AN AWAKE TEST TO MEASURE UPPER AIRWAY COLLAPSIBILITY IN ADOLESCENTS

Negative Expiratory Pressure Technique: An Awake Test to Measure Upper Airway Collapsibility in Adolescents

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Study Objectives: Upper airway (UA) collapsibility is a major pathophysiologic feature of the obstructive sleep apnea syndrome (OSAS). In adolescents, it is measured by obtaining the slope of pressure-flow relationship (SPF) while applying negative nasal pressure during sleep. An easier technique to assess UA collapsibility, consisting of application of negative expiratory pressure (NEP) during wakefulness, has demonstrated differences between control and OSAS subjects. We hypothesized that the NEP technique would correlate with SPF as a measurement of UA collapsibility in adolescents.

Design: During wakefulness, NEP of −5 cm H_2O in the seated and supine position was applied during the first second of expiration. The area under the expiratory flow-volume curve during NEP was compared to tidal breathing (RatioNEP). In addition, adolescents underwent SPF measurements during sleep. Two SPF techniques were performed to measure the activated and relatively hypotonic UA.

Setting: Pediatric sleep laboratory.

Participants: Seven adolescents with OSAS and 20 controls.

Results: In the seated position, there was a correlation between RatioNEP and both hypotonic SPF (r = −0.39, P = 0.04) and activated SPF (r = −0.62, P = 0.001). In the supine position, there was a correlation between RatioNEP and activated SPF (r = −0.43, P = 0.03) and a trend for hypotonic SPF (r = −0.38, P = 0.06).

Conclusions: The negative expiratory pressure (NEP) technique correlates with the hypotonic and activated slope of pressure-flow relationship measurements. The seated position showed the strongest correlation. The NEP technique can be used as an alternative method to evaluate upper airway collapsibility in adolescents.

Keywords: upper airway collapsibility, obstructive sleep apnea syndrome, negative expiratory pressure technique, adolescents

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INTRODUCTION

The pathophysiology of the obstructive sleep apnea syndrome (OSAS) is likely multifactorial with contributions from airway anatomy, the state-dependent control of upper airway (UA) dilator muscles, arousability, and ventilatory stability.[1,2] A collapsible pharyngeal airway is required in the pathogenesis of OSAS. As UA collapsibility is a major pathophysiological factor, techniques have been developed to assess it. An objective measurement of UA collapsibility is the critical pressure (P_{crit}) at which the pharynx collapses. It is obtained by measuring pressure changes via a mask during sleep.[3–5] P_{crit} is the linear extrapolation of the inspiratory flow versus the mask pressure to the zero flow x-intercept. Adults with OSAS have a more collapsible UA than controls, with the P_{crit} being close to atmospheric pressure. Although children and adolescents with OSAS have a higher P_{crit} than healthy children, the UA in healthy children and adolescents is very resistant to collapse. As UA collapse in this population may not occur even at substantial subatmospheric pressures, the P_{crit} intercept often cannot be determined without extreme extrapolation. Therefore, the slope of the pressure-flow relationship (SPF) is considered a more reliable measurement, as it quantifies overall sensitivity of the change in flow to pressure.[6–8] Children and adolescents with OSAS have a steeper (higher) SPF, indicating a more collapsible UA than those without OSAS. SPF is performed using two types of pressure challenges, which differ by degree of neuromuscular activation allowed. The relatively hypotonic technique consists of intermittent pressure drops from a positive holding pressure to minimize the effect of UA neuromuscular activation. By contrast, the activated technique uses a progressive drop in airway pressure, allowing UA muscle activation to proceed. Measurement of the airway structural factors under minimal muscle activity is evaluated with hypotonic SPF; measurement combining both structural and neuromuscular activity is assessed with activated SPF.[7,9,10] The SPF technique requires highly specialized personal and equipment; it is labor intensive and time consuming and only available in select research centers.

An alternative, less cumbersome, and easier method is the negative expiratory pressure (NEP) technique that has been developed for children and adults. The NEP technique provides a simple, quick, noninvasive test to measure expiratory flow limitation during wakefulness.[11–14] The technique consists of applying a timed negative pressure at the mouth during early expiration while the subject is awake and breathing quietly. The obtained expiratory flow-volume curve is compared with the curve of the preceding expiration. The application of

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negative pressure at the airway opening increases the expiratory pressure gradient between alveoli and airway opening, thereby increasing expiratory flow if the subject is not flow limited. Studies have shown that the flow-volume curve obtained during NEP is usually higher than the flow-volume curve of the preceding expiration in both normal subjects and subjects with OSAS; however, this effect is lessened or even absent in snorers and subjects with OSAS.[15–18] In our previous study, we determined that the NEP technique could distinguish between controls and children with sleep-disordered breathing (SDB). We also found overlapping values between snorers and OSAS, similar to previous studies in adults.[19] Therefore, we considered it appropriate to investigate whether the NEP test measured UA collapsibility in a manner consistent with SPF measurements during sleep in our sample.

The pathophysiology of adolescent OSAS differs from that observed in adults. Compared with adults, adolescents have a less collapsible UA in response to negative pressure continuously applied during sleep, a greater ventilatory drive, and increased UA neuromotor activation.[20–22] The robust UA muscle activity during wakefulness and sleep in adolescents could influence the relationship between NEP and SPF.[22] One study in adults suggested that NEP evaluates the hypotonic UA because it is correlated with the hypotonic P_{crit}.[23] In our previous study, we observed a small increase in UA muscle activity during NEP when measured by intraoral electromyography (EMG).[19] Thus, UA muscle activity may influence NEP measurement and could potentially correlate with the activated SPF which evaluates structural and neuromuscular factors. To our knowledge no studies of NEP have been conducted to evaluate its correlation with activated P_{crit} in adult or pediatric subjects.

As NEP is applied during wakefulness, it is possible to perform it in the seated and supine positions. It has been demonstrated that there is increased UA collapsibility in the supine position compared to the lateral position during sleep.[24] NEP studies, including ours, have suggested increased flow limitation in the supine compared to seated position.[12,14,19] In addition, we observed a slight increase in UA muscle activity in the supine position, indicating that some degree of UA muscle activation was being elicited. Therefore, positional differences in UA collapsibility could be relevant to determine the NEP position with the strongest SPF measurement correlation.

Overall, it is not known if NEP and SPF measurements of UA collapsibility in adolescents are correlated and if the NEP technique evaluates different components of UA collapsibility (hypotonic and/or activated SPF). Furthermore, the effect of positional differences on the correlation between NEP and SPF measurements is unknown. We hypothesized that the NEP technique in adolescents correlates with the hypotonic and activated SPF measurements, and potentially could serve as an alternative measure of UA collapsibility. We also hypothesized that differences in this correlation could be found in the hypotonic and activated state as well as in seated and supine positions.

METHODS

Data were obtained from adolescents with OSAS and controls who had participated in previous research studies.[19,22] Baseline polysomnography was performed to evaluate for OSAS. On a separate night, SPF and surface genioglossal electromyographic activity (EMG_{gg}) were measured during NREM sleep. Subjects also underwent NEP testing during wakefulness with the same intraoral electrodes. Spirometry was performed. The institutional review board at the Children's Hospital of Philadelphia approved the study. Informed consent was obtained from the parents/legal guardians of the subjects, and assent from the subjects.

Study Group

Two groups of individuals aged 12–16 years old were recruited: the OSAS group (defined as having an apnea-hypopnea index [AHI] $\geq$ 5/h) and the Control group (AHI < 1.5/h; no snoring).[25–27] The lower age limit was chosen to exclude subjects too young to participate with the experimental setup and the older age limit to exclude those whose physiology may resemble that of adults. The OSAS group was recruited from the Sleep Center at The Children's Hospital of Philadelphia. The control group, consisting of asymptomatic adolescents without a history of snoring, was recruited from the general population through advertisements. Inclusion criteria included no significant medical conditions other than OSAS. Exclusion criteria included prior adenotonsillectomy, major medical illnesses, and medications affecting the central nervous system. Because many children with OSAS have asthma,[28] children with asthma were included if symptoms were well controlled, spirometry was normal (forced vital capacity [FVC] and forced expiratory volume in 1 second [FEV_1] $\geq$ 80% predicted and FEV_1/FVC $\geq$ 80%) on the day of study, and albuterol had not been used on the day of study.

Polysomnography

Baseline overnight polysomnography (using Rembrandt, MedCare, Buffalo, NY) was performed using standard pediatric techniques.[29] The following parameters recorded: electroencephalograms (EEG) (F3/A2, F4/A1, C3/M2, C4/M1, O1/M2, O2/M1), electroculograms, submental and tibial electromyograms, chest and abdominal wall movement by inductance plethysmography (Respitrace, Ambulatory Monitoring Inc., Ardsley, NY), ECG, airflow by nasal pressure (Pro-Tech, Mukilteo, WA) and 3-pronged thermistor (Pro-Tech, Woodinville, WA), end-tidal PCO_2 (Novametrix 7000; Novametrix, Wallingford,CT), arterial oxygen saturation and pulse waveform, (Masimo, Irvine, CA or Nonin, Plymouth, MN) and digital, infrared video. Sleep architecture and respiratory parameters were analyzed using standard pediatric criteria.[29]

Spirometry

Spirometry (Morgan Scientific, Inc., Haverhill, MA) was performed using standard pediatric methods[30] in order to rule out pulmonary disease.

EMG_{gg}

EMG recordings during NEP were obtained using noninvasive, intraoral mouthpieces that were custom molded for each subject.[21] An impression of the sublingual fossa and lower teeth was made using a dental-grade, vinyl silicone putty (Splash!, Wennigsen, Germany) and a dental mandibular tray modified to allow impression material to contact the floor of the mouth

so that the material was closely opposed to the lower surface of the tongue. The mold enclosed the inferior front 4–5 teeth, and was then trimmed to remove excessive bulk. Unipolar surface electrodes made of 30-gauge Teflon-coated stainless steel wire (Sequim, WA) were sewn into the inferior surface of the mold. EMG signals were amplified, rectified, and integrated on a moving-time-average basis, with a time constant of 200 ms. The impedance was checked before each study to ensure it was < 20 Ω. Mask pressure, tidal volume, airflow, and EMG were collected at 200Hz using PowerLab software (ADInstruments, Colorado Springs, CO). Volume was obtained by integration of the flow signal. Data analysis was performed using custom software (PowerBasic, Inc, Englewood, FL).

NEP Measurements during Wakefulness

Flow was measured with a heated pneumotachograph (Hans-Rudolph, Inc., Shawnee, KS) with a linear range of ± 2.6 L/s, connected to an oronasal mask (Philips Respironics, Andover, MA) and a differential pressure transducer (Validyne, Northridge, CA). An oronasal mask was used, as many children with OSAS are mouth-breathers, and also to avoid interference with the EMG mouthpiece. Pressure was measured at the mask via a noncompliant tube connected to a differential pressure transducer (Validyne). A customized device capable of rapidly generating negative pressure (Phillips Respironics, Andover, MA) was connected to the pneumotachograph via a 2-way balloon valve (Hans-Rudolph). The balloon valve was activated by custom-written software when inspiratory flow reached a threshold level between 0.01–0.05 L/s, taking into account the time delay for balloon inflation (TestPoint, SuperLogics, Inc., Natick, MA). At that point, negative (subatmospheric) pressure was delivered during early expiration (within 0.1–0.2 sec) for 1 second. Flow and pressure transducers were calibrated prior to each study.

Tidal breathing and NEP (at −5 cm H_2O) flow-volume curves were obtained in both the supine and seated positions. Subjects sat comfortably while wearing the EMG mouthpiece and oronasal mask, and were distracted by watching television. First, in order to evaluate EMG_{gg} activity and distinguish voluntary movements such as swallows, subjects performed maximal genioglossal maneuvers such as protruding their tongue as forcibly as possible, and swallowing. To avoid artifact, the EMG_{gg} signal was assessed at the beginning and end of each trial and compared with the previous maneuvers and recordings. Furthermore, the EMG signal was displayed on the screen continuously during the study, allowing for the identification of artifact if the intraoral mouthpiece moved. After a period of regular quiet breathing, NEP was triggered automatically during early expiration and was maintained for 1 second. NEP was applied when inspiratory and expiratory tidal volumes were equal, using accepted guidelines for measuring tidal volume.[31] NEP was repeated several times in the seated and supine positions.

SPF and EMG_{gg} Measurements during Sleep

SPF was measured during a second overnight polysomnogram as previously described.[6,7,32] Routine polysomnographic measurements were obtained. In addition, the subject wore a continuous positive airway pressure oronasal mask (Philips Respironics, Murrysville, PA). Airflow was measured with a heated pneumotachometer (Hans Rudolph, Inc.) and pressure transducer (ADInstruments) attached to the mask. Nasal pressure (P_N) was measured at the mask with a differential pressure transducer (Validyne) referenced to atmosphere. Intraoral surface EMG_{gg} signals were obtained simultaneously from the subject's personal EMG mouthpiece.[7,8,21,33] Signals were acquired on a PowerLab system (ADInstruments) and simultaneously displayed on a Rembrandt polysomnography system (Embla, Denver, CO). P_N was altered in either a positive or subatmospheric direction, using the same device as for NEP (Phillips Respironics, Andover, MA). A toggle switch allowed the subject to be switched rapidly between positive and negative nasal pressure, ranging from −25 to +30 cm H_2O. Two techniques were applied to decrease the nasal pressure below the level of the holding pressure, resulting in an activated and relatively hypotonic upper airway, respectively.[7,9] For both techniques, the holding pressure, i.e., the P_N just above the pressure at which flow limitation first became discernible, was determined. Inspiratory airflow limitation was considered to occur when airflow failed to increase despite increasing respiratory effort, as demonstrated by the characteristic flow waveform consisting of increasing inspiratory flow followed by a mid-inspiratory plateau.[6] For the activated technique, the run was initiated at the holding pressure. P_N was then decreased in 2 cm H_2O steps every 5 breaths until the subject had an arousal or obstructive apnea. For the hypotonic technique, P_N was acutely decreased by 2 cm H_2O from the holding pressure for 5 breaths, following which it was rapidly returned to the holding pressure. P_N was dropped repeatedly to incrementally lower levels, with a return each time to the holding pressure, until either arousal or obstructive apnea occurred. This technique results in an upper airway with minimal activation during the first 3 breaths of negative pressure, and most of the changes in EMG activation are appreciated after the first 3 breaths.[7,32] Multiple trials using either of the 2 techniques in random order were performed during stable NREM sleep. For each technique, the trial reaching the lowest P_N before arousal/apnea was selected for data analysis.

RatioNEP was also correlated with the ratio of the peak inspiratory flow at P_N of 0 cm H_2O to the peak inspiratory flow on near-optimal P_N (CPAP) during sleep as a post hoc comparison in order to correlate RatioNEP with a more physiologically equivalent measurement (i.e., flow). The normalized peak flow was the peak flow at atmospheric pressure (P_N = 0 cm H_2O) divided by the peak flow at nearly optimal CPAP. The peak flow at P_N (CPAP) at 0 cm H_2O during sleep was estimated from the pressure-flow curves obtained during the P_{crit} protocol. Ideally, optimal flow on P_N sufficient to overcome flow limitation should be used as the denominator, but this data point was unavailable for the post hoc comparison as the protocol utilized a holding pressure at the point where flow limitation had just become apparent. Therefore, the holding pressure was used as the near-optimal P_N.

Data Analysis

RatioNEP

The flow-volume curve obtained during NEP was compared to the flow-volume curve of the preceding breath. We established a parameter termed RatioNEP as the ratio of the area

Table 1—Demographic and polysomnographic data.

	OSAS Group	Control Group	P value
N	7	20	
Age (yr)	15.0 ± 1.4	14.7 ± 1.5	0.69
Male, n (%)	6 (85.7)	10 (50)	0.09
Body mass index (kg/m^2)	36.6 ± 7.2	23.4 ± 6.9	< 0.0001
Body mass index z-score	2.5 (1.7–3.0)	0.7 (−3.8–2.7)	< 0.001
Apnea-Hypopnea Index (n/r)	38.6 (6.6–91.5)	0.1 (0–1.2)	< 0.0001
Arterial oxygen saturation nadir during sleep (%)	83 (88–95)	95 (88–97)	< 0.0001
Percentage of total sleep time with oxygen saturation < 90% (%)	3.1 (0–27.4)	0 (0–0)	< 0.0001
Percentage of total sleep time with end-tidal carbon dioxide > 50 mm Hg (%)	6.8 (0–50.7)	0.2 (0–2.5)	0.009

Data presented as mean ± standard deviation for normally distributed data and median (range) for nonparametric data. OSAS, obstructive sleep apnea syndrome.

under the flow-volume curve during NEP to the preceding flow-volume curve at the same time point (1 sec). Area under the curve of the flow-volume curve was used as it has been shown that this formula seems most sensitive in identifying lung measurement abnormalities.[34] Previous studies have used the area under the curve for NEP determination,[14] but we used a modification whereby the flow-volume curves (normal tidal breathing and NEP) were aligned by time at 1 second, in order to account for the age-related variability in respiratory rate and tidal volume in children.[19] The area under the curve was taken as the area under the flow-volume curve between 0 and 1 second, starting from the time at which the NEP pulse began. The average of the best NEP maneuvers (based on lack of EMG or respiratory artifacts, similar tidal volume, regular waveforms and similar expiratory times) in each subject was used for analysis. On average, 6 breaths were analyzed for each position.

RatioEMG

Similarly, EMG_{gg} area under the curve during NEP as a ratio of baseline was measured.

SPF

For the activated runs, the average mid-inspiratory flow was taken from the lowest two consecutive breaths at each level of pressure. For hypotonic runs, data were taken from the first 3 breaths after the pressure drop. Pressure-flow curves were constructed based on analysis of flow-limited breaths by plotting maximal inspiratory airflow (V_{Imax}) against P_N. P_N vs. V_{Imax} curves were fitted by least squares linear regression, and the slope of the pressure-flow curve (SPF) was determined in order to characterize the UA response.[6,20,32]

Statistical Analysis

Statistical analysis was performed with SPSS software version 21.0 for Windows (IBM Corp. SPSS Statistics for Windows, Version 21.0. Armonk, NY). The Kolmogorov-Smirnov test was used to test for normality. For demographic values, descriptive statistics were computed for each group. Categorical data (sex) were compared using the χ^2 test. Noncategorical data were presented as mean and standard deviation when the data were normally distributed and differences between groups were examined with the unpaired t-test. When the data were not normally distributed, data were presented as median and range, and differences between groups were examined with Mann-Whitney nonparametric tests. For each of the outcomes (RatioNEP in both positions, RatioEMG and SPF in both states), Mann-Whitney nonparametric tests were used to examine differences between groups and Wilcoxon matched-pairs signed-ranks were used to compare differences within the each group.

Linear regression was performed between RatioNEP and SPF for both positions and states using Pearson correlation and the coefficient (r) was determined. A P value of < 0.05 was used for statistical significance. A sample size of 29 subjects was the number of subjects required for obtaining a Pearson coefficient equal or greater than 0.5. Due to higher variability in controls than in OSAS subjects, we recruited a proportion of 1 OSAS: 3 Controls.

RESULTS

Study Group

Seven subjects with OSAS and 20 controls were studied. Subject characteristics are shown in Table 1. Adolescents with OSAS were more likely to have a higher BMI z-score.

RatioNEP and RatioEMG Comparisons between and within Groups

Differences in RatioNEP between and within groups are shown in Table 2. As previously shown,[19] RatioNEP was significantly lower (indicating a more collapsible UA) in the OSAS group than in controls. In both positions, RatioNEP differed between controls and OSAS ($P < 0.001$ and $P = 0.002$ in seated and supine positions, respectively). RatioNEP was generally lower in the supine compared to the seated position, although significant positional differences were found only in the control group ($P < 0.001$). For RatioEMG, no significant differences were found between groups in either position.

Slope of Pressure-Flow Curve Comparisons between and within Groups

Comparisons of hypotonic vs. activated SPF between and within groups are shown in Table 2. As previously shown,[22] activated SPF was significantly higher (more collapsible) in

Table 2—SPF and RatioNEP comparisons between and within groups.

	Slope of pressure-flow curve (SPF, ml/sec/cm H_2O)				
	OSAS		Control		OSAS vs. Controls
	Hypotonic	Activated	Hypotonic	Activated	
Median	20.68	18.09	9.06	5.37	Hypotonic SPF: P = 0.06
Range	5.99–40.92	8.65–49.28	−8.63–39.16	−8.84–30.51	Activated SPF: P = 0.002
	P = 0.86		P = 0.28		

	RatioNEP				
	OSAS		Control		OSAS vs. Controls
	Seated	Supine	Seated	Supine	
Median	2.04	1.47	2.81	2.34	RatioNEP seated: P < 0.001
Range	0.9–2.23	1.13–2.15	1.94–4.24	1.39–4.49	RatioNEP supine: P = 0.002
	P = 0.09		P < 0.001		

OSAS, obstructive sleep apnea syndrome.

the OSAS group compared with controls (P = 0.002). However, hypotonic SPF was similar between groups, indicating that some controls had a structural UA predisposed to collapse. Within the OSAS group, no difference in SPF was observed under activated or hypotonic conditions, indicating high UA collapsibility in both states. A wide range of hypotonic SPF values was found in the control group (i.e., high variability in the mechanical properties of the UA within controls) with a trend for a higher hypotonic than activated SPF (which was significant for the larger study group in the reference study).

RatioNEP and SPF Correlation

The data and linear regression of RatioNEP and SPF are depicted in Figures 1–4. In the seated position, there was an inverse correlation between RatioNEP and SPF in both states (hypotonic r = −0.39, P = 0.04; activated r = −0.62, P = 0.001). This significant interaction between RatioNEP and the SPF exhibited a different slope in each state (−6.5 mL/sec/cm H_2O for hypotonic SPF and −12.1 mL/sec/cm H_2O for activated SPF). In the supine position, the correlation between RatioNEP and hypotonic SPF showed a trend although significance was not reached (r = −0.38, P = 0.06). An inverse correlation between RatioNEP and activated SPF was found (r = −0.43, P = 0.03) with a lower slope (−9.0 mL/sec/cm H_2O) than the relationship in the seated position.

In the seated position, there was a correlation between RatioNEP and normalized peak flow at P_N 0 cm H_2O in both states (hypotonic r = 0.52, P = 0.007; activated r = 0.55, P = 0.004). In the supine position, there was also a correlation between RatioNEP and normalized peak flow at P_N 0 cm H_2O in both states (hypotonic r = 0.47, P = 0.03; activated r = 0.43, P = 0.04).

DISCUSSION

The major finding in our study is that the NEP technique in the seated position correlates with the SPF measurements, supporting the NEP technique as an alternative awake test to measure UA collapsibility in adolescents. Adolescents with OSAS have a more collapsible UA than controls as measured by the SPF during sleep and by NEP during wakefulness, with a good correlation between the two methods.

Correlation between RatioNEP and Hypotonic and Activated SPF

The NEP technique in the seated position showed a good correlation with both measurements of UA collapsibility during sleep, the hypotonic and activated SPF. The SPF characterizes the flow response to changes in nasal pressure during sleep. A high SPF corresponds to a highly collapsible UA. The hypotonic SPF is obtained with intermittent nasal pressure drops in order to minimize the UA muscle activation and primarily reflects the structural UA collapsibility. The activated SPF is obtained with a gradual drop in nasal pressure allowing muscle activation, and reflects both the structural and neuromotor components. The good correlation between RatioNEP and both measures of SPF indicates that RatioNEP is assessing UA structural and neuromuscular factors. The interaction of the structural (anatomic) factors with the effectiveness of neuromuscular compensation (UA reflexes) is key to the pathogenesis of OSAS.

Moreover, the current study demonstrated that the NEP technique had a stronger correlation with the activated SPF than the hypotonic SPF. Although the major cause for pediatric OSAS is considered to be adenotonsillar hypertrophy, residual OSAS persists in about 20% of children after adenotonsillectomy,[35] with a possibly higher percentage of residual OSAS in adolescents. This suggests that factors other than anatomical factors contribute to the presence of OSAS. In adolescents, neuromuscular factors appear to play an important role in addition to structural factors.[22] Therefore, it is not surprising that a relationship between measures of activated SPF and NEP can be demonstrated. In our previous study, we speculated that the NEP technique evaluated the hypotonic SPF (i.e., the structural properties of the UA) as the NEP technique had been correlated with the passive (hypotonic) P_{crit} in adults. Montemurro et al.[23] found a strong correlation between $V_1NEP_{0.5}$ (volume exhaled in the 1st 0.5 sec after NEP of −5 cm H_2O; a measurement obtained with the NEP technique in the supine position) and the hypotonic P_{crit}, although they did not measure the active P_{crit}. The difference in relationships between the age groups could be related to differences in UA muscle activity observed between adolescents and adults. Most adolescents have a robust compensatory neuromuscular response

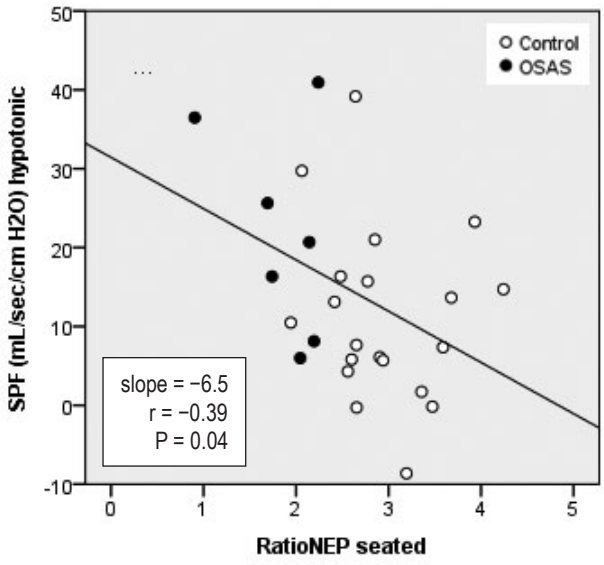

Figure 1—Correlation between hypotonic SPF and RatioNEP seated. Slopes of the hypotonic pressure-flow curves (SPF) plotted against RatioNEP obtained in the seated position for adolescent controls and adolescents with OSAS. There was a significant inverse correlation between hypotonic SPF and RatioNEP seated (r = −0.39; P = 0.04) with a slope of −6.5 mL/sec/cm H_2O. Higher hypotonic SPF correlated with lower RatioNEP, indicating high upper airway collapsibility.

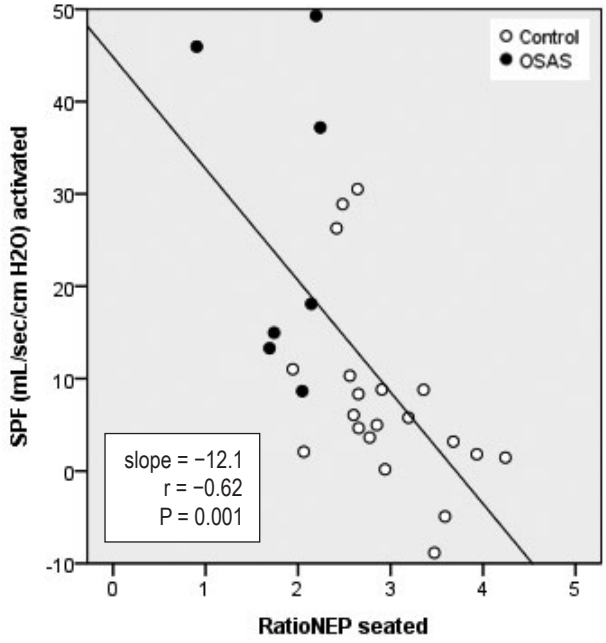

Figure 2—Correlation between activated SPF and RatioNEP seated. Slopes of the activated pressure-flow curves (SPF) plotted against RatioNEP obtained in the seated position for adolescent controls and adolescents with OSAS. There was a significant inverse correlation between activated SPF and RatioNEP seated (r = −0.62; P = 0.001) with a slope of −12.1 mL/sec/cm H_2O. RatioNEP obtained in the seated position showed the strongest correlation with activated SPF.

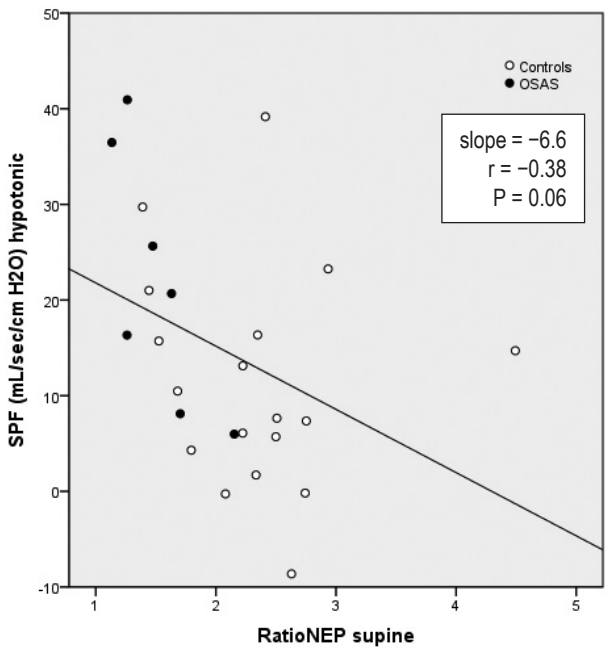

Figure 3—Correlation between hypotonic SPF and RatioNEP supine was not significant. Slopes of the hypotonic pressure-flow curves (SPF) plotted against RatioNEP obtained in the supine position of adolescent controls and adolescents with OSAS. There was a nonsignificant trend for a correlation between hypotonic SPF and RatioNEP supine (r = −0.38; P = 0.06).

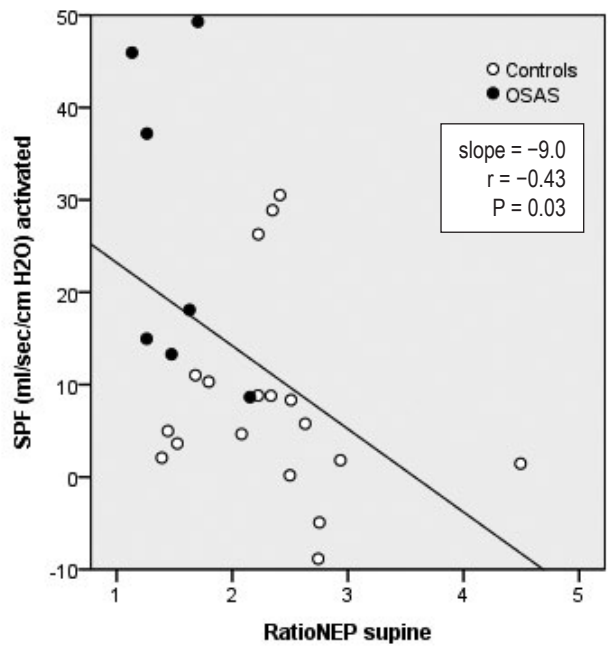

Figure 4—Correlation between activated SPF and RatioNEP supine. Slopes of the activated pressure-flow curves (SPF) plotted against RatioNEP in the supine position for adolescent controls and adolescents with OSAS. There was a significant inverse correlation between activated SPF and RatioNEP supine (r = −0.43; P = 0.03) with a slope of −9.0 mL/sec/cm H_2O. The correlation between activated SPF and RatioNEP was weaker in the supine position than in the seated position.

to subatmospheric pressure loads during sleep, making them less likely to develop UA collapse.[6] This reflex decreases with age.[7] Therefore, NEP correlation with activated P_{crit} may be different in adults, in whom UA muscle activity during sleep is diminished.

Effect of Position on the Correlation between RatioNEP and SPF

The study showed a decrease in both the strength of the correlation and the slope between RatioNEP and activated SPF in the supine compared to the seated position. Thus, in the supine position the relationship between RatioNEP and hypotonic SPF showed a trend correlation although not significant ($r = -0.38$, $P = 0.06$) and only correlated with activated SPF ($r = -0.43$, $P = 0.03$). The weakness of the correlation between SPF and RatioNEP in the supine position compared to the seated position might be due in part to the reduced spread of RatioNEP values when the UA is more severely compromised. Those subjects with more severe UA collapsibility could invoke a compensatory function during wakefulness in the supine position which is somewhat genioglossus independent (i.e., recruitment of muscles for jaw repositioning and positioning of the head and neck to allow more favorable airflow and not related to UA muscle activity during sleep. This is in accordance with the study conducted by Martin et al. showing that adults with OSAS during wakefulness had a significantly smaller decrease in oropharyngeal area (measured by the acoustic-reflection technique) from the seated to the supine position than did the snorers and the group of BMI- and neck circumference-matched controls.[36]

During sleep, it has been demonstrated that the supine position increases UA collapsibility compared to the lateral position.[24] NEP studies,[12,14] including ours, have suggested increased flow limitation in the supine compared to the seated position. Lower RatioNEP (i.e., greater collapsibility) in the supine position compared to the seated position in our group overall may be considered further validation of the NEP technique. However, the increased UA collapsibility in the supine position compared to the seated position did not reach statistically significance in children with OSAS in our previous study. Thus, as mentioned above, those with a more severely compromised UA could have compensatory mechanisms elicited in the supine position in order to prevent a compromised UA during wakefulness. Several factors can account for the increased UA collapsibility observed in the supine position. Reductions in lung volume result in decreases in caudal traction on the UA and a concomitant increase in UA collapsibility.[37–39] The direct effect of gravity on tissues anterior to the UA lumen (e.g., genioglossus) is a possible mechanism for increased collapsibility in the supine position. In addition, supine positioning promotes laryngeal edema and UA narrowing.[40,41] We observed a slight increase in UA muscle activity in the supine position. Although some muscle activation was elicited in the supine position (higher RatioEMG in the supine than in the seated position), there was no difference in the pattern of UA muscle activity between groups when NEP was applied. The mechanisms of altered UA collapsibility differ between positions. Thus, the positional difference in the relationship between RatioNEP and each SPF state is likely related to the change in contributing factors to UA collapsibility due to the position, rather than being related to different response to the NEP technique in each group. Interestingly, Baydur et al.[42] found that mechanisms to preserve patency in supine chronic obstructive pulmonary disease (COPD) patients seem not to be as effective as in supine individuals with OSAS. However, studies in adults with SDB showed that the differences between adult controls, snorers and OSAS subjects were less significant in the seated position.[12] Mechanisms underlying this postural effect may be different in adolescents compared to adults. Although the supine position during wakefulness elicited some genioglossal activation, it is similar for both groups. The important role that UA muscle activity plays in adolescents likely caused the NEP technique to only correlate significantly with the activated SPF, in the supine position.

As the impact of position on NEP measurements seems of particular importance in adolescents, we recommend performing the NEP technique in the seated position (i.e., the position with the strongest correlation).

NEP Technique: Tool to Evaluate UA Collapsibility, Not to Distinguish Snorers from OSAS

The potential interest for application in the pediatric population is that the NEP technique requires little cooperation. Several studies have shown the feasibility of the NEP technique in children and adolescents who are healthy or have respiratory diseases (asthma or cystic fibrosis).[43–45] Thus, Tauber et al. demonstrated that intrathoracic flow limitation was uncommon detected by NEP even when it was present by conventional PFT (e.g. severe obstructed children with cystic fibrosis).[43] D'Angelo et al. found that the application of NEP was useful for the assessment of the performance of FVC maneuvers in healthy children.[44] Of note, some of these children, particularly in the youngest group, showed a decrease in the expiratory flow related to a collapsible UA. Similarly, a relatively high frequency of expiratory flow limitation suggestive of UA collapsibility was found in another study; however, the semi-recumbent position used in that study might have influenced the prevalence and extent of the flow limitation observed.[45] The NEP technique was also used in 4 infants to verify the validity of flow limitation assessed during forced expiratory maneuvers by the rapid compression technique.[46]

We consider that the NEP technique is useful in evaluating the physiology of UA dynamics. An advantage of measuring UA dynamics rather than simply the AHI in research studies is that NEP and SPF methods allow evaluation of the entire spectrum of UA collapsibility (e.g., detection of subjects at high risk of developing OSAS). Measurement of UA collapsibility is a useful tool in understanding UA physiology and the propensity to obstructive apnea. Finding subclinical abnormalities in UA collapsibility would suggest that subjects have an increased risk of developing OSAS in the future if they acquire additional risk factors. However, the NEP technique is not able to differentiate snorers from those with OSAS in clinical practice. Therefore, the NEP technique is potentially useful as a tool for awake evaluation of UA collapsibility and of the mechanisms involved in the presence of OSAS, but not to distinguish adolescent snorers from OSAS.

Although anatomy is an important determinant of the presence and severity of OSAS, in many adolescents other non-anatomic pathophysiologic factors may be particularly important in contributing to the presence or absence of OSAS and its

severity. Interestingly, the hypotonic SPF in some of the controls was elevated and within the range of the adolescents with OSAS. This is in accordance with several studies in adults, with P_{crit} of the hypotonic UA showing substantial overlap between patients with OSAS and controls.[47] Structural loads did not fully account for the variability in OSAS severity in some cases, suggesting that UA neuromotor responses also play a pivotal role in the maintenance of pharyngeal patency during sleep. However, neuromotor responsiveness is not systematically different in OSAS patients compared with controls. This suggests substantial variability between subjects, and the consideration that different factors can play a predominant role in each individual (even neuromuscular compensation could not always distinguish snorers from OSAS subjects). Therefore, simple and easy tests to evaluate different pathophysiological risk factors are needed.

Techniques for assessment of pathophysiological factors such as structural UA collapsibility and neuromotor factors during sleep are expensive, labor intensive, and require effort and cooperation from the subject. Measurement of SPF is only performed in a few centers. The NEP technique is a practical, simple and noninvasive test; it requires little cooperation from the subject and can be performed at rest during wakefulness in any body position. As the NEP technique correlates with SPF measurements, it can be an alternative to evaluate UA collapsibility in OSAS and its mechanisms while awake, particularly in places with low research resources. However, it is necessary to validate the NEP technique with a reliable measurement of UA collapsibility such as pressure-flow measurements during sleep.

The NEP technique could be a useful tool for studying UA mechanics in pediatric patients with habitual snoring and OSAS, with abnormalities being evident even during wakefulness. Measurements of UA collapsibility by the NEP technique showed overlap between snorers and subjects with OSAS, indicating that the UA in snorers is more collapsible even during wakefulness than controls, but different compensatory responses (i.e., neuromuscular reflexes) may modulate the presence of OSAS. The relevance of neuromuscular activity appears in obese adults without OSAS. Recently, it has been demonstrated that overweight/obese adults without apnea counteract a moderately compromised UA with enhanced UA dilator muscles responses during sleep which is threefold greater compared with their OSA counterparts and normal weight control subjects.[48] Although obesity increase the individual´s susceptibility to sleep apnea in part by elevating the passive/hypotonic Pcrit as demonstrated by Kirkness et al.,[49] some of these subjects can elicit active neuromuscular responses that mitigate the obstruction and avoid OSA. Sustained periods of upper airway obstruction induced greater increases in genioglossus activity in adult controls, suggesting that neuromuscular responses protect them from developing UA obstruction.[50] Therefore, it is possible that more than one technique may be needed to explore all factors involved in OSAS pathophysiology. One such technique could be NEP, but further studies such as functional imaging tests may be helpful.

Study Limitations

Most of the adolescents with OSAS in this study were obese. Current evidence indicates that obesity plays a prominent role in the pathogenesis of OSAS in adolescents. However, some of the controls in this study were also obese, and showed a steeper hypotonic SPF indicating an anatomically compromised UA. This variability in our controls takes into account that both methods were able to distinguish between controls and subjects with OSAS, providing evidence that NEP can be a reliable measurement of UA collapsibility even in obese subjects. On the other hand, the causal association between obesity and OSAS in the pediatric population is not well understood. Visceral adipose tissue is not useful in predicting UA collapsibility in obese adolescents.[51] Pulmonary function abnormalities related to obesity in the pediatric population are limited and conflicting. Many studies have not demonstrated differences in lung volumes between obese and control subjects; although overweight/obese children and adolescents may breathe at lower lung volumes at rest.[52] The reduced lung volume in an obese recumbent patient during sleep also may reduce caudal traction on the trachea promoting pharyngeal collapse.[47]Although the findings of this study could be related to obesity and lung volumes, both are contributing factors to UA collapsibility.

In conclusion, the NEP technique is a reliable method for assessment of UA collapsibility in adolescents, with correlation in the seated position to hypotonic and activated SPF measurements. The NEP technique may be useful in studies of the pathophysiology of OSAS as an easy and simple tool.

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