute

ΔPm: Change in mask pressure swings (C-Flex 3 minus CPAP)

ΔPs: Change in supraglottic pressure swings (C-Flex 3 minus CPAP)

Values for total group are means ± standard deviation.

6.2.1.2.2 Mechanical model with exponential respiratory pattern

Figure 22 shows raw-tracing data of airflow, mask pressure, and supraglottic pressure from the mechanical model of the UA when a healthy volunteer, breathing through the system, produced a nonsinusoidal (normal) respiratory pattern with a rapid peak in expiratory airflow followed by an exponential decay of flow. In this situation, low simulated UA resistance during CPAP (constant mask pressure) produced expiratory pressure swings at the supraglottis (Ps) of +4.09 ± 2.74 cm H_2O. Again, as expected, high simulated UA resistance increased Ps to +6.61 ± 4.86 cm H_2O.

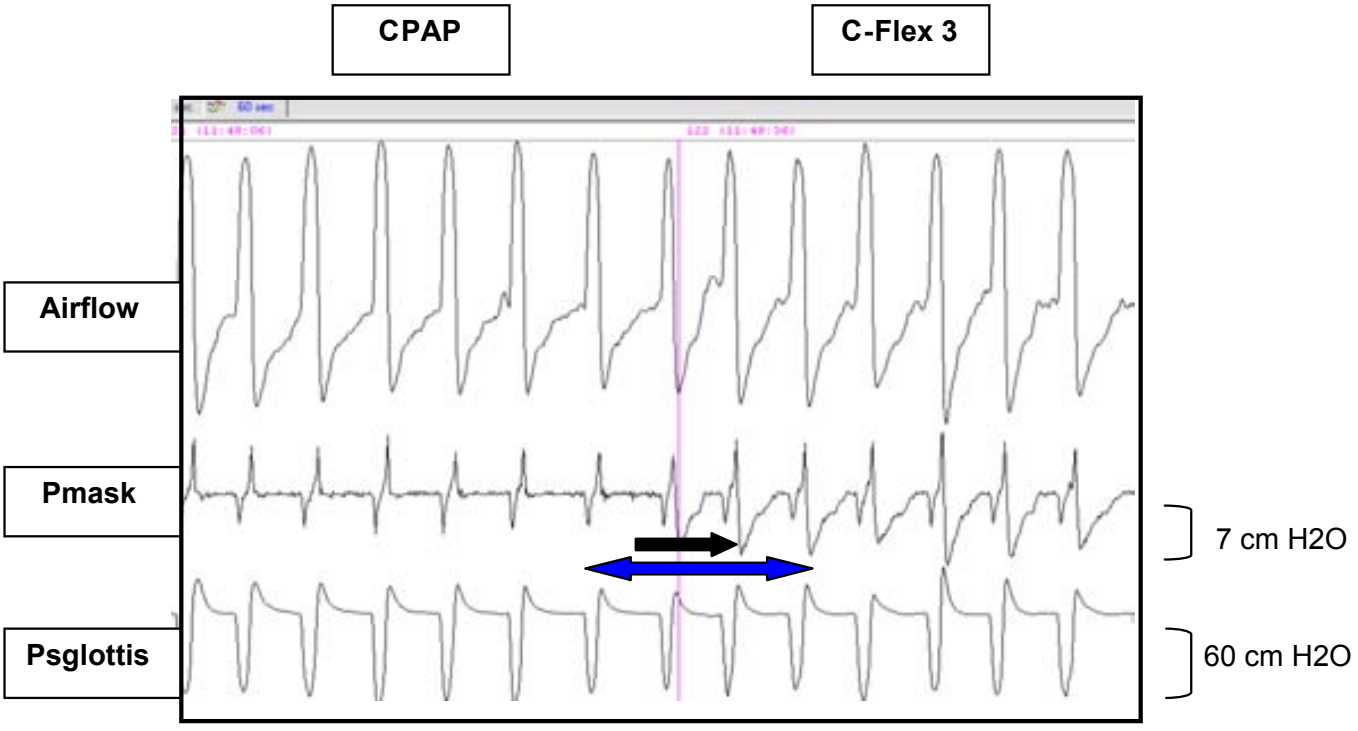


Figure 22 - The black arrow shows the reduction of mask pressure during expiration with the application of C-Flex 3. Blue arrow shows a similar (visual analysis) expiratory peak of supraglottic pressure with the application of C-Flex 3 compared to CPAP.

During the highest level of C-Flex (C-Flex 3), mask pressure developed expiratory dips and Pm was -2.61 ± 0.62 cm H2O on low simulated UA resistance and -2.35 ± 0.70 cm H_2O on high simulated UA resistance. Concurrently, expiratory supraglottic pressure swings (Ps) were +3.30 ± 2.01 cm H_2O on low simulated UA resistance and +6.42 ± 4.60 cm H_2O on high simulated UA resistance.

Table 8 shows the effect of C-Flex compared with CPAP on mask and supraglottic pressure swings in the model data. The data across a range of imposed tidal volumes and frequencies are grouped according to whether there was a low or high simulated upstream "UA" resistance. In contrast with the findings during sinusoidal breathing, ΔPs was lower than the ΔPm ($p = 0.024$ for low simulated UA resistance and $p = 0.003$ for high simulated UA resistance). The lack of transmission of pressure swings from mask to supraglottis was most evident during the simulated high UA resistance.

Table 8 - Effect of C-Flex compared to CPAP on mask and supraglottic expiratory pressure swings in the mechanical model with exponential breathing

Upper Airway Model	**Change** (C-Flex 3 minus CPAP)	
Exponential respiratory pattern	**ΔPm** (cm H_2O)	**ΔPs** (cm H_2O)
Low upper airway resistance *(0.040 ± 0.014 cm H_2O/L/min)*		
RR 14 bpm, TV~500 ml	-2.45	-0.37
RR 28 bpm, TV~500 ml	-2.21	-0.38
RR 16 bpm, TV~(2x baseline) ml	-2.80	-1.63
Total group	-2.48 ± 0.3	-0.79 ± 0.72
High upper airway resistance *(0.075 ± 0.004 cm H_2O/L/min)*		
RR 16 bpm, TV~500 ml	-1.69	0
RR 26 bpm, TV~500 ml	-2.11	-0.09
RR 16 bpm, TV~(2x baseline) ml	-2.34	-0.47
Total group	-2.05 ± 0.33	-0.19 ± 0.25

RR: Respiratory rate TV: Tidal volume Bpm: Breath per minute

ΔPm: Change in mask pressure swings (C-Flex 3 minus CPAP)

ΔPs: Change in supraglottic pressure swings (C-Flex 3 minus CPAP)

Values for total group are means ± standard deviation

Figure 23 combines the data in Tables 7 and 8 to contrast the effect of sinusoidal (23A) and "normal" nonsinusoidal (23B) breathing patterns on ΔPm and ΔPs in the model. Whereas there is a consistent transmission of mask pressure swings to the supraglottis in sinusoidal breathing patterns, mask pressure swings were NOT transmitted to the supraglottis during "normal" nonsinusoidal breathing (eg, ΔPm was significantly more negative than ΔPs [p = 0.024 for low simulated UA resistance and p = 0.003 for high simulated UA resistance]).

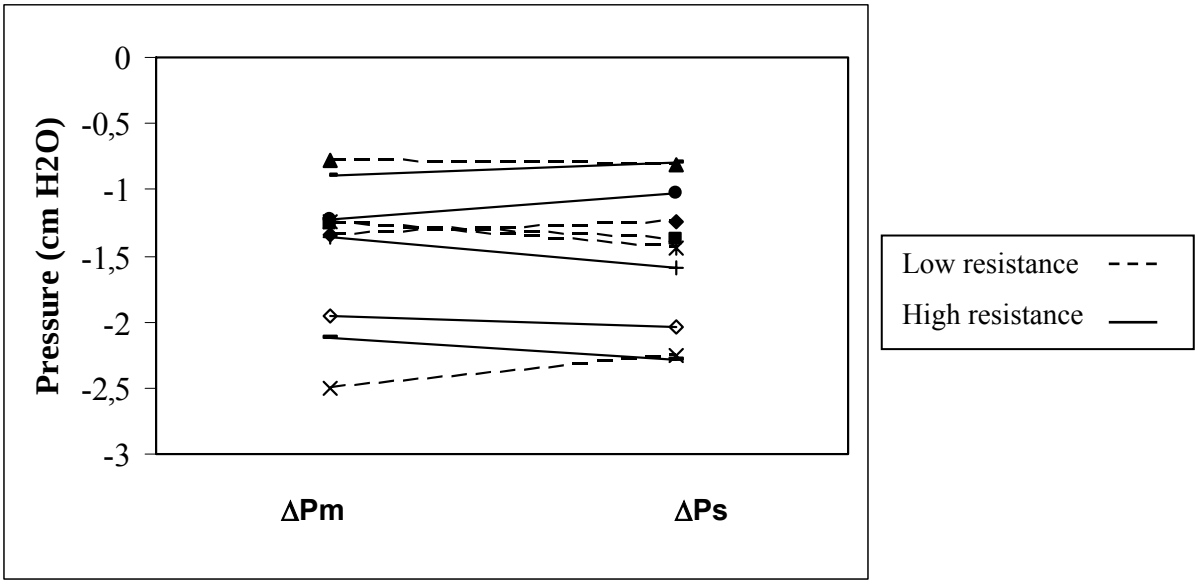


Figure 23A - Upper airway model with sinusoidal respiratory pattern.—change in expiratory pressure swings with C-Flex 3. Each line represents a different tidal volume or frequency. Dashed lines are simulations with low upper airway resistance, and the solid lines are simulations with high upper airway resistance connecting the change of expiratory expiratory mask pressure between continuous positive airway pressure and C-Flex 3 and the change of expiratory supraglottic pressure. There is a consistent transmission of expiratory mask pressure swings to the supraglottis (eg ΔPm is similar to ΔPs).

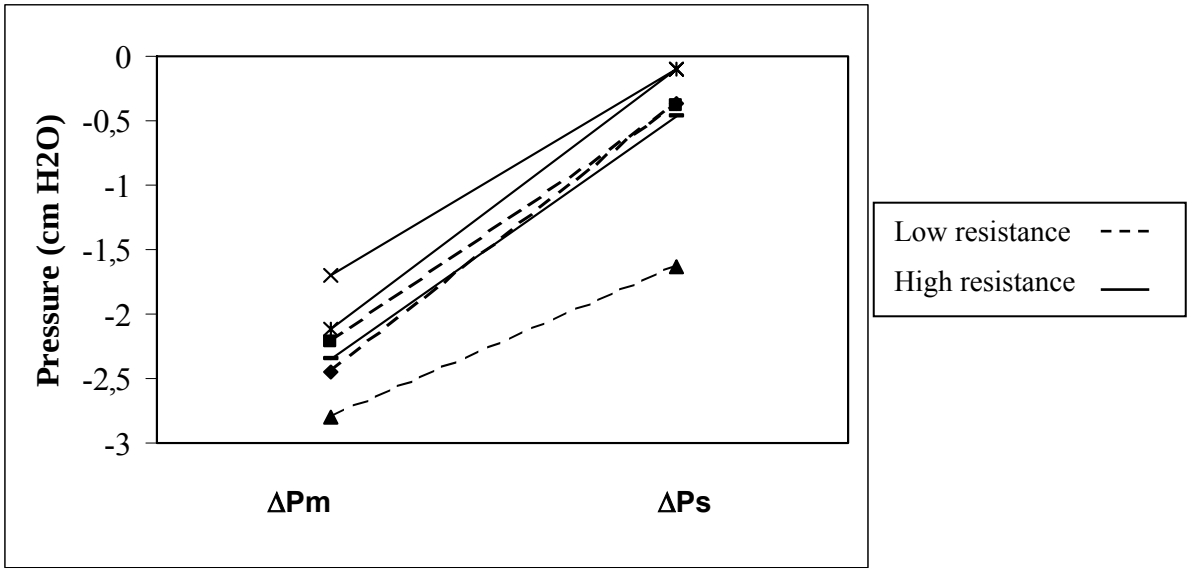


Figure 23B - Upper airway model with "normal" (exponential expiration) respiratory pattern.—change in expiratory pressure swings with C-Flex 3. Each line represents a different tidal volume or frequency. Dashed lines are simulations with low upper airway resistance, and the solid lines are simulations with high upper airway resistance connecting the change of expiratory expiratory mask pressure between continuous positive airway pressure and C-Flex 3 and the change of expiratory supraglottic pressure. Expiratory mask pressure swings were not transmitted to the supraglottis (eg ΔPm was significantly more negative than ΔPs).

6.2.1.3 Analysis of Expiratory Pressure-Time Curve

In addition to the analysis of the effect of C-Flex on expiratory peak pressures at the supraglottis, we also integrated the pressure-time curve as an estimate of expiratory work in patient and model data. This area measurement was used to re-evaluate the effectiveness of application of C-Flex to the UA of patients with SAHS and our UA model (Figures 24 and 25). In Figure 25 for each condition (low and high resistance, sinusoidal

and nonsinusoidal model data and patient data) the percentage change from CPAP to C-Flex 3 is shown for supraglottic expiratory pressure swings and expiratory area. We defined a change of 100% from the CPAP to C-Flex 3 value as complete reversal of the expiratory pressure swing in the supraglottis. In the UA model when UA resistance was low, application of C-Flex 3 produced complete reversal of expiratory Ps with sinusoidal breathing but produced a partial reversal with “normal” breath shape. Patients with SAHS behaved similarly to the model data with “normal” breath and did not show much reversal of the expiratory pattern for Ps or Ws. When UA resistance was high, application of C-Flex 3 produced incomplete reversal of expiratory Ps and Ws in all cases for the model and patients. Thus, application of C-Flex reduced the integrated expiratory pressure in the supraglottis but not the peak (Figure 24). This indicates that mask pressure is transmitted to the supraglottis but the transmission is not fast enough to reduce peak Ps. However, it does reduce the integrated pressure and may reduce expiratory work.

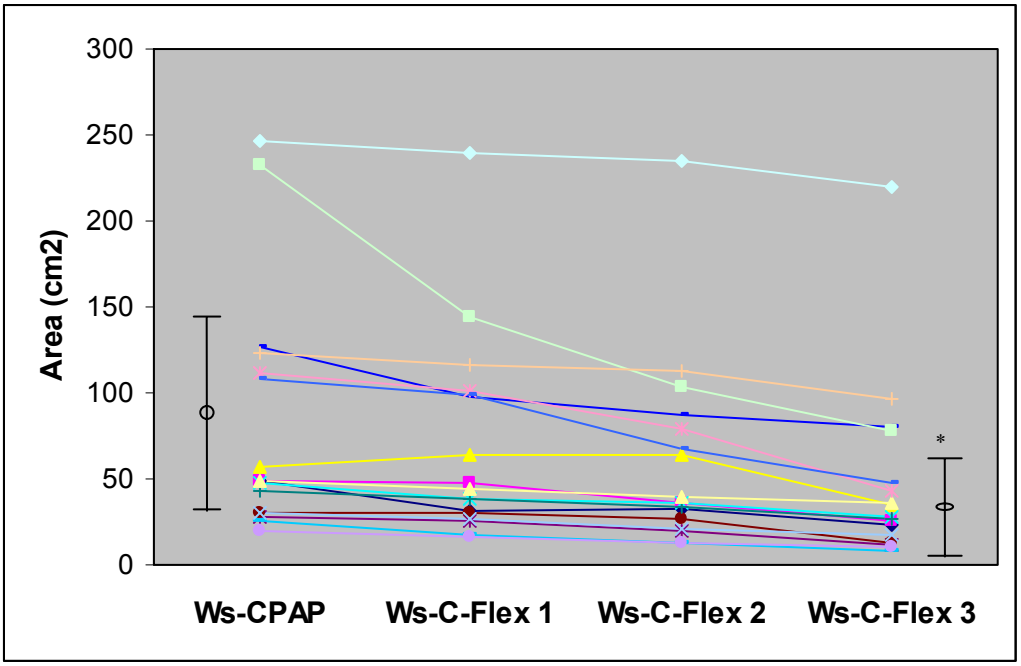


Figure 24 - Patients with obstructive sleep apnea-hypoponea syndrome—the effect of C-Flex compared with continuous positive airway pressure (CPAP) on the estimated expiratory work (Ws). Patients showed a variable reduction of the integrated expiratory pressure in the supraglottis with C-Flex. This reduction may be most evident when comparing CPAP with the highest level of C-Flex 3. The mean ± SD value of the CPAP and C-Flex 3 are shown, and the * indicates a significant difference in the mean ($p < 0.0001$).

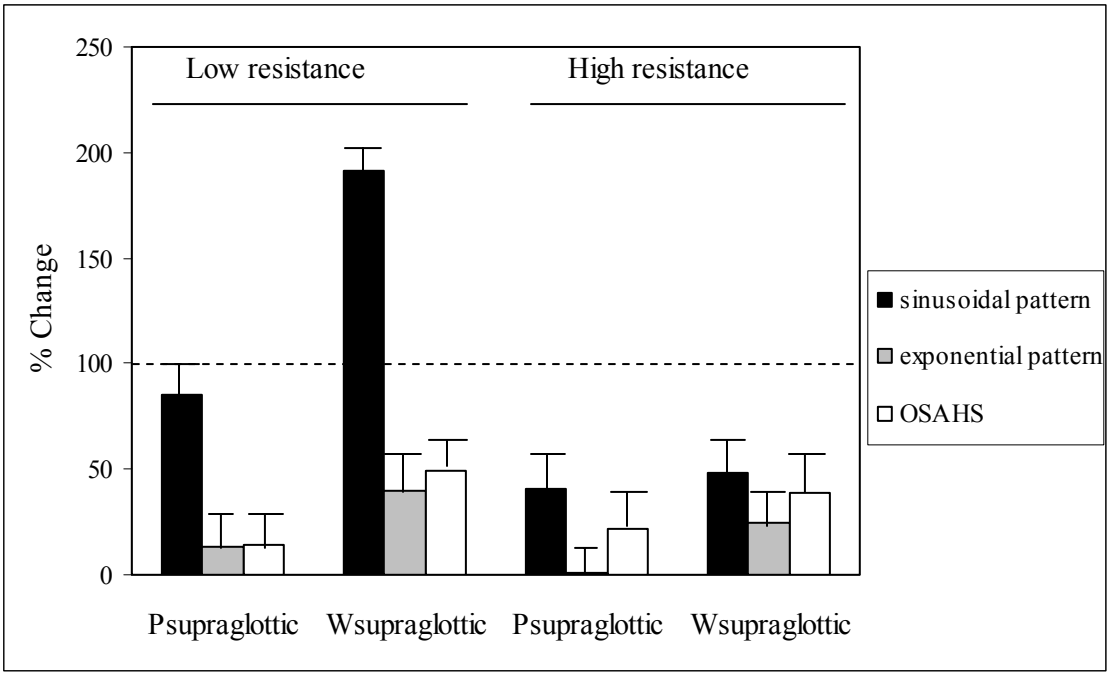


Figure 25 - The effectiveness of application of C-Flex to the upper airway model and to patients with obstructive sleep apnea-hypopnea syndrome. The Y axis shows the percentage change from continuous positive airway pressure to C-Flex 3 values for peak expiratory supraglottic pressure and the estimated expiratory work (Ws) for conditions with low and high resistance. The black bars show data from simulations done using a sinusoidal respiratory pattern. The grey bars show data in simulations done using an exponential respiratory pattern. The white bars show data in patients with obstructive sleep apnea-hypopnea syndrome. On the left are shown data collected in situations of low resistance, and, on the right, with high resistance. The dashed line (100% change) represents complete reversal of the expiratory pressure swing in the supraglottis, defined by a change of 100% from the continuous positive airway pressure to C-Flex 3 value and is the desired result of applying C-Flex.

7. DISCUSSION

7.1 STUDY 1-Awake measures of nasal resistance and upper airway resistance on CPAP during sleep. J Clin Sleep Med 2011.

The data of this research show that measures of nasal resistance made in the sitting position while subjects were awake (AR and RM) had little or no correlation to each other. An exception was the significant, if weak, relationship between AR and RM measurements of resistance in the supine position. However, this finding was driven largely by one data point. This lack of agreement between nasal resistance measurements in the sitting and supine positions suggests that the two techniques may measure different aspects of nasal physiology. In addition, as others have previously shown, we did not find a clear relationship between severity of SAHS[232,287] and either reported subjective nasal symptoms[288-290] or the measures of awake nasal function (AR and RM).

Upper airway resistance measured during sleep did not show significant relationships to any of the awake measures of nasal resistance (AR or RM).

The effect of position on awake nasal function merit further comment. First, for both AR and RM, repeated measurements (made on two occasions, daytime and nighttime) were consistent within a single patient, suggesting that the values obtained have physiological meaning. In addition, intra-patient changes in the measurements of both AR and RM from sitting to supine were also consistent on repeat testing. Despite this, across patients we did not find consistent changes in AR or RM with change to the supine position. In healthy subjects a consistent increase in nasal resistance and a decrease of CSA has been reported when subjects go from sitting to supine position.[245,291,246] However, similar to our data, studies in patients with SAHS[248,250,292] report variable changes in nasal resistance and CSA with positional change, suggesting that SAHS patients may respond differently from normal subjects to positional changes. One can speculate that the

increased vascular volume frequently associated with obesity, may have caused nasal mucosal edema that saturated mechanisms for postural changes in resistance. However, our data did not include these measures. Other possible mechanisms that could explain the "atypical" response to change in position in patients with SAHS are altered neurovascular control of the nasal mucosa in supine position, perhaps due to increased sympathetic neurovascular activity with a consequent reduction of the influx of blood through the vessels or to increased levels of inflammatory activity that could affect the nose via circulating adrenalin and noradrenalin or inflammatory cytokines, as these have been reported in SAHS.[293-295]

The purpose of the present study was to obtain a daytime/wake noninvasive measurement predictive of nighttime/ sleep physiology that might have implications for patients with SAHS on CPAP. High upstream (nasal) resistance in the Starling resistor model of the upper airway implies that increased UA resistance increases the collapsing force at the (downstream) collapsible segment, but this is not relevant to the condition of sleep on optimum nasal *CPAP* (titrated to prevent collapse). Thus, on CPAP, behavior of the upper airway should be similar to the awake condition, where there is rigidity of the upper airway at the collapsible area. In contrast to the collapsible behavior of the velopharynx during sleep, nasal behavior is most closely approximated by a single rigid constriction (i.e., a non Starling constant resistance) and is not affected by sleep.[124] This conceptualization leads us to predict that high nasal resistance should be perceived by the patient even on CPAP and might contribute to intolerance. Our aim was to identify the best technique to measure the relevant nasal resistance prior to the sleep study (and subsequently to test whether this can be used to anticipate CPAP non-compliance). However, our data do not demonstrate any relationship between awake nasal resistance by AR or RM and upper airway resistance during sleep.

It seems unlikely that the lack of relationship between awake AR and RM with direct measurement of UA resistance during sleep was due to deficiencies in our technique of obtaining AR and RM. We used standard techniques and equipment with multiple measurements, as recommended by standards[272-274] and our data show reproducible measurements within a single position and on separate occasions within each patient.

To examine the relationship between AR and RM, we converted both to a form conceptually related to "resistance." For RM resistance is directly obtained for each measurement and we chose to combine the nostrils as parallel resistors.[274] For AR, the measurement is of cross-sectional area, which did not itself show a statistical relationship to RM in our dataset. To use this as a "resistance" analog, we made the simplest assumption that flow was turbulent and proportional to $1/R^4$ or $1/(\text{cross sectional area})^2$. While this assumption may be simplistic, one would expect at least a monotonic relationship using this approach, and we did not find this to be present.

The lack of correlation between AR and RM we found is similar to what is reported in the literature. AR assesses a local minimal cross sectional area at a specific site, whereas airflow resistance by RM is a dynamic parameter that assesses all the serial components of the nasal cavity.[296-298]

There are several limitations in this study. First, lack of correlations may have been due to the small number of unselected patients. However, we studied patients with a wide range of nasal resistances and SAHS, and this should have maximized our ability to find relationships. A power calculation suggests we can reject the hypothesis of a high correlation (>0.8) between our variables with a power of 80% to 85% and α of 0.025 with the 14 subjects we studied. While a significant lower correlation between our variables could have existed and become evident with a larger sample size, a lower correlation would not have satisfied the primary goal of our study, which was to find a noninvasive

daytime test highly correlated to (and therefore predictive of) the nocturnal directly measured resistance. Second, it can be argued that there was no reason to expect correlations between measurements made during wakefulness and those made during sleep. However, we wished to test this directly as it is generally assumed that sleep does not affect the nose in the same way as it affects the collapsible segment of the nasopharynx responsible for SAHS.[254] In addition, it is difficult to make AR and RM measurements during sleep without disturbing normal sleep. Furthermore, our purpose was to examine potential predictors of nocturnal physiology that could be easily obtained during the daytime.

7.2 STUDY 2-The supraglottic effect of a reduction in expiratory mask pressure during continuous positive airway pressure. Sleep 2012.

Our data show that, when mask pressure is constant during CPAP use, significant pressure swings occur in the supraglottis during expiration. The essential new finding of this study is that imposed expiratory changes in mask pressure produced by C-Flex did not uniformly transmit to the supraglottis in either patients with SAHS on CPAP or in a mechanical model of the upper airway with a fixed resistance. Our model data comparing breaths with a sinusoidal shape to breaths with an exponential expiratory decay (“normal”) of airflow suggest to us that the observed lack of expiratory drop in supraglottic pressure swings is related to dynamics of the C-Flex algorithm that controls mask pressure rather than to intrinsic properties of the upper airway.

In our mechanical model of the UA on CPAP, we found that, during expiration, as expected, high nasal resistance (upstream) produced greater pressure swings in the supraglottis than did low nasal resistance. Only with a sinusoidal respiratory pattern did the expiratory pressure drop in the mask produced by C-Flex successfully mitigate the expiratory rise in pressure seen in the supraglottis, which is the intended purpose we

attribute to C-Flex. In contrast, when tested in our model with breaths having the more physiologically typical exponential respiratory pattern, application of C-Flex caused little reduction of supraglottic pressure swings during expiration, despite a similar drop of mask pressure. Similarly, in the patients with SAHS, application of C-Flex produced a drop in expiratory mask pressure in all patients; however, most patients did not demonstrate the expected fall in supraglottic pressures swings.

One explanation of our primary finding, ie, that the C-Flex algorithm may not work as well with nonsinusoidal patterns of breathing as with pure sinusoidal expiration, may be related to the occurrence of rapid changes in flow during early expiration with an exponential pattern. Inspection of the pressure and flow tracings suggests that a phase delay in the pressure response to expiratory flow was present. Figure 26 shows a typical example from one patient. The drop in mask pressure occurs well after the initiation of the rise of supraglottic pressure during early expiration. This phase lag between flow and mask pressure, and the persistence of supraglottic pressure swings on C-Flex, was seen in all of the patients (mean phase lag 0.31 ± 0.06 sec; range, 0.19-0.42 sec) and also during the exponential expiratory pattern in the model data (mean phase lag 0.28 ± 0.10 sec; range, 0.15-0.41 sec). To further understand this phenomenon, we attempted to find a relationship between the presence of a phase lag between peak expiratory flow and peak mask expiratory pressure drop and respiratory frequency but were not able to do so within the range of respiratory patterns recorded. Thus, we cannot say with certainty whether the failure of C-Flex to abolish the expiratory supraglottic pressure swings was due to only a rapid change in expiratory flow or to some other aspect of nonsinusoidal breathing.

An alternate explanation of our findings of a lack of change in expiratory supraglottic pressure despite a drop in mask pressure during C-Flex in the patients with SAHS is that there was unexplained development of expiratory flow limitation in the upper airway that occurred only in association with C-Flex. We are aware of no neural or

mechanical reason for such a behavior of the relatively rigid nasal airway on CPAP. Specifically, the behavior of the UA while the patient is on CPAP should be relatively invariant because the collapsible segment of the UA that is usually responsible for changes in airway resistance during sleep is being "splinted" throughout the respiratory cycle above optimal CPAP.

Although C-Flex did not show much effect on peak expiratory supraglottic pressure swings, we did record some reduction in the Ws, (our estimate of expiratory work). However, we achieved only a partial reversal of the "expiratory phenomenon" with the maximum available settings of C-Flex. We have no way of assessing whether comfort, or the perception of discomfort by a patient during expiration, is affected more by mitigating the peak pressure or by mitigating work of exhalation; this may need to be tested directly.

One limitation of our study is that we did not recruit patients based on nasal resistance and, thus, did not have a large number of patients with high nasal resistance. We could have attempted to increase the number of patients in this study who had high nasal resistance by recruiting based on awake subjects' complaints of nasal symptoms or on the results of testing obtained during wake (such as with rhinomanometry or acoustic rhinometry) that showed a high nasal resistance. However, we have previously shown that awake noninvasive measures of nasal resistance are not predictive of nasal resistance asleep. Furthermore, despite a limited range in nasal resistances in the present data, we did show in the present dataset that, *on CPAP*, patients with high UA resistance had greater supraglottic pressure swings than did patients with low resistance.

A second possible limitation is that we did not specifically select patients who had reported intolerance to CPAP, and, in this study, we did not assess level of comfort. Thus, we cannot relate increased expiratory supraglottic pressure swings (or work) to perceived comfort on CPAP or an effect of C-Flex on reported comfort. However, this was not the objective of the present study. Furthermore, our patients were being studied during a first

exposure to CPAP, during which they had multiple interventions (CPAP titration, trial with different settings of C-Flex), and these circumstances would have made collecting patients' acute impressions of comfort difficult to interpret.

An additional criticism is that we did not obtain a subjective patient report of CPAP "comfort." However this was not the purpose of the present study, as we felt that the first night of CPAP titration was not the optimal time to assess comfort (as it was the patient's first exposure to CPAP).

A final caveat exists in interpreting the results of these data: by design, we studied the effect of C-Flex-induced pressure drops at the mask on supraglottic pressure in patients only *during sleep;* "comfort" may be partially or wholly affected by the conditions *during wake*. The analysis reported here is based on measurements made during stage N2 sleep; in our current data set, we did not record much data when subjects were breathing in the wake state. In the limited wake periods available for analysis, we saw no trends toward a greater transmission of mask to supraglottic pressure swings while patients were on C-Flex.

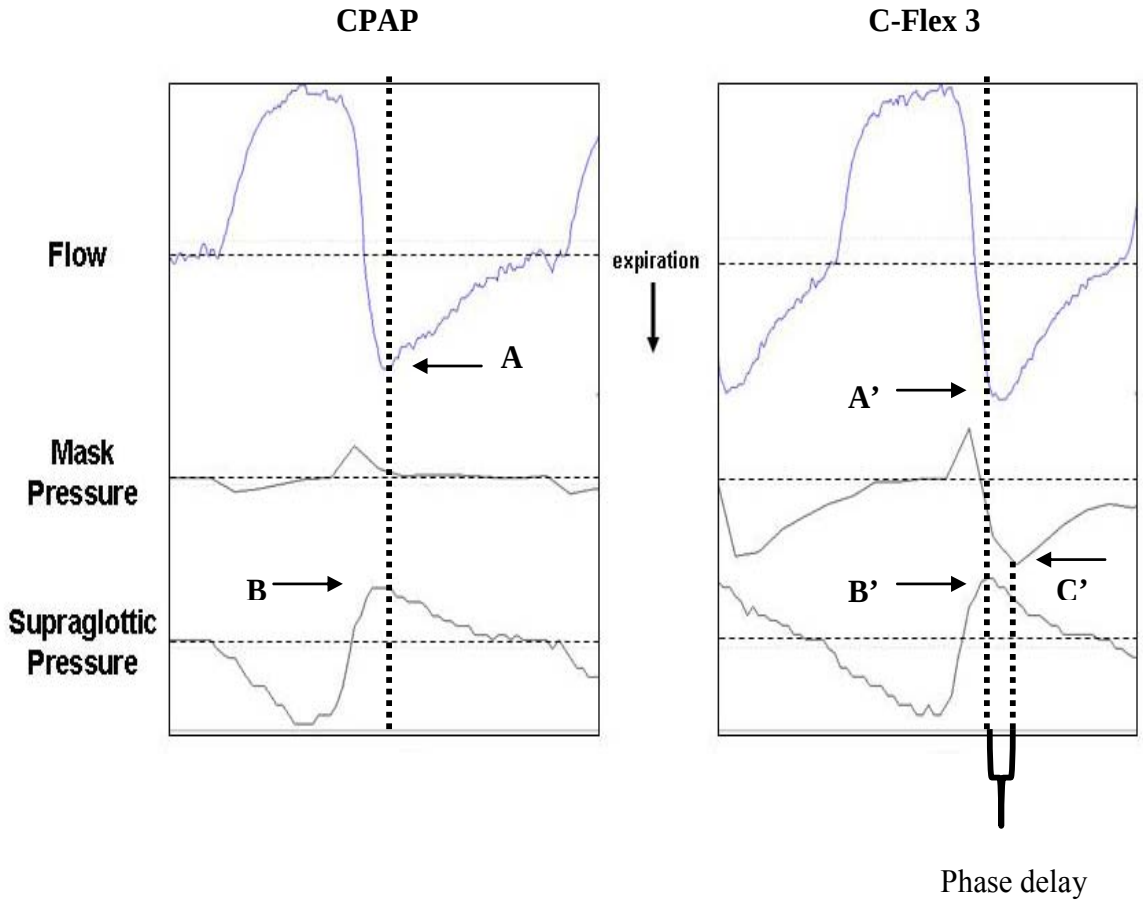


Figure 26 - Phase delay in pressure response to expiratory airflow. Representative tracing of 1 breath obtained in 1 patient of airflow, mask pressure, and supraglottic pressure. A and A' indicate timing of expiratory peak flow on continuous positive airway pressure, and C-Flex, B, and B' indicate the peak of expiratory supraglotic pressure. C indicates the timing of peak drop in mask pressure on C-Flex. The phase delay is indicated.

8. CONCLUSIONS

8.1 STUDY 1-Awake measures of nasal resistance and upper airway resistance on CPAP during sleep. J Clin Sleep Med 2011.

While acoustic rhinometry and rhinomanometry as often obtained (sitting) were not consistently related to each other they, were correlated in the *supine* position. However neither of these *awake* measurements of nasal resistance was predictive of upper airway resistance during *sleep* on CPAP, suggesting that differences in upper airway pathophysiology in patients with SAHS may affect awake and sleep nasal resistances in complex ways.

8.2 STUDY 2-The supraglottic effect of a reduction in expiratory mask pressure during continuous positive airway pressure. Sleep 2012.

We were not able to show that C-Flex reduces expiratory pressure swings in the supraglottis in patients with SAHS on CPAP during sleep. Although C-Flex did succeed in reducing “supraglottic” pressure swings in our modeling studies using sinusoidal breathing, the magnitude of C-Flex mask-pressure reductions was not sufficient to eliminate expiratory supraglottic pressure swings at *any* setting for other patterns. These nonsinusoidal model data are similar to the data in patients. Our observations suggest that maximum potential physiologic impact of C-Flex on supraglottic pressure may not have been achieved by the present algorithm, and this may account for the recent data showing little effect of C-Flex use on overall CPAP compliance. Because there was surprisingly little physiologic expiratory effect at the supraglottis of C-Flex during sleep with the present implementation of expiratory pressure modification by C-Flex, it is not possible to test the hypothesis that optimal mitigation of supraglottis expiratory pressure swings will improve

patient comfort and compliance. However, if C-Flex does improve comfort, it is unlikely to do so by the mechanism of reducing the peak expiratory supraglottic pressure.

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10. PUBLICATION STUDY 1

- Masdeu MJ, Seelall V, Patel AV, Ayappa I, Rapoport DM. Awake measures of nasal resistance and upper airway resistance on CPAP during sleep. J Clin Sleep Med 2011;7:31-40.

11. PUBLICATION STUDY 2

- Masdeu MJ, Patel AV, Seelall V, Rapoport DM, Ayappa I. The supraglottic effect of a reduction in expiratory mask pressure during continuous positive airway pressure. Sleep 2012;35(2):263-272.

NEW RESEARCH

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SCIENTIFIC INVESTIGATIONS

Awake Measures of Nasal Resistance and Upper Airway Resistance on CPAP during Sleep

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Study Objectives: Since on CPAP, the nose is the primary determinant of upper airway resistance, we assess utility of noninvasive measures of nasal resistance during wakefulness as a predictor of directly assessed upper airway resistance on CPAP during sleep in patients with obstructive sleep apnea/hypopnea syndrome.

Methods: Patients with complaints of snoring and excessive daytime sleepiness were recruited. 14 subjects underwent daytime evaluations including clinical assessment, subjective questionnaires to assess nasal symptoms and evaluation of nasal resistance with acoustic rhinometry (AR) and active anterior rhinomanometry (RM) in the sitting and supine positions. Patients underwent nocturnal polysomnography on optimal CPAP with measurements of supraglottic pressure to evaluate upper airway resistance. Comparisons were made between nasal resistance using AR and RM during wakefulness, and between AR and RM awake and upper airway resistance during sleep.

Results: Our study shows that measures of awake nasal resistance using AR and RM had little or no correlation to each other in the sitting position, whereas there was significant but weak correlation in the supine position. Upper airway resistance measured while on CPAP during sleep did not show significant relationships to any of the awake measures of nasal resistance (AR or RM).

Conclusion: *Awake* measurements of nasal resistance do not seem to be predictive of upper airway resistance during *sleep* on CPAP.

Keywords: Obstructive sleep apnea/hypopnea syndrome, CPAP, acoustic rhinometry, rhinomanometry, supraglottic catheter, nasal resistance, nasal cross-sectional area, upper airway resistance

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Continuous positive airway pressure (CPAP) is the primary treatment for obstructive sleep apnea/hypopnea syndrome (OSAHS),[1,2] and has been shown to normalize sleep architecture,[3] reduce daytime sleepiness,[4] enhance daytime function,[5,6] reduce automobile accidents,[7] improve hypertension[8,9] and decrease cardiovascular events[10,11] in a dose-related fashion.[12]

Despite the efficacy of CPAP treatment, 29% to 83% of patients use CPAP less than 4 hours per night[13,14] with the most common complaint of patients relating to problems with the mask.[15,16] However, nasal symptoms may account for 30% to 50% of CPAP intolerance[13] and the otolaryngology literature suggests that, unrelated to sleep and to CPAP, a relationship exists between nasal symptoms and an elevated nasal resistance.[17,18] Although some authors attribute only a minor role of nasal symptoms on CPAP compliance,[19,20] "difficulty exhaling" against positive pressure is frequently cited by patients on CPAP, and may be increased by elevated nasal resistance. Data directly addressing the relationship of assessments of nasal resistance measured noninvasively and CPAP use remain inconclusive. Several small studies have suggested that initial rejection of CPAP treatment correlates with measures of increased nasal resistance,[21,22] while others have failed to show any correlation.[23] At least one study shows that reducing nasal resistance by surgery improves CPAP use.[24]

BRIEF SUMMARY

Current Knowledge/Study Rationale: The role of nasal resistance on CPAP use is not completely established. The aim of this study was to identify a technique to measure the relevant nasal resistance during daytime that could predict the upper airway resistance during sleep and subsequently to test whether this could be used as a predictor of CPAP compliance.

Study Impact: Neither of the awake measurements of nasal resistance was predictive of upper airway resistance during sleep on CPAP, suggesting that differences in upper airway pathophysiology in patients with OSAHS may affect awake and sleep nasal resistances in complex ways.

While the expiratory pressure of CPAP may contribute to "difficulty exhaling," it also dilates the velopharynx, reducing the contribution of this area to overall upper airway resistance, leaving the nose and related structures as the predominant determinants of resistance.[25] Unlike the velopharyngeal resistance, nasal resistance has been shown to be unaffected by sleep state,[26,27] and CPAP has been shown to produce only a 15% to 25% drop in nasal resistance.[25,28] There has been no comparison of awake *noninvasive* measures of nasal resistance and total upper airway resistance on CPAP (which, as pointed out above, is assumed to reflect primarily nasal factors).

Two potential noninvasive techniques for measuring awake physiology of the nasal cavity are rhinomanometry (RM), which

directly assesses resistance of the nose,[29] and acoustic rhinometry (AR),[30] which measures cross-sectional area (CSA). It is generally assumed that the minimal cross-sectional area (mCSA) bears a monotonic relationship to the resistance of the upper airway (UA).

Prior to studying the relationship of nasal resistance to CPAP use, in the present study we examine the relationship between awake noninvasive measures of nasal resistance (AR and RM) and directly assessed UA resistance while on CPAP during sleep.

METHODS

Twenty-seven adult patients with complaints of snoring and excessive daytime sleepiness, presenting to the New York University Sleep Disorders Center for evaluation of OSAHS were recruited. All patients underwent nocturnal polysomnography (NPSG) to confirm the diagnosis of OSAHS. A nasal cannula pressure transducer system (Protech PTAF2) was used to measure airflow and an oral thermistor to detect mouth breathing and calculate apnea-hypopnea index 4% (AHI 4%) and respiratory disturbance index (RDI) by American Academy of Sleep Medicine criteria.[31] If CPAP treatment was clinically indicated, the patients were referred for CPAP titration during which supraglottic pressure (SGP) measurements were performed during the NPSG. Patients were excluded if they had a medically unstable condition (i.e., recent myocardial infarction, congestive heart failure) or if they were unable to sleep with CPAP.

All subjects included in the study underwent daytime evaluation including clinical assessment, subjective questionnaires to assess nasal symptoms and evaluation of NR with AR and anterior RM in the sitting and supine positions. Nighttime tests performed were in-laboratory CPAP titration NPSG with measurements of SGP on optimal CPAP.

Clinical Assessment

We recorded demographic and clinical variables: age, gender, body mass index, medical history, physical examination, and menopausal status. Subjective daytime sleepiness was measured using the Epworth Sleepiness Scale.[32]

Subjective Questionnaires of Nasal Symptoms

The assessment of subjective nasal symptoms was made with the nasal obstruction symptom evaluation (NOSE) instrument. The NOSE questionnaire is a validated tool in the subjective assessment of nasal obstruction.[33,34] It consists of 5 assessments of nasal obstruction-related symptoms scored using a 5-point Likert scale (not a problem, very mild problem, moderate problem, fairly bad problem, severe problem). Patients are asked to rate their symptoms as perceived over the past month. Higher scoring on the test implies more severe nasal obstruction.

Acoustic Rhinometry

AR measures nasal CSA at different distances from the nasal inlet using acoustic reflections. It has been validated as reproducible, accurate, and noninvasive method.[35] Three areas of constriction are identified: CSA1 represents the internal nasal valve at the junction of the upper lateral cartilage and septum (relatively constant in a given patients, independent of congestion); CSA2 represents the head of the inferior turbinate; and CSA3 is bounded by the head of the middle turbinate and the anterior portion of the inferior turbinate. CSA2 and CSA3 are highly variable due to erectile mucovascular tissue. Measurements were performed using the RhinoScan instrument (Rhinometrics A/S, Lynge, Denmark) using standard techniques.[29,36,37] This AR device displays the mCSA in 2 sections of the nose, CSA1 with distance range 0-2.20 cm and CSA2 with distance range 2.20-5.40 cm. Before each use the AR device was calibrated using a standardized probe. Sterile surgical lubricant was applied to the nosepiece to create an acoustic seal. The wand was held to each nostril without causing any distortion of the anatomy, and the patient was asked to hold his breath until a stable reading emerged. Three measurements were obtained at each nostril and accepted as normal when they had a coefficient of variation < 2%. We collected daytime data in the sitting position after 30 min of acclimatization to the laboratory environment and in supine position after 15 min of recumbency. Measurements were repeated in a separate session on the night of the CPAP titration NPSG study prior to sleep. From the awake daytime and night measurements, mean CSA1 and CSA2 were calculated for each visit and position by pooling the data from left and right nostrils. Minimal CSA for each patient was defined as the lowest of CSA1 and CSA2. In order to obtain a value proportional to NR, we assumed resistance (NR) was proportional to $1/CSA^2$, where CSA was the minimum of CSA1 and CSA2 for each nostril, and that the 2 resistances acted in parallel during normal breathing $1/\text{total NR} = 1/NR_{left} + 1/NR_{right}$.

Rhinomanometry

Rhinomanometry assesses the nasal airway by simultaneously recording transnasal pressure and airflow during occlusion of one nostril. Measurements were performed using a commercialized rhinomanometer instrument (RhinoStream, Rhinometrics A/S, Lynge, Denmark). We obtained direct measurement of NR by the active anterior technique in accordance with the standard set by the International Committee on Standardization of rhinomanometry.[29] The RM was performed during wakefulness in both sitting and supine positions on 2 occasions, on the day of the recruitment and again at night prior to the CPAP titration NPSG.

For each nostril, flow resistance for inspiration and expiration was separately measured at 75 Pa of pressure using the average of three measurements with a maximum deviation between measurements of 10%. Total NR was calculated separately in inspiration and expiration by combining the parallel NR from the 2 nostrils using the formula: $1/\text{total NR} = 1/NR_{left} + 1/NR_{right}$.

Nocturnal Polysomnography

The diagnostic and CPAP titration NPSGs were performed in the New York University Sleep Disorders Center as per American Academy of Sleep Medicine recommended clinical guidelines.[38] Pressure was directly measured at the CPAP mask using a pressure transducer (Ultima Dual Airflow Pressure Sensor, Braebon 0585, Ontario, Canada). Airflow to the mask was recorded from the output of a Respironics BiPAP Auto M Series device in CPAP mode. CPAP was titrated manually during the first hour of the study to a level that eliminated all sleep disordered breathing events including obstructive apneas, hypopneas, and runs of flow limitation. The optimal pressure was defined as the minimum pressure at which flow limitation dis-

appeared. The minimal therapeutic pressure was confirmed by performing step-down measures dropping the pressure every 2 min by 1 cm H_2O until the appearance of flow limitation; this established the minimum therapeutic pressure.

In addition to standard monitoring, SGP was measured using a pressure transducer-tipped catheter (Millar MPC 500, Millar Instruments, Houston, TX, USA). The nose was anesthetized using atomized lidocaine 5% and lidocaine 2% jelly for the throat. The Millar catheter was introduced transnasally, and the tip of the catheter was placed just below the uvula. The catheter position was confirmed visually through the mouth. The catheter was taped to the nose to secure its position throughout the study. The nasal CPAP mask was then applied and leak at the exit site of the catheter was minimized. The output of the Millar catheter was amplified and recorded at 64 Hz.

To verify that the supraglottic catheter tip was placed just below the collapsible segment of the upper airway, the behavior of difference between the supraglottic and CPAP inspiratory pressures after the patient fell asleep was inspected during a brief "step-down" of CPAP pressure. Correct positioning of the catheter tip required that the delta pressure between the mask and the supraglottic area increases substantially during inspiration simultaneously with the appearance of inspiratory flow limitation. If this increase in delta pressure was not observed as CPAP was reduced, it was assumed the catheter position was too high and the catheter was advanced.

We analyzed 5 min segments of pressures recording obtained during at least 2 separate periods of stable stage N2 sleep in the same position for each patient, during which there was no evidence of any sleep disordered breathing event. Mask pressure (MP) and SGP were averaged over 3 breaths. UA resistance was calculated for each inspiration and expiration using the relevant peak flow and the difference between SGP and MP for that breath, then averaged for the 3 breaths.

Measurements of pressure and resistance were repeated both over short periods (< 10 min) and at longer intervals (> 1 h) to assess the stability of the UA resistance across the night. We assessed reproducibility/stability of the UA resistance measurement in three different situations: short-term sleep (in stage N2 sleep and within 10 min), long-term sleep, and long-term awake (measurements in the same position in stage N2 sleep or wake but ≥ 1 h apart). In each of these situations we compared 3 measurements of UA resistance for inspiration and expiration.

All the subjects signed a consent form approved by the Institutional Review Board at the New York University School of Medicine.

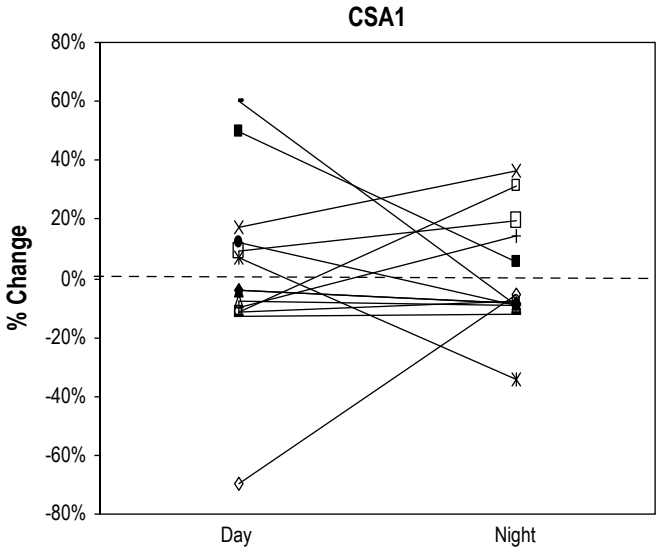
STATISTICS

For each variable, comparisons between positions (sitting versus supine) and between daytime, nighttime wake and sleep were made using paired *t*-test with $p < 0.05$ as significant. Correlations between variables were evaluated using Pearson correlation coefficient with $p < 0.05$ as significant.

RESULTS

Of the 27 subjects recruited, 14 patients (10 male/4 female) completed the study. Five subjects dropped out, 8 were excluded due to insufficient sleep (2), excessive mask leak (2), poor supraglottic catheter signal quality (1) and poor AR and RM signal quality (3). The mean age was 47.8 ± 11.7 years, mean body mass index 35.3 ± 10.4 kg/m^2, mean AHI 62.8 ± 34.4/h, mean RDI 66.6 ± 33.5/h, mean Epworth Sleepiness Scale 12.7 ± 5.6, mean CPAP level 9.8 ± 3.1 cm H_2O. On the NOSE questionnaire, 9 subjects showed no or mild symptoms of nasal obstruction (NOSE scores < 8 of 20) and 5 subjects showed moderate-severe symptoms (NOSE score 11-18). No subject had a NOSE score > 18.

Figure 1A—Positional change of CSA1 from sitting to supine position during wakefulness in both sessions, daytime and nighttime



The Y axis shows the percentage of change of CSA1 from sitting to supine position. Each line represents a subject (n = 14) and the first point of the line shows the change of CSA1 from sitting to supine position during the daytime session. Second point of the line represents the change of CSA1 from sitting to supine position during the nighttime session.

Acoustic Rhinometry

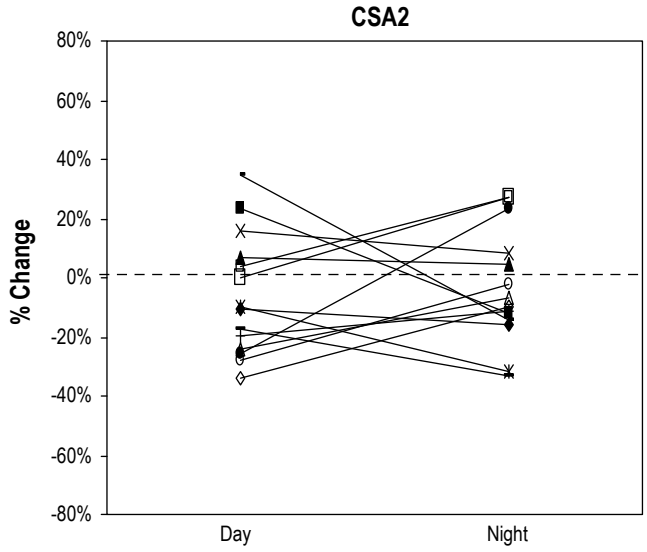
Within each subject and for each position, CSA1 (awake day vs. awake night, $p = 0.15$ [sitting], $p = 0.07$ [supine]) and CSA2 (awake day vs. awake night, $p = 0.37$ [sitting], $p = 0.16$ [supine]) were reproducible across sessions. CSA1 and CSA2 showed changes from sitting to supine position that tended to stay constant across sessions in each individual. However both increases and decreases in CSA occurred with equal frequency and averaged to zero for the group (**Figure 1A, B**). Of note, decreases/increases did not always occur in the same subjects for CSA1 and CSA2. **Table 1** shows the group mean data for CSA1 and CSA2 by position. In each patient, a single value of CSA1 and CSA2 was calculated using the average of daytime and nighttime awake data.

Similar to the results for CSA itself, NR as calculated from CSA did not show any change across sessions or a consistent position effect for the group (**Table 1**).

Active Anterior Rhinomanometry

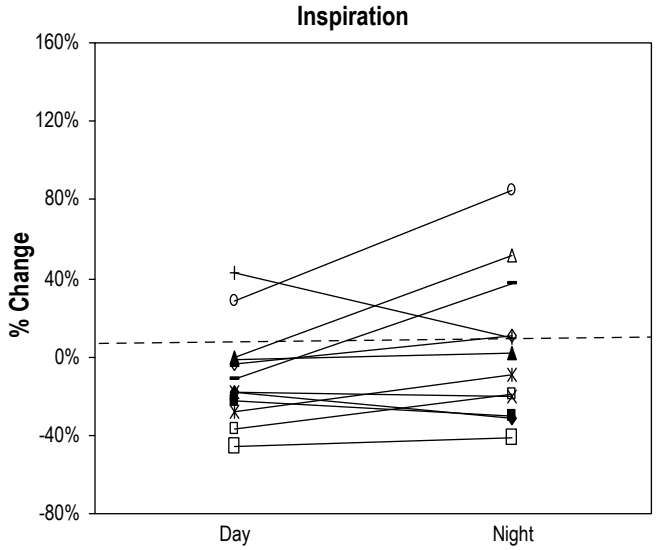
Similar to the data for CSA, measurements of NR by anterior RM did not vary across sessions (day vs. night). Changes of NR

Figure 1B—Positional change of CSA2 from sitting to supine position during wakefulness in both sessions, daytime and nighttime



The Y axis shows the percentage of change of CSA2 from sitting to supine position. Each line represents a subject (n = 14) and the first point of the line shows the change of CSA2 from sitting to supine position during the daytime session. Second point of the line represents the change of CSA2 from sitting to supine position during the nighttime session.

Figure 2A—Positional change of inspiratory nasal resistance by rhinomanometry from sitting to supine position during wakefulness in both sessions, daytime and nighttime



The Y axis shows the percentage of change of inspiratory nasal resistance from sitting to supine position. Each line represents a subject (n = 12) and the first point of the line shows the change of inspiratory nasal resistance from sitting to supine position during the daytime session. Second point of the line represents the change of inspiratory nasal resistance from sitting to supine position during the nighttime session.

Table 1—Awake acoustic rhinometry - Values of CSA and nasal resistance (n = 14)*

	Mean (SD)	Range
CSA1 (cm^2)		
Sitting	0.58 ± 0.10	0.40 – 0.77
Supine	0.56 ± 0.09	0.38 – 0.76
CSA2 (cm^2)		
Sitting	0.53 ± 0.12	0.29 – 0.72
Supine	0.50 ± 0.15	0.31 – 0.83
Minimal CSA (cm^2)†		
Sitting	0.50 ± 0.11	0.29 – 0.70
Supine	0.47 ± 0.12	0.31 – 0.76
Nasal Resistance (arbitrary units)		
Sitting	2.46 ± 1.32	1.1 – 6.27
Supine	2.66 ± 1.31	0.87 – 5.21

CSA refers to cross-sectional area; †Minimal CSA, minimal cross-sectional area between CSA1 and CSA2; SD, standard deviation. *Values for CSA1, CSA2 and nasal resistance were obtained for each patient by averaging daytime and nighttime measurements. Values in the table are the mean values for all subjects.

from sitting to supine during inspiration and expiration also did not show a statistically significant variation across sessions (**Figure 2A, B**). In view of this, for each patient a single value of NR was calculated for each position from the average of daytime and nighttime awake measurements and is shown in **Table 2**.

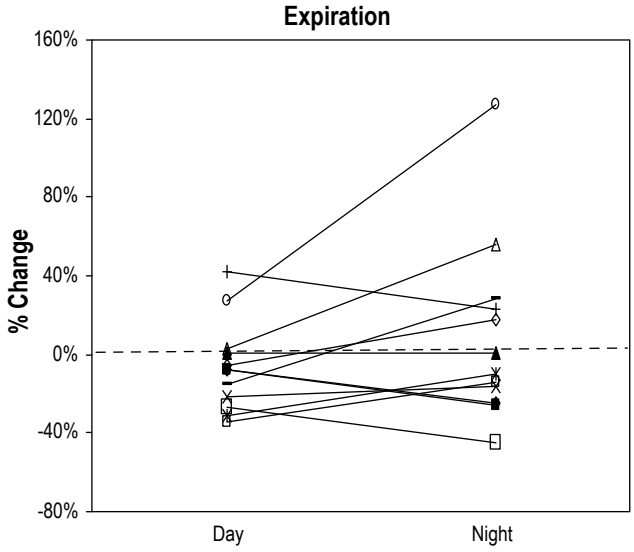
Our patients had a wide range of NR by rhinomanometry, with 8 having normal values and 6 having high values. This is similar to other published rhinomanometry data in OSAHS.[39] By anterior RM, 6/14 patients showed a sitting NR (average of inspiration and expiration) > 0.25 Pa s/cm^3, which has been suggested as the upper limit of normal by Cole et al.[40] In the group with NR (8/14) < 0.25 Pa s/cm^3, 6 patients showed an increase of NR in supine position; one of these patients had a change > 30%. An increase of 30% of NR with position has been suggested by Altissimi et al.[41] as being clinically significant. In the group with high NR by anterior RM, although 4 subjects showed a decrease of NR from sitting to supine position, only one of these patients had a change > 30%.

Upper Airway Resistance

Pressure in the mask remained within 0.5 cm H_2O of set pressure at the machine. As expected from the UA resistive behavior, mean SGP fell during inspiration and rose during expiration from that set at the mask/machine. Overall, the mean value of the difference between set pressure and SGP during wakefulness across subjects was 2.63 ± 2.18 cm H_2O in inspiration (range from 0.6 to 7.7 cm H_2O) and 1.66 ± 1.42 cm H_2O in expiration (range from 0.3 to 6.1 cm H_2O). During sleep, the mean value of the difference between set pressure and SGP across subjects was 3.02 ± 2.62 cm H_2O in inspiration (range from 0.6 to 9.2 cm H_2O) and 1.56 ± 1.27 cm H_2O in expiration (range from 0.4 to 2.8 cm H_2O).

Table 3 shows the results of the resistances calculated for the UA, derived from peak flow and the peak pressure drop from

Figure 2B—Positional change of expiratory nasal resistance by rhinomanometry from sitting to supine position during wakefulness in both sessions, daytime and nighttime



The Y axis shows the percentage of change of expiratory nasal resistance from sitting to supine position. Each line represents a subject (n = 12), and the first point of the line shows the change of expiratory nasal resistance from sitting to supine position during the daytime session. Second point of the line represents the change of expiratory nasal resistance from sitting to supine position during the nighttime session.

Table 2—Awake rhinomanometry - Values of nasal resistance (n = 14)*

	Mean (SD) Pa s/cm^3	Range Pa s/cm^3
Inspiration		
Sitting	0.24 ± 0.08	0.15 – 0.44
Supine	0.24 ± 0.09	0.13 – 0.42
Expiration		
Sitting	0.23 ± 0.08	0.13 – 0.43
Supine	0.23 ± 0.07	0.14 – 0.43
Mean Nasal Resistance		
Sitting	0.23 ± 0.07	0.14 – 0.44
Supine	0.23 ± 0.08	0.14 – 0.43

SD refers to standard deviation. *Values for inspiratory and expiratory nasal resistance are the combined measurements for each patient from daytime and nighttime measurements. Values for mean nasal resistance are the combined data during inspiration and expiration for each position.

Table 3—Sleep upper airway resistance by supraglottic catheter (n = 14)

	Mean (SD) cm H_2O/L/min	Range cm H_2O/L/min
Wakefulness		
Inspiration	0.09 ± 0.06	0.03 – 0.21
Expiration	0.09 ± 0.06	0.04 – 0.22
Sleep		
Inspiration	0.12 ± 0.08	0.02 – 0.27
Expiration	0.10 ± 0.09	0.01 – 0.26
Wakefulness		
(Inspiration & Expiration)	0.09 ± 0.06	0.03 – 0.22
Sleep		
(Inspiration & Expiration)	0.11 ± 0.08	0.01 – 0.26

SD refers to standard deviation.

mask to supraglottic area. In 11/14 subjects, inspiratory UA resistance was similar to expiratory UA resistance. However, in 3 subjects inspiratory UA resistance was much higher than expiratory UA resistance, suggesting suboptimal CPAP may have been present. Inspiratory and expiratory resistances were larger during sleep than during wakefulness on CPAP, although the difference did not reach statistical significance.

Measurement of UA resistances within a single patient remained stable between repeated measures both short term (within 10 min with multiple measures) and across the night (measurements 1 h apart in the same position in stage 2 sleep or wake) at a statistical significance of 0.05 (**Figure 3**).

Relationship Between Techniques

Table 4 shows the correlation coefficients between measurements from the AR and RM. No strong relationships could be shown between the 2 techniques in the sitting position, but there was significant correlation in the supine position. **Figure 4** shows the correlation between NR by AR and anterior RM. **Table 5** shows the correlation coefficients between UA resistance and NR by AR and RM. Although correlation coefficients were statistically significant they do not seem physiologically plausible, as patients with *lower* CSA awake have *lower* UA resistance during sleep on CPAP. In addition, we found no relationship between direct measurement of UA resistance and awake RM.

No significant relationships were found between measures of nasal resistance (AR and RM) or UA resistance and RDI, NOSE questionnaire, and CPAP level. The correlation coefficients were all near zero (< 0.12), and p values of these correlations were all > 0.6.

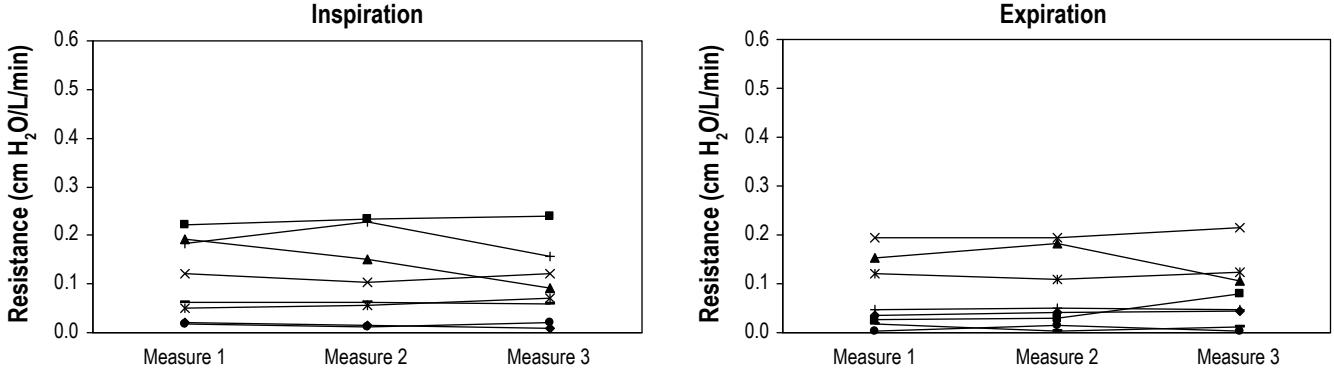
We could not show any association between positional change in RDI from supine to *lateral* and supine to *sitting* measurement of resistance in the 7 patients with all measurements. Only 3 patients had positional changes in AHI > 50%.

DISCUSSION

The data in our study show that measures of nasal resistance *made in the sitting position* while subjects were awake (AR and RM) had little or no correlation to each other. An exception was the significant, if weak, relationship between AR and RM measurements of resistance in the supine position. However, this finding was driven largely by one data point. This lack of agreement between nasal resistance measurements in the sitting and supine positions suggests that the two techniques may measure different aspects of nasal physiology. In addition, as oth-

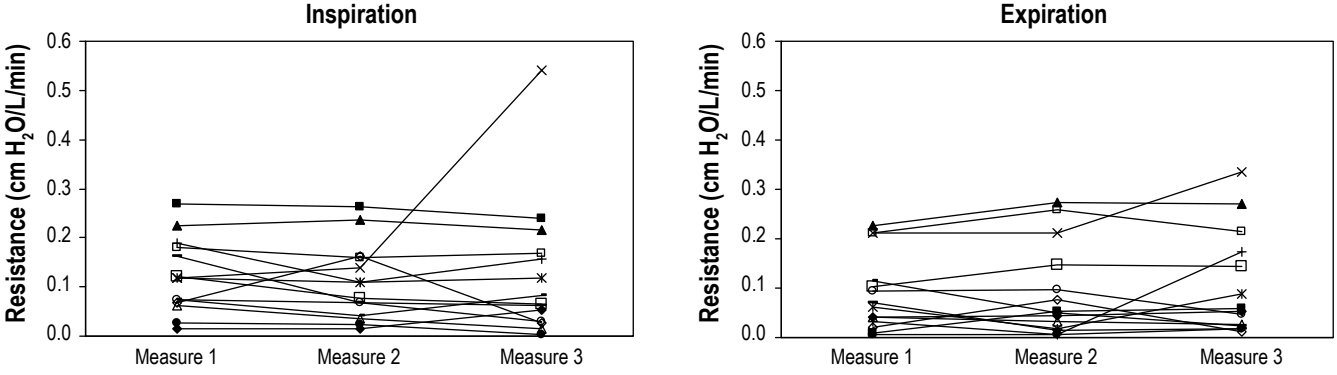
ers have previously shown, we did not find a clear relationship between severity of OSAHS[42,43] and either reported subjective nasal symptoms[44-46] or the measures of awake nasal function (AR and RM). Upper airway resistance measured during sleep did not show significant relationships to any of the awake measures of nasal resistance (AR or RM).

Figure 3A, B—Reproducibility of the upper airway resistance in short-term sleep (within 10 min of stage N2 sleep)



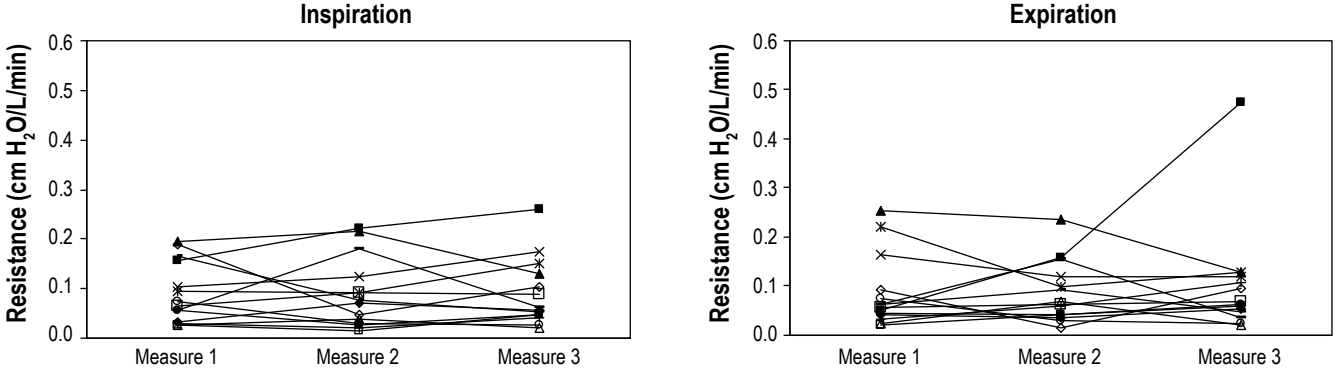
Panel A represents inspiration. Panel B represents expiration. X axis represents 3 points in time within a period of 10 min of stable stage N2 sleep. Y axis is the value of upper airway resistance measured by supraglottic catheter. Each line represents a subject (n = 8).

Figure 3C, D—Reproducibility of the upper airway resistance in long-term sleep (measurements at 1 h apart in the same position in stage N2 sleep)



Panel C represents inspiration. Panel D represents expiration. X axis represents 3 points in time across the night of stable stage N2 sleep and separated by ≥ 1 hour. Y axis is the value of upper airway resistance measured by supraglottic catheter. Each line represents a subject (n = 14).

Figure 3E, F—Reproducibility of the upper airway resistance in long-term awake (measurements at 1 h apart in the same position awake)



Panel E represents inspiration. Panel F represents expiration. X axis represents 3 points in time across the night of stable breathing during wakefulness and separated at least by 1 hour. Y axis is the value of upper airway resistance measured by supraglottic catheter. Each line represents a subject (n = 14).

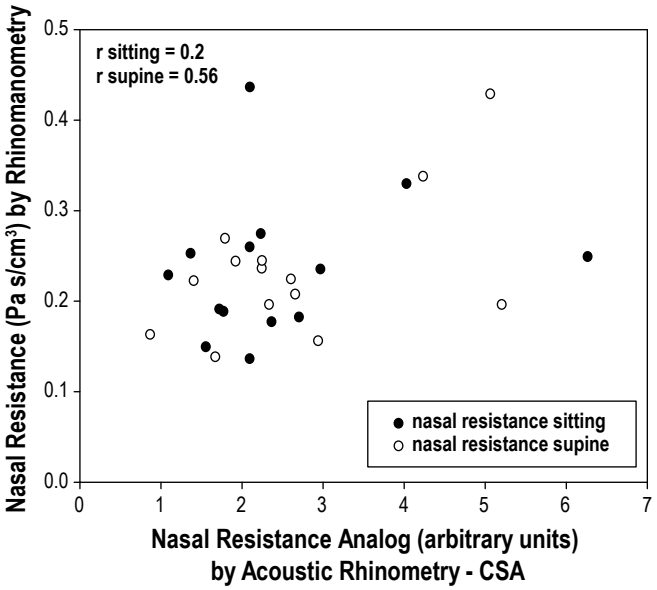
Our measures of the effect of position on awake nasal function merit further comment. First, for both AR and RM, repeated measurements (made on two occasions, daytime and nighttime) were consistent within a single patient, suggesting that the values obtained have physiological meaning. In addition, intra-patient changes in the measurements of both AR and RM from sitting to supine were also consistent on repeat testing. Despite this, across patients we did not find consistent changes in AR or RM with change to the supine position. In healthy subjects a consistent increase in nasal resistance and a decrease of CSA has been has been reported when subjects go from sitting to supine position.[47-49] However, similar to our data, studies in patients with OSAHS[39,50,51] report variable changes in nasal resistance and CSA with positional change, suggesting that OSAHS patients may respond differently from normal subjects to positional changes. One can speculate that the increased vascular volume frequently associated with obesity, may have caused nasal mucosal edema that saturated mechanisms for postural changes in resistance. However, our data did not include these measures. Other possible mechanisms that could explain the "atypical" response to change in position in patients with OSAHS are altered neurovascular control of the nasal mucosa in supine position, perhaps due to increased sympathetic neurovascular activity with a consequent reduction of the influx of blood through the vessels

Table 4—Correlation coefficients between acoustic rhinometry and rhinomanometry (n = 14)

	Acoustic Rhinometry			
Rhinomanometry	**CSA1** sitting	**CSA2** sitting	**Minimal CSA** sitting	**Nasal Resistance** sitting
Nasal Resistance (sitting)				
Inspiration	-0.16	-0.26	-0.27	0.18
Expiration	-0.17	-0.34	-0.32	0.23
Mean†	-0.17	-0.30	-0.29	0.20
	CSA1 supine	**CSA2** supine	**Minimal CSA** supine	**Nasal Resistance** supine
Nasal Resistance (supine)				
Inspiration	-0.13	-0.52	-0.52	0.59*
Expiration	-0.08	-0.44	-0.41	0.47
Mean†	-0.11	-0.51	-0.49	0.56*

CSA refers to cross-sectional area. †Values for mean nasal resistance are the combined data during inspiration and expiration for each position. *Statistically significant ($p < 0.05$)

Figure 4—Correlation between nasal resistance by acoustic rhinometry (X axis) and nasal resistance by rhinomanometry (Y axis)



Each point represents a subject (n = 14). Black dots represents measures of nasal resistance in sitting position, and open dots are measures of nasal resistance in supine position. Values for mean nasal resistance by rhinomanometry are the combined data during inspiration and expiration for each position.

Table 5—Correlation coefficients between directly assessed upper airway resistance and nasal resistance by acoustic rhinometry and rhinomanometry (n = 14)

	Directly Assessed Upper Airway Resistance (sleep)		
	UA Resistance Inspiration	**UA Resistance Expiration**	**UA Resistance Mean**
Acoustic Rhinometry (awake)			
CSA1			
Sitting	-0.15	0.45	-0.54
Supine	0.37	0.54*	0.50
CSA2			
Sitting	0.44	0.37	0.45
Supine	0.64*	0.69*	0.73*
Minimal CSA			
Sitting	0.14	0.20	0.19
Supine	0.59*	0.64*	0.68*
Nasal Resistance			
Sitting	-0.21	-0.16	-0.20
Supine	-0.51	-0.54*	-0.58
Rhinomanometry (awake)			
Nasal Resistance Inspiration			
Sitting	-0.12	—	—
Supine	-0.47	—	—
Nasal Resistance Expiration			
Sitting	—	0.22	—
Supine	—	-0.03	—
Mean Nasal Resistance			
Sitting	—	—	0.64
Supine	—	—	-0.30

UA refers to upper airway; CSA, cross-sectional area. *Statistically significant ($p < 0.05$)

or to increased levels of inflammatory activity that could affect the nose via circulating adrenalin and noradrenalin or inflammatory cytokines, as these have been reported in OSAHS.[52-54]

The purpose of the present study was to obtain a daytime/wake noninvasive measurement predictive of nighttime/sleep physiology that might have implications for patients with OSAHS on CPAP. High upstream (nasal) resistance in the Starling resistor model of the upper airway implies that increased UA resistance increases the collapsing force at the (downstream) collapsible segment, but this is not relevant to the condition of sleep *on optimum nasal CPAP* (titrated to prevent collapse). Thus, on CPAP, behavior of the upper airway should be similar to the awake condition, where there is rigidity of the upper airway at the collapsible area. In contrast to the collapsible behavior of the velopharynx during sleep, nasal behavior is most closely approximated by a single rigid constriction (i.e., a non Starling constant resistance) and is not affected by sleep.[26] This conceptualization leads us to predict that high nasal resistance should be perceived by the patient even on CPAP and might contribute to intolerance. Our aim was to identify the best technique to measure the relevant nasal resistance prior to the sleep study (and subsequently to test whether this can be used to anticipate CPAP non-compliance). However, our data do not demonstrate any relationship between awake nasal resistance by AR or RM and upper airway resistance during sleep.

It seems unlikely that the lack of relationship between awake AR and RM with direct measurement of UA resistance during sleep was due to deficiencies in our technique of obtaining AR and RM. We used standard techniques and equipment with multiple measurements, as recommended by standards,[29,36,37] and our data show reproducible measurements within a single position and on separate occasions within each patient.

To examine the relationship between AR and RM, we converted both to a form conceptually related to "resistance." For RM resistance is directly obtained for each measurement and we chose to combine the nostrils as parallel resistors.[29] For AR, the measurement is of cross-sectional area, which did not itself show a statistical relationship to RM in our dataset. To use this as a "resistance" analog, we made the simplest assumption that flow was turbulent and proportional to $1/R^4$ or $1/(\text{cross sectional area})^2$. While this assumption may be simplistic, one would expect at least a monotonic relationship using this approach, and we did not find this to be present.

The lack of correlation between AR and RM we found is similar to what is reported in the literature. AR assesses a local minimal cross sectional area at a specific site, whereas airflow resistance by RM is a dynamic parameter that assesses all the serial components of the nasal cavity.[55-57]

There are several limitations in our study. First, lack of correlations may have been due to the small number of unselected patients. However, we studied patients with a wide range of nasal resistances and OSAHS, and this should have maximized our ability to find relationships. A power calculation suggests we can reject the hypothesis of a high correlation (> 0.8) between our variables with a power of 80% to 85% and α of 0.025 with the 14 subjects we studied. While a significant lower correlation between our variables could have existed and become evident with a larger sample size, a lower correlation would not have satisfied the primary goal of our study, which was to find a noninvasive daytime test highly correlated to (and therefore predictive of) the nocturnal directly measured resistance. Second, it can be argued that there was no reason to expect correlations between measurements made during wakefulness and those made during sleep. However, we wished to test this directly as it is generally assumed that sleep does not affect the nose in the same way as it affects the collapsible segment of the nasopharynx responsible for OSAHS.[26] In addition, it is difficult to make AR and RM measurements during sleep without disturbing normal sleep. Furthermore, our purpose was to examine potential predictors of nocturnal physiology that could be easily obtained during the daytime. An additional criticism is that we did not obtain a subjective patient report of CPAP "comfort." However this was not the purpose of the present study, as we felt that the first night of CPAP titration was not the optimal time to assess comfort (as it was the patient's first exposure to CPAP).

CONCLUSION

While acoustic rhinometry and rhinomanometry as often obtained (sitting) were not consistently related to each other they, were correlated in the *supine* position. However neither of these *awake* measurements of nasal resistance was predictive of upper airway resistance during *sleep* on CPAP, suggesting that differences in upper airway pathophysiology in patients with OSAHS may affect awake and sleep nasal resistances in complex ways. It remains possible that we did not find the predicted relationship between awake and sleep measures of nasal resistance because of the small sample size or because patients were not selected specifically for their nasal symptoms.

ABBREVIATIONS

CPAP, Continuous positive airway pressure
OSAHS, Obstructive sleep apnea/hypopnea syndrome
NR, Nasal resistance
AR, Acoustic rhinometry
RM, Rhinomanometry
CSA, Cross-sectional area
mCSA, Minimal cross-sectional area
UA, Upper airway
NPSG, Nocturnal polysomnography
AHI, Apnea/hypopnea index
RDI, Respiratory disturbance index
SGP, Supraglottic pressure
NOSE, Nasal obstruction symptom evaluation
MP, Mask pressure

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The Supraglottic Effect of a Reduction in Expiratory Mask Pressure During Continuous Positive Airway Pressure

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Study Objectives: Patients with obstructive sleep apnea may have difficulty exhaling against positive pressure, hence limiting their acceptance of continuous positive airway pressure (CPAP). C-Flex is designed to improve comfort by reducing pressure in the mask during expiration proportionally to expiratory airflow (3 settings correspond to increasing pressure changes). When patients use CPAP, nasal resistance determines how much higher supraglottic pressure is than mask pressure. We hypothesized that increased nasal resistance results in increased expiratory supraglottic pressure swings that could be mitigated by the effects of C-Flex on mask pressure.

Design: Cohort study.

Setting: Sleep center.

Participants: Seventeen patients with obstructive sleep apnea/hypopnea syndrome and a mechanical model of the upper airway.

Interventions: In patients on fixed CPAP, CPAP with different C-Flex levels was applied multiple times during the night. In the model, 2 different respiratory patterns and resistances were tested.

Measurements and Results: Airflow, expiratory mask, and supraglottic pressures were measured on CPAP and on C-Flex. Swings in pressure during expiration were determined. On CPAP, higher nasal resistance produced greater expiratory pressure swings in the supraglottis in the patients and in the model, as expected. C-Flex 3 produced expiratory drops in mask pressure (range -0.03 to -2.49 cm H_2O) but mitigated the expiratory pressure rise in the supraglottis only during a sinusoidal respiratory pattern in the model.

Conclusions: Expiratory changes in mask pressure induced by C-Flex did not uniformly transmit to the supraglottis in either patients with obstructive sleep apnea on CPAP or in a mechanical model of the upper airway with fixed resistance. Data suggest that the observed lack of expiratory drop in supraglottic pressure swings is related to dynamics of the C-Flex algorithm.

Keywords: Upper airway resistance, nasal resistance, obstructive sleep apnea, fixed CPAP, flexible CPAP, CPAP compliance

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INTRODUCTION

Continuous positive airway pressure (CPAP) is the primary treatment for obstructive sleep apnea/hypopnea syndrome (OSAHS).[1,2] CPAP use normalizes breathing, improves sleep architecture,[3] enhances daily function,[4,5] and reduces the number and severity of cardiovascular events.[6-8] Despite the efficacy of CPAP, studies defining adherence as use for at least 4 hours per night have reported that 29% to 83% of patients did not adhere to CPAP therapy.[9,10] Although multiple factors may contribute to CPAP intolerance, including mask fit, humidity, excessive mask leak, claustrophobia, and nasal symptoms,[11] pressure intolerance is a frequent complaint.[9] In 2 studies,[12,13] 29% and 18% of patients reported "difficulty exhaling" during CPAP treatment. Several small studies have also suggested that initial rejection of CPAP correlates with increased nasal resistance.[14-16] Nasal resistance may contribute to CPAP intolerance through several mechanisms, including alterations in the route of breathing,[17,18] the need for high CPAP pressure, and increased leak.[19] During expiration, nasal resistance causes the pressure experienced by the patient to be higher than the prescribed CPAP. This is because the resistance interacts with expiratory flow to produce a backpressure that adds to the CPAP (mask pressure), and this may contribute to discomfort.

Multiple technologic strategies have been proposed to improve CPAP adherence (including continuous automatic titration and bilevel therapy), but there is little evidence that these strategies significantly improve patient adherence.[20-23] A recently introduced approach, C-Flex (Respironics; Murraysville, PA), is designed to improve comfort by modifying pressure in the mask during CPAP only during expiratory flow (in contrast with bilevel therapy, which maintains a low expiratory pressure throughout expiration). Although it is possible that any increased comfort (and consequent effect on compliance) achieved through reducing expiratory pressure may be achieved by reducing the pressure affecting the nose, it seems more likely that improved comfort would arise from reduction of **excessive** supraglottic pressure swings (i.e., that the drop in mask pressure would offset the expiratory rise in pharyngeal pressure above the prescribed CPAP).

Prospective randomized studies have demonstrated that C-Flex is not inferior to conventional fixed CPAP,[24,30] but increased adherence rates have not been uniformly demonstrated. Some studies have shown that C-Flex reduces discomfort[26,28] and improves satisfaction[25] and compliance,[27,31] but larger randomized studies[29,30] have shown no difference in compliance between CPAP and C-Flex.

During well-titrated CPAP, collapsibility of the upper airway (UA) is abolished. In this condition, total UA resistance is dic-

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tated by nasal resistance, which, at constant CPAP, necessarily produces flow-related effects on supraglottic pressure. During expiration, this supraglottic pressure (pressure from the mask plus any pressure resulting from the expiratory flow) determines the expiratory work of breathing and could contribute to patient symptoms and CPAP intolerance. The purpose of the present study was to examine whether C-Flex decreases supraglottic pressure swings during expiration, providing a mechanism for improved comfort. This study did not examine comfort, treatment adherence, or clinical outcomes per se; our goal was to define the underlying physiology and effects of C-Flex to better address the role it has in the clinical setting (e.g., defining its relevance to patients with high nasal resistance). Specifically, we examined the expiratory pressure profile at the mask and in the upper airway at the supraglottis in asleep patients while they were on CPAP with and without C-Flex. We also examined whether expiratory supraglottic pressure swings could be mitigated with the application of C-Flex. In addition to testing the application of C-Flex in patients with OSAHS, we also used a mechanical model of the UA to control respiratory flow and pattern and to eliminate reflex changes seen in patients

METHODS

Patients with OSAHS

Twenty-two adults presenting for evaluation of OSAHS with complaints of snoring and excessive daytime sleepiness were recruited for this study. Demographic and clinical variables were documented. Patients were excluded if they had a medically unstable condition (i.e., recent myocardial infarction, congestive heart failure) or if they were unable to sleep with CPAP.

All patients underwent full nocturnal polysomnography to confirm the diagnosis of OSAHS, and the polysomnogram was performed as per American Academy of Sleep Medicine recommended clinical guidelines.[32,33] If CPAP treatment was clinically indicated, the patients were referred for in-laboratory CPAP-titration polysomnography.[34] In addition to the usual measurements of mask flow and mask pressure, supraglottic pressure measurements were also obtained during optimal fixed CPAP and at the same CPAP level with expiratory pressure reduction (C-Flex). C-Flex produces a constant inhalation pressure but reduces airway pressure during exhalation in proportion to the patient's expiratory airflow (thus, a drop in pressure occurs primarily during early expiration). C-Flex allows for 3 setting, C-Flex 1, C-Flex 2, C-Flex 3, which correspond to an increasing proportionality constant between expiratory flow and pressure reduction.

During the CPAP-titration polysomnography, pressure was directly measured at the mask using a pressure transducer (Ultima Dual Airflow Pressure Sensor™, Braebon 0585, Ontario, Canada). Airflow was recorded from the output of a Respironics BiPAP Auto M Series device in CPAP mode. CPAP was titrated manually during the first hour of the study to a level that eliminated all sleep disordered breathing events, including obstructive apneas and hypopneas and runs of inspiratory flow limitation. The optimal pressure was defined as the minimum pressure at which flow limitation disappeared. This pressure was determined by performing step-down measures, i.e., dropping the pressure every 2 minutes by 1 cm H_2O until indications of inspiratory flow limitation occurred. The pressure prior to the appearance of flow limitation established the minimum therapeutic pressure.

In addition to standard monitoring, supraglottic pressure was obtained using a pressure transducer-tipped catheter (Millar MPC 500, Millar Instruments, Houston, TX). The patient's nose was anesthetized using atomized lidocaine 5% and lidocaine 2% jelly for the throat. The Millar catheter was introduced transnasally, and the tip of the catheter was placed just below the uvula. The catheter position was confirmed visually through the mouth. The catheter was taped to the nose to secure its position throughout the study. The nasal CPAP mask was then applied, and leak at the exit site of the catheter was minimized. The output of the Millar catheter was amplified and recorded at 64 Hz. To verify that the supraglottic catheter tip was placed just below the collapsible segment of the UA, the tracings from the supraglottic and CPAP inspiratory pressures after the patient fell asleep were inspected during a brief "step-down" of CPAP pressure. Correct positioning of the catheter tip required that the delta pressure between the mask and the supraglottic area increased substantially during inspiration and that evidence of inspiratory flow limitation appeared simultaneously. If this increase in delta pressure was not observed while the CPAP was reduced, the technician assumed that the catheter position was too high and advanced the catheter.

Interventions were performed after 5 minutes of stable stage N2 sleep with the patient on optimal CPAP. The data were discarded if an arousal occurred. Three different levels of C-Flex were applied cyclically multiple times throughout the night. The order of application of C-Flex level was not randomized. Each level was maintained for 1 minute, and fixed CPAP was restored at the end of the sequence, which was repeated at least twice, up to 10 times, across the night. Changes in pressure were accomplished with a single machine while patients were asleep, and, thus, patients were effectively blinded to the intervention.

Subjects signed a consent form approved by the Institutional Review Board of the New York University School of Medicine.

Mechanical Model of the Upper Airway

To create a bench test for some of our observations in patients, we designed a mechanical model of the upper airway in patients on CPAP (i.e., without a collapsible airway) (Figure 1). This model consisted of a rigid resistive tube, the resistance of which could be varied by changing the aperture size. A pure sinusoidal respiratory pattern was generated using a mechanical pump (Respiration Pump 607, Harvard Apparatus Co, INC. Dover, MA). In a separate data collection, a healthy volunteer breathing through the system generated a "normal" breathing pattern (exponential expiration with pause). Airflow was measured from the output of a Respironics BiPAP Auto M Series device in CPAP mode. Simulated mask pressure was measured with a pressure transducer (Ultima Dual Airflow Pressure Sensor). Simulated supraglottic pressure was obtained using the Millar catheter. Measurements were obtained using these 2 respiratory patterns at 2 respiratory rates and 2 tidal volumes. All measurements were performed with 2 different resistances on CPAP and on C-Flex settings. Three different levels of C-Flex were applied and maintained for 1 minute each, and fixed CPAP was restored at the end of the sequence, which was repeated.

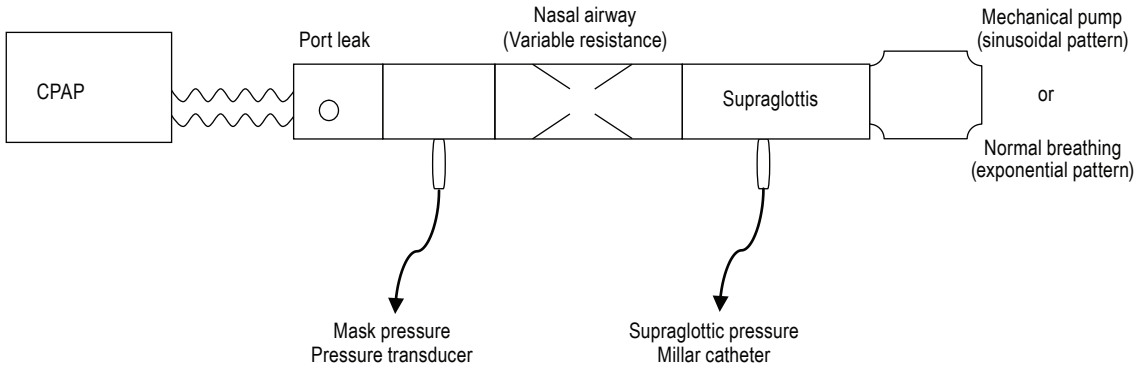

Figure 1—Mechanical model of the upper airway. The model consists of a rigid resistive tube with a variable "upstream" upper airway resistance controlled by changing the aperture size to mimic a patient using nasal continuous positive airway pressure (CPAP). A rigid tube was used to model the upper airway because dynamic collapse does not occur in patients on CPAP. The pressure taps are placed within the model to obtain measurements that simulate nasal and supraglottic pressures in a patient. Patterns of breathing were applied by a mechanical pump (sinusoidal) or a healthy volunteer breathing on a mouthpiece ("normal" pattern).

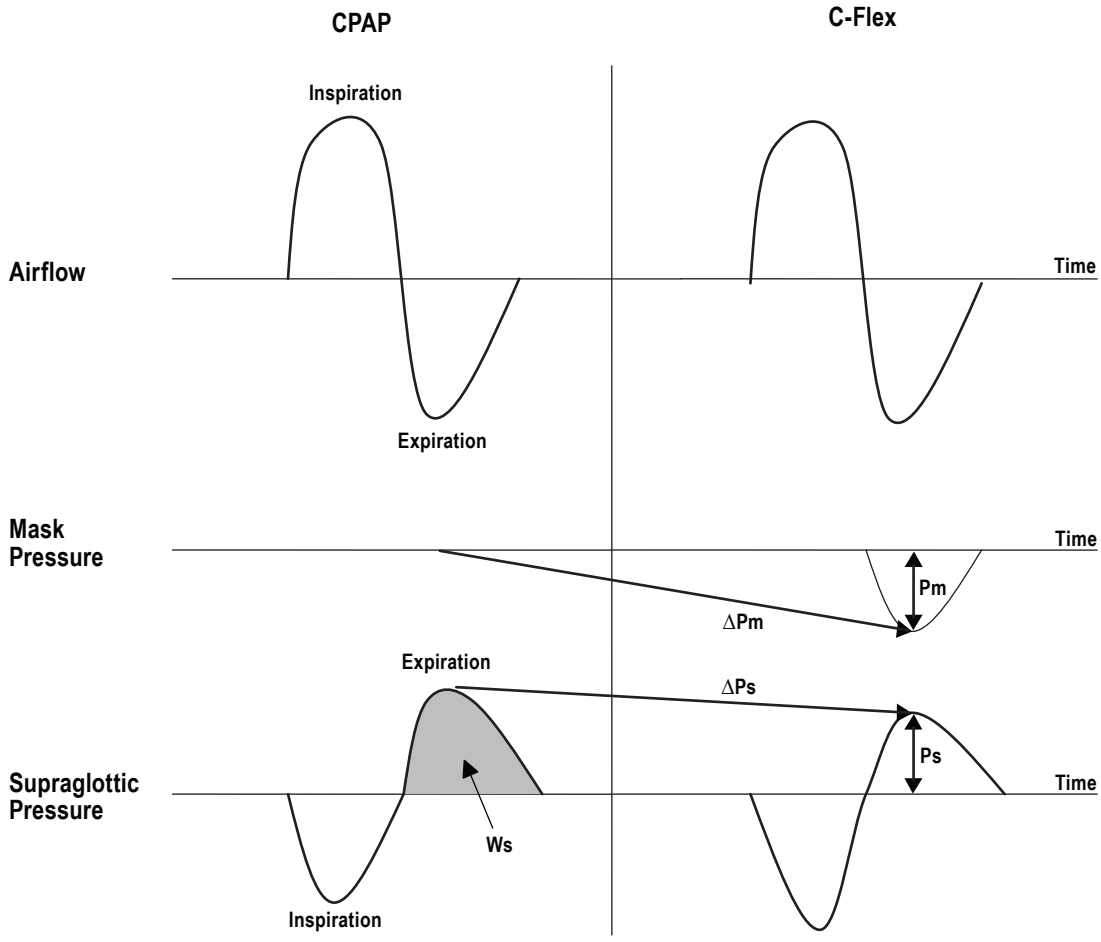

Figure 2—This drawing shows data collected and variables analyzed for a single breath. The left panel shows continuous positive airway pressure (CPAP) and the right shows C-Flex 3. The top tracing shows airflow (inspiration up). The middle tracing is pressure at the mask, and the bottom tracing is supraglottic pressure (inspiration down). Pm refers to the expiratory pressure swing in the mask; Ps, expiratory pressure swing in the supraglottis; ΔPm, change in expiratory mask pressure swings (C-Flex 3 minus CPAP); ΔPs, change in expiratory pressure swings in the supraglottis (C-Flex 3 minus CPAP); Ws, estimated expiratory work by calculating the integrated supraglottic pressure during expiration (grey area).

Analysis

Figure 2 shows a drawing of airflow, mask pressure, and supraglottic pressure signals and the derived variables. Respiratory variables were analyzed only during the expiratory phase. We assessed values of variables on CPAP and on different C-Flex settings. Mask pressure (Pm in Figure 2) is the expiratory

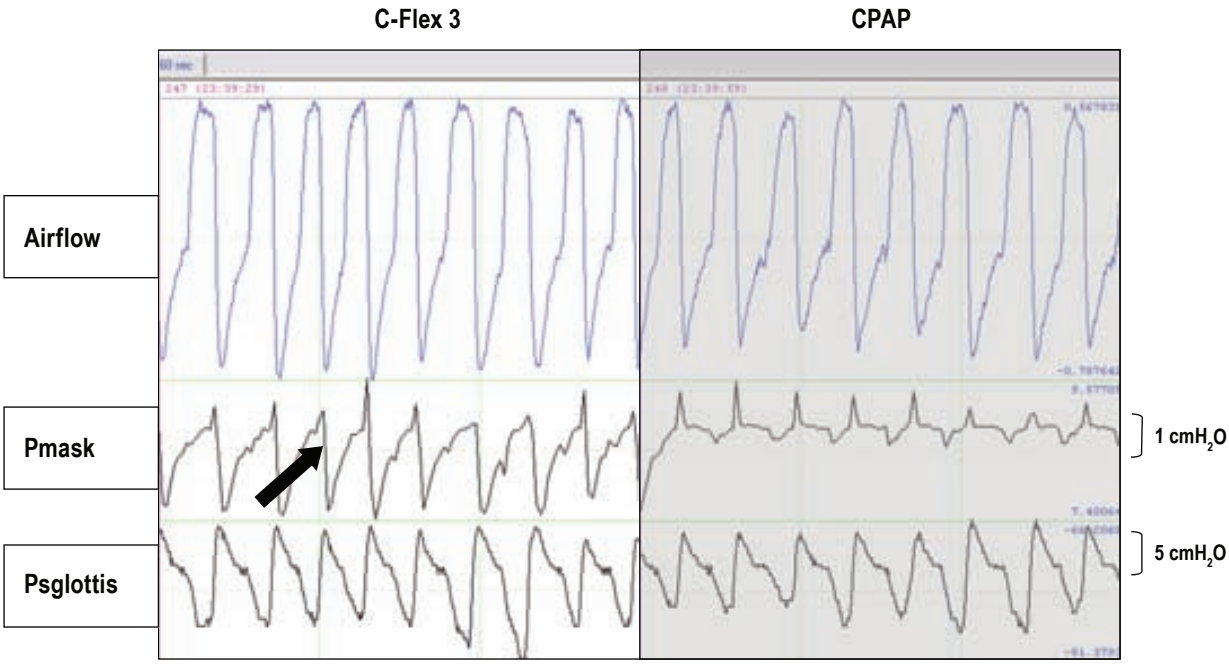

Figure 3—The raw tracing data of airflow, mask pressure (Pmask), and supraglottic pressure (Psglottis) from a patient with obstructive sleep apnea-hypopnea syndrome on C-Flex 3 and continuous positive airway pressure. The arrow shows the reduction of mask pressure during expiration with the application of C-Flex 3.

pressure swing in the mask (the difference between mask pressure at peak expiratory airflow and mask pressure at the end of expiration, which is the set CPAP). Supraglottic pressure (Ps) is the expiratory pressure swing in the supraglottis (the difference between the supraglottic pressure at peak expiratory airflow and the supraglottic pressure at the end of expiration). Delta Pm (ΔPm) is the change in mask-pressure swings with application of C-Flex (Pm on C-Flex minus Pm on CPAP). Delta Ps (ΔPs) is the change in supraglottic pressure swings with application of C-Flex (Ps on C-Flex minus Ps on CPAP). We calculated the integrated supraglottic pressure during expiration (Ws) as a surrogate for expiratory work. The UA resistance was calculated as the difference between mask pressure and supraglottic pressure at peak airflow divided by peak airflow.

In patients (during stage N2 sleep and in the same position) and in the UA model, we identified 2 separate periods suitable for data collection during which stable respiration was present. In each of these periods, data from 3 consecutive breaths were averaged to obtain the value for each variable on C-Flex 1, C-Flex 2, C-Flex 3, and fixed CPAP. The average value from 2 segments is reported as a single value for each variable on C-Flex 1, C-Flex 2, C-Flex 3, and fixed CPAP. Analysis of the supraglottic pressure signal was done without hiding the mask pressure signal, and the investigator was, thus, not blinded as to the presence of C-Flex.

Statistical analysis was performed using SPSS for Windows (version 17; SPSS, Chicago, IL). An independent samples t-test was used for comparisons between low and high resistance. Comparisons of ΔPm and ΔPs were made using paired-samples t-test comparing CPAP with C-Flex 3. Significance was assumed at a P value of less than 0.05. Values are shown as mean ± SD.

RESULTS

Patients with OSAHS

Of the 22 patients with OSAHS who were recruited, 17 (13 men/4 women) completed the study: the remaining potential subjects were excluded due to insufficient sleep (n = 2), excessive mask leak (n = 2), and poor signal quality from the supraglottic catheter (n = 1). The mean age was 49.2 ± 11.1 years, mean body mass index, 35.1 ± 9.8 kg/m^2; the mean apnea-hypopnea index, 61.2 ± 35.1 events/h; the mean respiratory index disturbance 64.8 ± 35.1 events/h, mean Epworth Sleepiness Scale score, 12.7 ± 5.4; and the mean CPAP level, 10.11 ± 3.5 cm H_2O.

Figure 3 shows raw-tracing data of airflow, mask pressure, and supraglottic pressure from 1 patient with OSAHS. Swings in the expiratory mask pressure in the patients during CPAP were near 0 (Pm = +0.09 ± 0.08 cm H_2O) and, as expected, swings in the supraglottic expiratory pressure did occur (Ps = +1.87 ± 1.30 cm H_2O). During C-Flex 3, all patients developed expiratory mask pressure dips (Pm = -1.13 ± 0.48 cm H_2O), and the drop of Pm was progressive as C-Flex went from setting 1 to setting 3 (Figure 4A). Concurrently, expiratory supraglottic pressure swings (Ps) were +1.75 ± 1.19 cm H_2O (Figure 4B). Thus, unexpectedly, there was no significant reduction in supraglottic expiratory pressure swings during C-Flex, compared with the swings present in Ps during CPAP alone (P = 0.46). Figure 5A shows the effect of C-Flex compared with CPAP on Pm in the individual patients. The transmission of the expiratory mask pressure swings to the supraglottis did not occur in 15 of the 17 patients (e.g., ΔPm was -1.23 ± 0.53 cm H_2O and ΔPs was -0.06 ± 0.47 cm H_2O, P = 0.000, see Figure 5B). This behavior was in contrast to the expectation that C-Flex would reduce or abolish changes in expiratory supraglottic pressures.

When patients were using CPAP during sleep, no differences occurred between the mean inspiratory and mean expiratory instantaneous UA resistance (0.12 ± 0.08 cm $H_2O \cdot L^{-1} \cdot min^{-1}$ vs 0.10 ± 0.09 cm $H_2O \cdot L^{-1} \cdot min^{-1}$, P = 0.11). Table 1 examines the role of expiratory UA (upstream) resistance on our findings by separating our patients whose expiratory UA resistance was less than (n = 12) and greater than (n = 5) 0.1 cm $H_2O \cdot L^{-1} \cdot min^{-1}$, in accord with what has been shown in the literature on nasal resistance.[35-37] Patients with low UA resistance during CPAP use (constant mask pressure) showed expiratory pressure swings at the supraglottis (Ps) of +1.15 ± 0.45 cm H_2O. As expected, Ps was significantly greater (P = 0.001) in patients with high levels of UA resistance (+3.59 ± 0.99 cm H_2O). On C-Flex 3, there were no discernable differences between groups for ΔPm and ΔPs.

To examine this unexpected lack of change in supraglottic pressure—despite a drop in expiratory pressure at the mask—we used a mechanical model in which the pattern of airflow could be controlled.

Mechanical Model of the Upper Airway

Sinusoidal respiratory pattern

When we implemented our mechanical model of the upper airway with a sinusoidal respiratory pattern and a *low* simulated UA resistance during CPAP (constant mask pressure), expiratory pressure swings at the simulated supraglottis (Ps) were +1.94 ± 1.47 cm H_2O. As expected, with a *high* simulated UA resistance, Ps increased to +4.40 ± 3.03 cm H_2O.

During the highest level of C-Flex (C-Flex 3), mask pressure developed expiratory dips and Pm was -1.45 ± 0.74 cm H_2O on low simulated UA resistance and -1.57 ± 0.66 cm H_2O on high simulated UA resistance. Concurrently, expiratory Ps was +0.51 ± 1.11 cm H_2O on low simulated UA resistance and +2.87 ± 2.41 cm H_2O on high simulated UA resistance.

Table 2 shows the effect of C-Flex compared with CPAP on Pm and Ps in our mechanical-model data. The data across a range of imposed tidal volumes and frequencies are grouped according to whether there was a low or high simulated upstream "UA" resistance. The change in Ps (ΔPs) when going from CPAP to C-Flex 3 was similar to the change in Pm (ΔPm) (e.g., there was no statistically significant difference in the magnitude of the swings between Ps and Pm). Furthermore, in the model, expiratory pressure swings were transmitted similarly from mask to supraglottis for all patterns of breathing and for low and high UA resistance.

Exponential respiratory pattern

When a healthy volunteer breathing on the upper airway model produced a nonsinusoidal (normal) respiratory pattern with a rapid peak in expiratory airflow followed by an exponential decay of flow, *low* simulated UA resistance during CPAP (constant mask pressure) produced expiratory pressure swings at the supraglottis (Ps) of +4.09 ± 2.74 cm H_2O. Again, as expected, high simulated UA resistance increased Ps to +6.61 ± 4.86 cm H_2O.

During the highest level of C-Flex (C-Flex 3), mask pressure developed expiratory dips and Pm was -2.61 ± 0.62 cm H_2O on low simulated UA resistance and -2.35 ± 0.70 cm H_2O on high simulated UA resistance. Concurrently, expiratory supraglot-

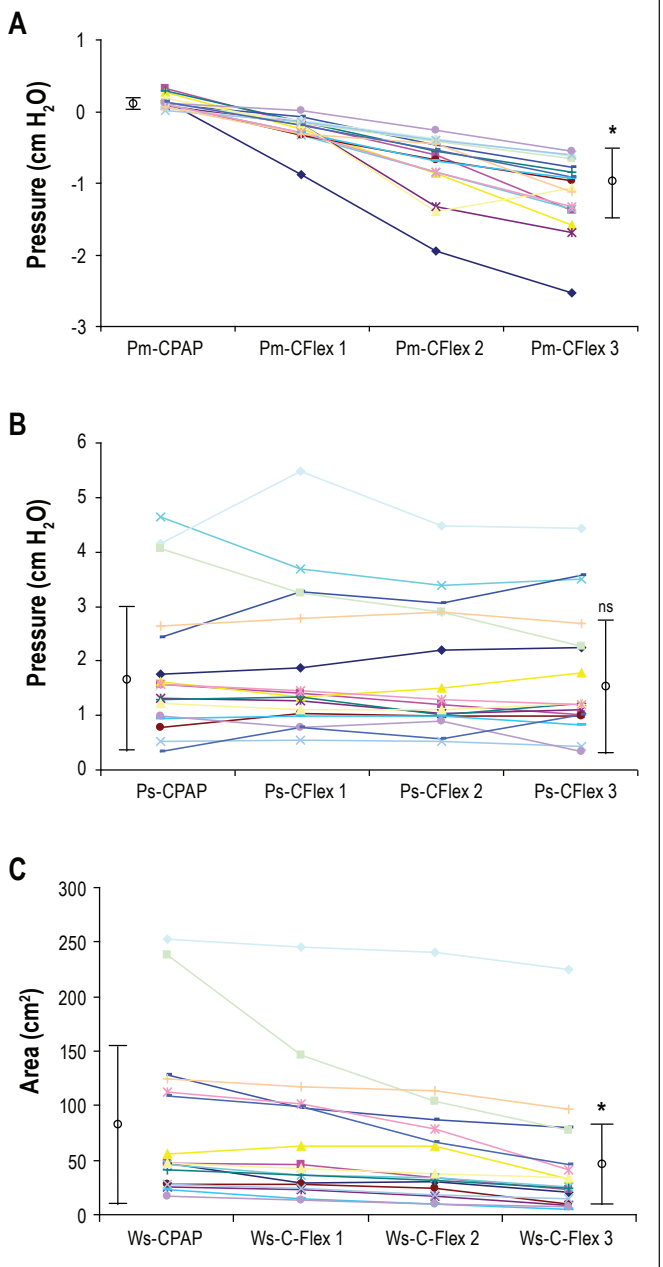

Figure 4—Data from patients with obstructive sleep apnea-hypopnea syndrome—the effect of C-Flex compared with continuous positive airway pressure (CPAP) on mask pressure swings (Pm), supraglottic pressure swings (Ps), and the estimated expiratory work (Ws). Each line represents a patient (n = 17) with lines connecting the magnitude of the expiratory pressure swing within the mask when the patient was using CPAP to the expiratory pressure swing within the mask when the patient was using C-Flex 3. **(A)** All patients developed expiratory dips, and the Pm showed progressive reduction on C-Flex 1, C-Flex 2, and C-Flex 3 compared with CPAP. The mean ± SD values of the CPAP and C-Flex 3 are shown, and the * indicates a significant difference in the mean (P < 0.0001). **(B)** Patients did not show a reduction in expiratory supraglottic pressure swings (Ps) with the application of various levels of C-Flex. The mean ± SD value of the CPAP and C-Flex 3 are shown, and ns indicates no significant difference in the means. **(C)** Patients showed a variable reduction of the integrated expiratory pressure in the supraglottis with C-Flex. This reduction may be most evident when comparing CPAP with the highest level of C-Flex 3. The mean ± SD value of the CPAP and C-Flex 3 are shown, and the * indicates a significant difference in the mean (P < 0.0001).

Table 1—Expiratory mask and supraglottic pressure swings and effect of C-Flex compared to CPAP in OSAHS patients

	Low UA resistance (n = 12) (< 0.1 cm H_2O/L/min)		High UA resistance (n = 5) (> 0.1 cm H_2O/L/min)	
OSAHS Patients	**CPAP**	**C-Flex 3**	**CPAP**	**C-Flex 3**
Pm (cm H_2O)	0.11 ± 0.09	-1.21 ± 0.53	0.03 ± 0.02	-0.93 ± 0.31
Ps (cm H_2O)	+1.15 ± 0.45	+1.11 ± 0.52	+3.59 ± 0.99	+3.29 ± 0.84
ΔPm (cm H_2O)	-1.32 ± 0.55		-0.96 ± 0.31	
ΔPs (cm H_2O)	-0.04 ± 0.39		-0.29 ± 1.18	

Values are means ± standard deviation. UA, upper airway; CPAP, continuous positive airway pressure; C-Flex, reduction of expiratory pressure during CPAP; Pm, expiratory pressure swing in the mask; Ps, expiratory pressure swing in the supraglottis; ΔPm, change in mask pressure swings (C-Flex 3 minus CPAP); ΔPs, change in supraglottic pressure swings (C-Flex 3 minus CPAP).

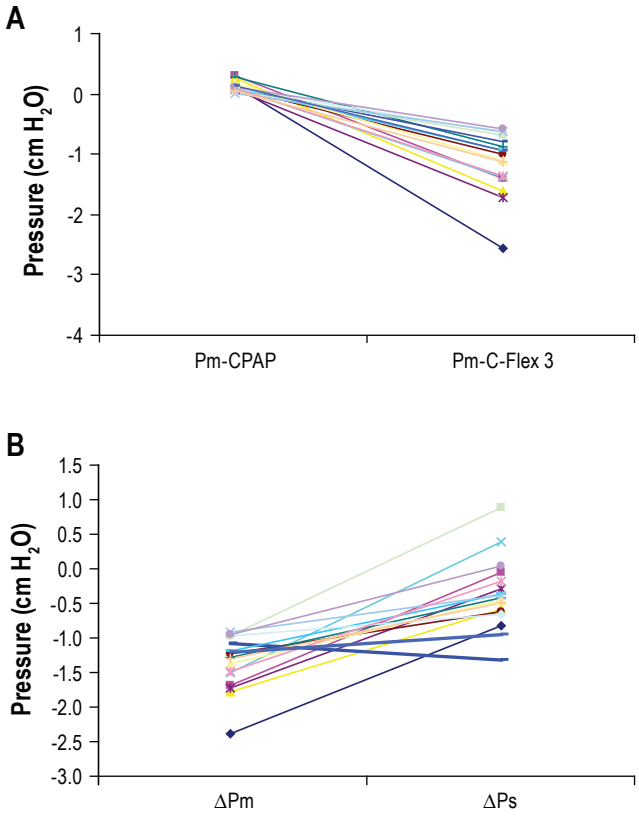

Figure 5—(A) Patients with obstructive sleep apnea-hypopnea syndrome—the effect of C-Flex compared with the effect of continuous positive airway pressure (CPAP) on mask pressure swings (Pm). Each line represents a patient (n = 17) with lines connecting the magnitude of expiratory pressure swing within the mask when the patient was using CPAP to the expiratory pressure swing within the mask when the patient was using C-Flex 3. All patients developed expiratory dips, and Pm showed reduction when patients were using C-Flex 3, compared with CPAP. **(B)** Patients with obstructive sleep apnea-hypopnea syndrome—the change in expiratory pressure swings with C-Flex 3. Each line represents a patient with lines connecting the change of expiratory mask pressure (Pm) between continuous positive airway pressure and C-Flex 3 and the change in expiratory supraglottic pressure (Ps). There was no transmission of the mask pressure swings to the supraglottis in 15 of the 17 patients (e.g., change in Pm [ΔPm] was more negative than change in Ps [ΔPs]). The 2 thick lines represent the 2 patients with a parallel drop in Pm and ΔPs.

tic pressure swings (Ps) were +3.30 ± 2.01 cm H_2O on low simulated UA resistance and +6.42 ± 4.60 cm H_2O on high simulated UA resistance.

Table 3 shows the effect of C-Flex compared with CPAP on mask and supraglottic pressure swings in the model data. The data across a range of imposed tidal volumes and frequencies are grouped according to whether there was a low or high simulated upstream "UA" resistance. In contrast with the findings during sinusoidal breathing, ΔPs was lower than the ΔPm ($P = 0.024$ for low simulated UA resistance and $P = 0.003$ for high simulated UA resistance). The lack of transmission of pressure swings from mask to supraglottis was most evident during the simulated high UA resistance.

Figure 6 combines the data in Tables 2 and 3 to contrast the effect of sinusoidal (Figure 6A) and "normal" nonsinusoidal (Figure 6B) breathing patterns on ΔPm and ΔPs in the model. Whereas there is a consistent transmission of mask pressure swings to the supraglottis in sinusoidal breathing patterns, mask pressure swings were NOT transmitted to the supraglottis during "normal" nonsinusoidal breathing (e.g., ΔPm was significantly more negative than ΔPs [$p = 0.024$ for low simulated UA resistance and $P = 0.003$ for high simulated UA resistance]).

Analysis of Expiratory Pressure-Time Curve

In addition to the analysis of the effect of C-Flex on expiratory peak pressures at the supraglottis, we also integrated the pressure-time curve as an estimate of expiratory work in patient and model data. This area measurement was used to re-evaluate the effectiveness of application of C-Flex to the UA of patients with OSAHS and our UA model (Figures 4C, 7). In Figure 7, for each condition (low and high resistance, sinusoidal and nonsinusoidal model data and patient data) the percentage change from CPAP to C-Flex 3 is shown for supraglottic expiratory pressure swings and expiratory area. We defined a change of 100% from the CPAP to C-Flex 3 value as complete reversal of the expiratory pressure swing in the supraglottis. In the UA model when UA resistance was low, application of C-Flex 3 produced complete reversal of expiratory Ps with sinusoidal breathing but produced a partial reversal with "normal" breath shape. Patients with OSAHS behaved similarly to the model data with "normal" breath and did not show much reversal of the expiratory pattern for Ps or Ws. When UA resistance was high, application of C-Flex 3 produced incomplete reversal of expiratory Ps and Ws in all cases for the model and patients. Thus, application of C-Flex reduced the integrated expiratory pressure in the supraglottis but not the peak (Figure 4C). This indicates that mask pressure is transmitted to the supraglottis but the transmission is not fast enough to reduce peak Ps. However, it does reduce the integrated pressure and may reduce expiratory work.

DISCUSSION

Our data show that, when mask pressure is constant during CPAP use, significant pressure swings occur in the supraglottis during expiration. The essential new finding of this study is

Table 2—Effect of C-Flex compared with CPAP on mask and supraglottic expiratory pressure swings in the mechanical model with sinusoidal breathing

Upper Airway Model	Change (C-Flex 3 minus CPAP)	
Sinusoidal respiratory pattern	**ΔPm (cm H_2O)**	**ΔPs (cm H_2O)**
Low upper airway resistance (0.028 ± 0.018 cm H_2O/L/min)		
RR 10 bpm, TV 450 ml	-0.80	-0.81
RR 16 bpm, TV 450 ml	-1.34	-1.25
RR 24 bpm, TV 450 ml	-1.26	-1.37
RR 12 bpm, TV 800 ml	-1.25	-1.44
RR 24 bpm, TV 800 ml	-2.5	-2.25
Total group	-1.43 ± 0.64	-1.42 ± 0.52
High upper airway resistance (0.059 ± 0.022 cm H_2O/L/min)		
RR 12 bpm, TV 450 ml	-0.89	-0.80
RR 16 bpm, TV 450 ml	-1.22	-1.02
RR 24 bpm, TV 450 ml	-1.35	-1.60
RR 12 bpm, TV 800 ml	-1.95	-2.04
RR 24 bpm, TV 800 ml	-2.13	-2.29
Total group	-1.51 ± 0.52	-1.55 ± 0.64

Values for total group are means ± standard deviation. RR, respiratory rate; TV, tidal volume; bpm, breath per minute; ΔPm, change in mask pressure swings (C-Flex 3 minus CPAP); ΔPs, change in supraglottic pressure swings (C-Flex 3 minus CPAP).

Table 3—Effect of C-Flex compared to CPAP on mask and supraglottic expiratory pressure swings in the mechanical model with exponential breathing

Upper Airway Model	Change (C-Flex 3 minus CPAP)	
Exponential respiratory pattern	**ΔPm (cm H_2O)**	**ΔPs (cm H_2O)**
Low upper airway resistance (0.040 ± 0.014 cm H_2O/L/min)		
RR 14 bpm, TV~500 ml	-2.45	-0.37
RR 28 bpm, TV~500 ml	-2.21	-0.38
RR 16 bpm, TV~(2× baseline) ml	-2.80	-1.63
Total group	-2.48 ± 0.3	-0.79 ± 0.72
High upper airway resistance (0.075 ± 0.004 cm H_2O/L/min)		
RR 16 bpm, TV~500 ml	-1.69	0
RR 26 bpm, TV~500 ml	-2.11	-0.09
RR 16 bpm, TV~(2× baseline) ml	-2.34	-0.47
Total group	-2.05 ± 0.33	-0.19 ± 0.25

Values for total group are means ± standard deviation. RR, respiratory rate; TV, tidal volume; bpm, breath per minute; ΔPm, change in mask pressure swings (C-Flex 3 minus CPAP); ΔPs, change in supraglottic pressure swings (C-Flex 3 minus CPAP).

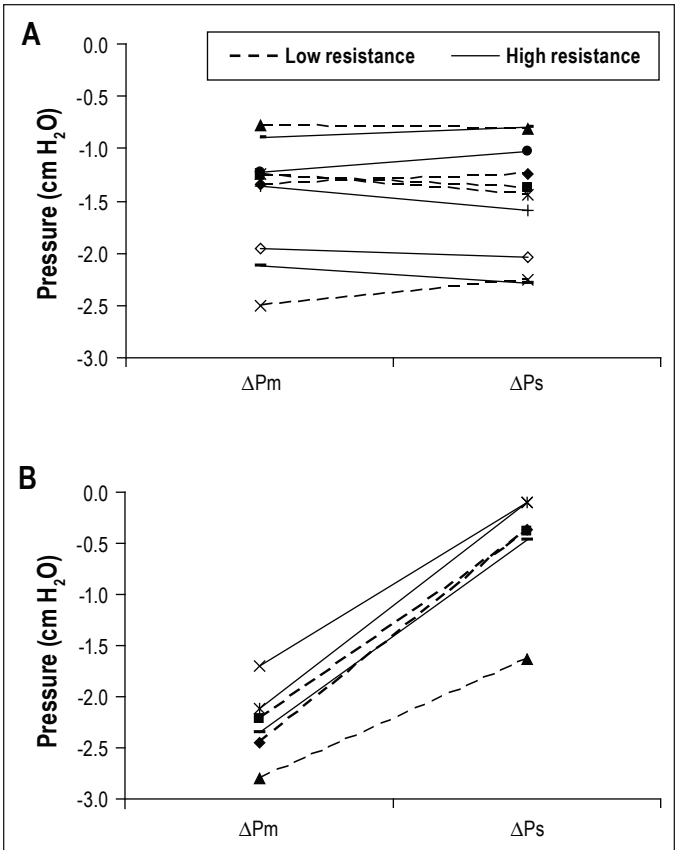

Figure 6—Upper airway model—change in expiratory pressure swings with C-Flex 3. Each line represents a different tidal volume or frequency. Dashed lines are simulations with low upper airway resistance, and the solid lines are simulations with high upper airway resistance connecting the change of expiratory expiratory mask pressure between continuous positive airway pressure and C-Flex 3 and the change of expiratory supraglottic pressure. **(A)** Sinusoidal respiratory pattern. There is a consistent transmission of expiratory mask pressure swings to the supraglottis (eg ΔPm is similar to ΔPs). **(B)** "Normal" (exponential expiration) respiratory pattern. Expiratory mask pressure swings were not transmitted to the supraglottis (eg ΔPm was significantly more negative than ΔPs).

that imposed expiratory changes in mask pressure produced by C-Flex did not uniformly transmit to the supraglottis in either patients with OSAHS on CPAP or in a mechanical model of the upper airway with a fixed resistance. Our model data comparing breaths with a sinusoidal shape to breaths with an exponential expiratory decay ("normal") of airflow suggest to us that the observed lack of expiratory drop in supraglottic pressure swings is related to dynamics of the C-Flex algorithm that controls mask pressure rather than to intrinsic properties of the upper airway.

In our mechanical model of the UA on CPAP, we found that, during expiration, as expected, high nasal resistance (upstream) produced greater pressure swings in the supraglottis than low nasal resistance. Only with a sinusoidal respiratory pattern did the expiratory pressure drop in the mask produced by C-Flex successfully mitigate the expiratory rise in pressure seen in the supraglottis, which is the intended purpose we attribute to C-Flex. In contrast, when tested in our model with breaths having the more physiologically typical exponential respiratory pattern, application of C-Flex caused little reduction of supraglottic pressure swings during expiration, despite a similar drop of mask pressure. Similarly, in the patients with OSAHS, application of C-Flex produced a drop in expiratory mask pressure in all patients; however, most patients did not demonstrate the expected fall in supraglottic pressures swings.

One explanation of our primary finding, i.e., that the C-Flex algorithm may not work as well with nonsinusoidal patterns of breathing as with pure sinusoidal expiration, may be related to

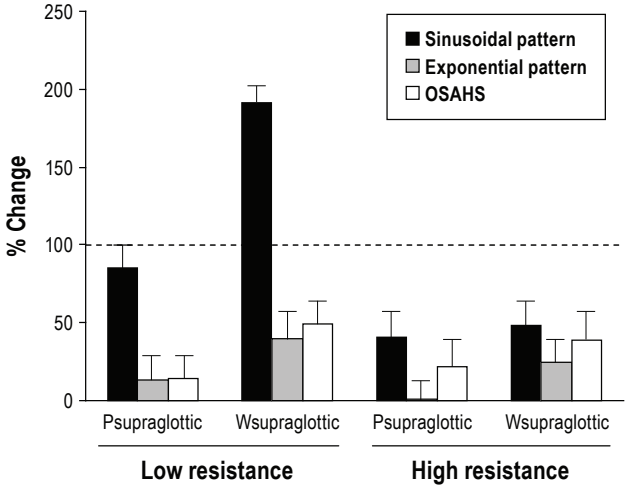

Figure 7—The effectiveness of application of C-Flex to the upper airway model and to patients with obstructive sleep apnea-hypopnea syndrome. The Y axis shows the percentage change from continuous positive airway pressure to C-Flex 3 values for peak expiratory supraglottic pressure and the estimated expiratory work (Ws) for conditions with low and high resistance. The black bars show data from simulations done using a sinusoidal respiratory pattern. The gray bars show data in simulations done using an exponential respiratory pattern. The white bars show data in patients with obstructive sleep apnea-hypopnea syndrome. On the left are shown data collected in situations of low resistance, and, on the right, with high resistance. The dashed line (100% change) represents complete reversal of the expiratory pressure swing in the supraglottis, defined by a change of 100% from the continuous positive airway pressure to C-Flex 3 value and is the desired result of applying C-Flex. See text for discussion.

the occurrence of rapid changes in flow during early expiration with an exponential pattern. Inspection of the pressure and flow tracings suggests that a phase delay in the pressure response to expiratory flow was present. Figure 8 shows a typical example from one patient. The drop in mask pressure occurs well after the initiation of the rise of supraglottic pressure during early expiration. This phase lag between flow and mask pressure, and the persistence of supraglottic pressure swings on C-Flex, was seen in all of the patients (mean phase lag 0.31 ± 0.06 sec; range, 0.19-0.42 sec) and also during the exponential expiratory pattern in the model data (mean phase lag 0.28 ± 0.10 sec; range, 0.15-0.41 sec). To further understand this phenomenon, we attempted to find a relationship between the presence of a phase lag between peak expiratory flow and peak mask expiratory pressure drop and respiratory frequency but were not able to do so within the range of respiratory patterns recorded. Thus, we cannot say with certainty whether the failure of C-Flex to abolish the expiratory supraglottic pressure swings was due to only a rapid change in expiratory flow or to some other aspect of nonsinusoidal breathing.

An alternate explanation of our findings of a lack of change in expiratory supraglottic pressure despite a drop in mask pressure during C-Flex *in the patients with OSAHS* is that there was unexplained development of *expiratory* flow limitation in the upper airway that occurred only in association with C-Flex. We are aware of no neural or mechanical reason for such a behavior of the relatively rigid nasal airway on CPAP. Specifically, the behavior of the UA while the patient is on CPAP should be relatively invariant because the collapsible segment of the UA that is usually responsible for changes in airway resistance during

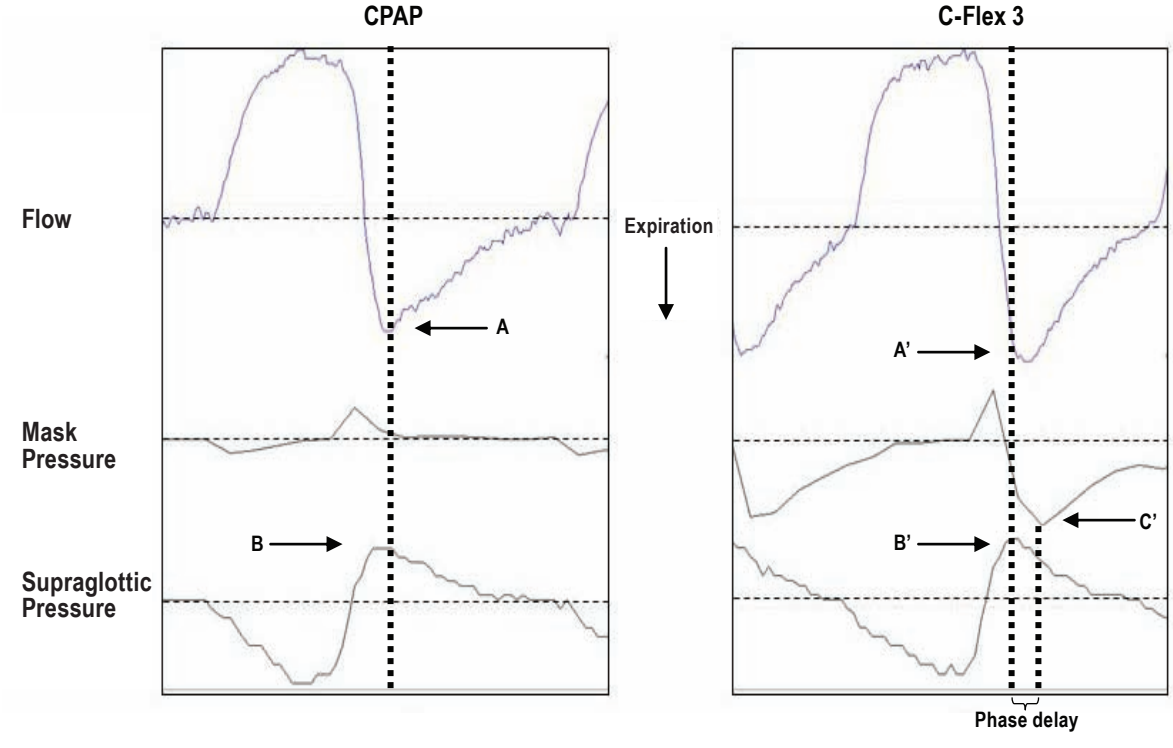

Figure 8—Phase delay in pressure response to expiratory airflow. Representative tracing of 1 breath obtained in 1 patient of airflow, mask pressure, and supraglottic pressure. A and A' indicate timing of expiratory peak flow on continuous positive airway pressure, and C-Flex, B, and B' indicate the peak of expiratory supraglotic pressure. C indicates the timing of peak drop in mask pressure on C-Flex. The phase delay is indicated.

sleep is being "splinted" throughout the respiratory cycle above optimal CPAP.

Although C-Flex did not show much effect on peak expiratory supraglottic pressure swings, we did record some reduction in the Ws, (our estimate of expiratory work). However, we achieved only a partial reversal of the "expiratory phenomenon" with the maximum available settings of C-Flex (Figure 7). We have no way of assessing whether comfort, or the perception of discomfort by a patient during expiration, is affected more by mitigating the peak pressure or by mitigating work of exhalation; this may need to be tested directly.

One limitation of our study is that we did not recruit patients based on nasal resistance and, thus, did not have a large number of patients with high nasal resistance. We could have attempted to increase the number of patients in this study who had high nasal resistance by recruiting based on awake subjects' complaints of nasal symptoms or on the results of testing obtained during wake (such as with rhinomanometry or acoustic rhinometry) that showed a high nasal resistance. However, we have previously shown that awake noninvasive measures of nasal resistance are not predictive of nasal resistance asleep.[38] Furthermore, despite a limited range in nasal resistances in the present data, we did show in the present dataset that, *on CPAP*, patients with high UA resistance had greater supraglottic pressure swings than did patients with low resistance.

A second possible limitation is that we did *not* specifically select patients who had reported intolerance to CPAP, and, in this study, we did not assess level of comfort. Thus, we cannot relate increased expiratory supraglottic pressure swings (or work) to perceived comfort on CPAP or an effect of C-Flex on reported comfort. However, this was not the objective of the present study. Furthermore, our patients were being studied during a first exposure to CPAP, during which they had multiple interventions (CPAP titration, trial with different settings of C-Flex), and these circumstances would have made collecting patients' acute impressions of comfort difficult to interpret.

A final caveat exists in interpreting the results of these data: by design, we studied the effect of C-Flex-induced pressure drops at the mask on supraglottic pressure in patients only *during sleep;* "comfort" may be partially or wholly affected by the conditions *during wake*. The analysis reported here is based on measurements made during stage N2 sleep; in our current data set, we did not record much data when subjects were breathing in the wake state. In the limited wake periods available for analysis, we saw no trends toward a greater transmission of mask to supraglottic pressure swings while patients were on C-Flex.

In conclusion, we were not able to show that C-Flex reduces expiratory pressure swings in the supraglottis in patients with OSAHS on CPAP during sleep. Although C-Flex did succeed in reducing "supraglottic" pressure swings in our modeling studies using sinusoidal breathing, the magnitude of C-Flex mask-pressure reductions was not sufficient to eliminate expiratory supraglottic pressure swings at *any* setting for other patterns. These nonsinusoidal model data are similar to the data in patients. Our observations suggest that maximum potential physiologic impact of C-Flex on supraglottic pressure may not have been achieved by the present algorithm, and this may account for the recent data showing little effect of C-Flex use on overall CPAP compliance.[29,30] Because there was surprisingly little physiologic expiratory effect at the supraglottis of C-Flex during sleep with the present implementation of expiratory pressure modification by C-Flex, it is not possible to test the hypothesis that optimal mitigation of supraglottis expiratory pressure swings will improve patient comfort and compliance. However, if C-Flex does improve comfort, it is unlikely to do so by the mechanism of reducing the peak expiratory supraglottic pressure

ABBREVIATIONS

CPAP, continuous positive airway pressure
OSAHS, obstructive sleep apnea/hypopnea syndrome
UA, upper airway
Pm, mask pressure
Ps, supraglottic pressure
ΔPm, delta mask pressure
ΔPm, delta supraglottic pressure
Ws, integral of pressure × expiratory time (surrogate for expiratory work)

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