CLINICAL SCIENCE

Upper airway collapsibility evaluated by a negative expiratory pressure test in severe obstructive sleep apnea

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OBJECTIVES: To investigate the usefulness of measuring upper airway collapsibility with a negative expiratory pressure application as a screening test for severe obstructive sleep apnea (OSA).

INTRODUCTION: OSA is a risk factor for cardiovascular disease, and it may have serious consequences. Its recognition may have important implications during the perioperative period. Increased upper airway collapsibility is one of the main determinants of OSA, and its evaluation could be useful for identifying this condition.

METHODS: Severe OSA and normal subjects (24 in each group) were matched by body mass index and referred to our sleep laboratory. The subjects were enrolled in an overnight sleep study, and a diurnal negative expiratory pressure test was performed. Flow drop ($\Delta\dot{V}$) and expiratory volume were measured in the first 0.2 s ($V_{0.2}$) of the negative expiratory pressure test.

RESULTS: $\Delta\dot{V}$ (%) and $V_{0.2}$ (%) values were statistically different between normal and OSA subjects. OSA patients showed a greater decrease in flow than normal subjects. In addition, severely OSA patients exhaled during the first 0.2 s of the negative expiratory pressure application was an average of only 11.2% of the inspired volume compared to 34.2% for the normal subjects. Analysis of the receiver operating characteristics showed that $V_{0.2}$ (%) and $\Delta\dot{V}$ (%) could accurately identify severe OSA in subjects with sensitivities of 95.8% and 91.7%, respectively, and specificities of 95.8% and 91.7%, respectively.

CONCLUSIONS: $V_{0.2}$ (%) and $\Delta\dot{V}$ (%) are highly accurate parameters for detecting severe OSA. The pharyngeal collapsibility measurement, which uses negative expiratory pressure during wakefulness, is predictive of collapsibility during sleep.

KEYWORDS: Upper airways; Sleep; Screening test; Sensitivity; Specificity.

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INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of complete or partial interruption of ventilation during sleep, which is caused by a collapse in the upper airway. OSAs are associated with ongoing increasing respiratory efforts, intermittent hypoxia, systemic and pulmonary arterial blood pressure fluctuations and sleep disruption. The prevalence of OSA, which is associated with daytime sleepiness, is approximately 3-7% for adult men and 2-5% for adult women in the general population.[1] A diagnosis of OSA syndrome is made when a patient has an apnea-hypopnea index (AHI; number of apneas and hypopneas per hour of sleep) $\geq$ 5/h and symptoms of excessive daytime sleepiness.[2]

OSA is an independent risk factor for cardiovascular disease,[3-4] which includes hypertension, atrial fibrillation, coronary artery disease, and stroke. In addition, OSA has important social implications related to road[5] and occupational[6-7] accidents, neuropsychological impairment,[8] reduction in the quality of life,[9] and increased healthcare utilization;[10-11] therefore, under-recognizing OSA may have important consequences. Unfortunately, OSA diagnostic procedures are

expensive, and predictive criteria are still unsatisfactory. Identifying new predictive tools with extensive applications would therefore be useful.

Increased upper airway collapsibility is one of the main determinants for OSA,[12-14] and it has been suggested that responses to negative expiratory pressure (NEP) may reflect upper airway collapsibility.[15] The basis of the technique is to apply a negative pressure at the start of expiration during spontaneous breathing. In normal subjects, an increase in expiratory flow is observed. In subjects with intrathoracic airway obstruction, however, the flow measured under NEP will not exceed spontaneous flow. In subjects with upper airway collapsibility and under NEP, the flow can show a transient decrease, which is caused by airway collapse.

NEP has been used to study upper airway properties in subjects with obesity and OSA[16-21] to evaluate if this application could be used to predict OSA. Characteristics of the NEP test have been evaluated by different methods, and various AHI thresholds have been used to classify subjects with and without OSA. With the application of NEP during quiet breathing the flow drop during early expiration is predictive of OSA. This procedure is better than measuring an expiratory flow limitation equal to or less than the corresponding flow in any part of the control expired tidal volume.[20] The purpose of this study was to investigate the usefulness of measuring upper airway collapsibility by NEP to detect severe OSA in subjects.

MATERIAL AND METHODS

Subjects

Subjects were first referred to our sleep laboratory and evaluated with spirometry to exclude subjects with bronchial obstruction. Normal and severe OSA (AHI>30)[2] subjects (24 in each group) were matched by body mass index (BMI) and then recruited for this study (Table 1). None of the subjects had major craniofacial, acute or known chronic cardiopulmonary or neuromuscular disease. Each patient gave informed consent, and the study protocol was approved by the local scientific committee. Nocturnal monitoring with a portable cardio-respiratory system[22] and a diurnal NEP test performed during tidal expiration[20] were performed on all subjects.

Pulmonary function tests

Pulmonary function tests were performed during the day with a MedGraphics Elite plethysmograph (Med Graphics Corporation; St. Paul, Minnesota, USA) according to the guidelines of the European Respiratory Society.[23]

Nocturnal monitoring

Nocturnal monitoring was performed using a portable computerized system (Somté, Compumedics Inc.; Abbotsford, VIC, Australia). All recordings lasted more than 6 h. Flow was detected by a nasal cannulas connected to a pressure transducer, and apneas and hypopneas were visually scored. Apneas were defined as a lack of airflow or greater than a 90% reduction in the airflow signal for at least 10 s. Hypopneas were defined as discernible reductions in flow or thoracoabdominal movements ≥10 s followed by a SaO_2 decrease (≥4%).[24] AHI was calculated as (apneas + hypopneas)/h of the estimated total sleep time.

Table 1 – Subject anthropometric and respiratory data according to apnea hypopnea index.

Variables	AHI <5/h (n = 24)	AHI >30/h (n = 24)	p
Male gender, n	19	21	
Age, yr	44 ± 10	50 ± 8	0.015
Height, m	169 ± 8	169 ± 9	NS
Weight, kg	80.3 ± 12.5	86 ± 12	NS
BMI, kg/m^2	28 ± 3.4	30 ± 2.6	NS
Neck, cm	40 ± 3.0	41 ± 2.8	NS
AHI, events/h	2.0 ± 1.4	59 ± 18	<0.0001
FVC, % predicted	106 ± 14	97 ± 12	0.047
FEV_1, % predicted	107 ± 13	96 ± 13	0.008
FEF_{25-75}, % predicted	97 ± 22	85 ± 24	NS

Values are mean ± SD; BMI = Body Mass Index; AHI = Apnea Hypopnea Index; FVC = Forced Vital Capacity; FEV_1 = Forced Expiratory Volume in 1 s; FEF_{25-75} = Forced Expiratory Flow between 25% and 75% of the Forced Vital Capacity.

Negative Expiratory Pressure test (NEP)

Negative Expiratory Pressure test (NEP) was generated by a Super Air Amplifier (Exair model 120021; Cincinnati, Ohio, USA) attached to a tank of compressed air by an electrically operated solenoid valve (Norgren Ltd model 95004; Warwickshire, UK). The valve was automatically activated in early expiration and kept open for 2 s by software control. A pneumotachograph (Hans Rudolph model 3830; Kansas City, MO, USA) was connected to an air amplifier and a mouthpiece to measure airflow ($\dot{V}$) with a pressure transducer (PCLA02X5; Sensortechnics GmbH, Puchheim; D). The mouth pressure was measured by a pressure transducer (PCLA0050; Sensortechnics GmbH Puchheim; D). NEP (-10 cm H_2O) was set by occluding the pneumotachograph with a stopper and adjusting the flow of compressed air to the air amplifier (Fig. 1).

In all subjects, NEP tests (-10 cm H_2O) were performed in a sitting position during quiet breathing with a nose clip. During the test, care was taken to keep the neck in a neutral position and the subjects awake. Breathing pattern stabilization was required between two consecutive NEP tests. Signal analysis and solenoid valve control were performed using software developed in our laboratory written in Labview 8.2 (National Instruments; Austin, TX, USA).

During tidal expiration, the NEP application produced an immediate peak flow that was followed by a sudden drop by variable degrees. Upper airway collapsibility was evaluated by measuring the flow limitation as the flow drop ($\Delta\dot{V}$) % expressed as a percent of the peak flow immediately after NEP application[20] (Fig. 2). The minimum flow was identified in the first 200 ms of NEP application to avoid reflex and

Table 2 - Receiver Operating Characteristic curve analysis for NEP flow drop and expiratory volume at 0.2 s.

AHI <5 vs. AHI >30	$\Delta\dot{V}$ (%)	$V_{0.2}$ (%)
Optimal cut-off point	70	22.2
Sensitivity, %	91.7 (73-99)	95.8 (79-100)
Specificity, %	91.7 (73-99)	95.8 (79-100)
Area under ROC curve	0.97 (0.88-0.99)	0.99 (0.90-1)

Data are presented as the mean (95% confidence interval); NEP = Negative Expiratory Pressure; AHI = Apnea Hypopnea Index; $\Delta\dot{V}$ (%) = Flow drop percent of the peak flow; $V_{0.2}$ (%) = expiratory volume at 0.2 s after NEP application in percent of the mean inspiratory volume of three preceding breaths.

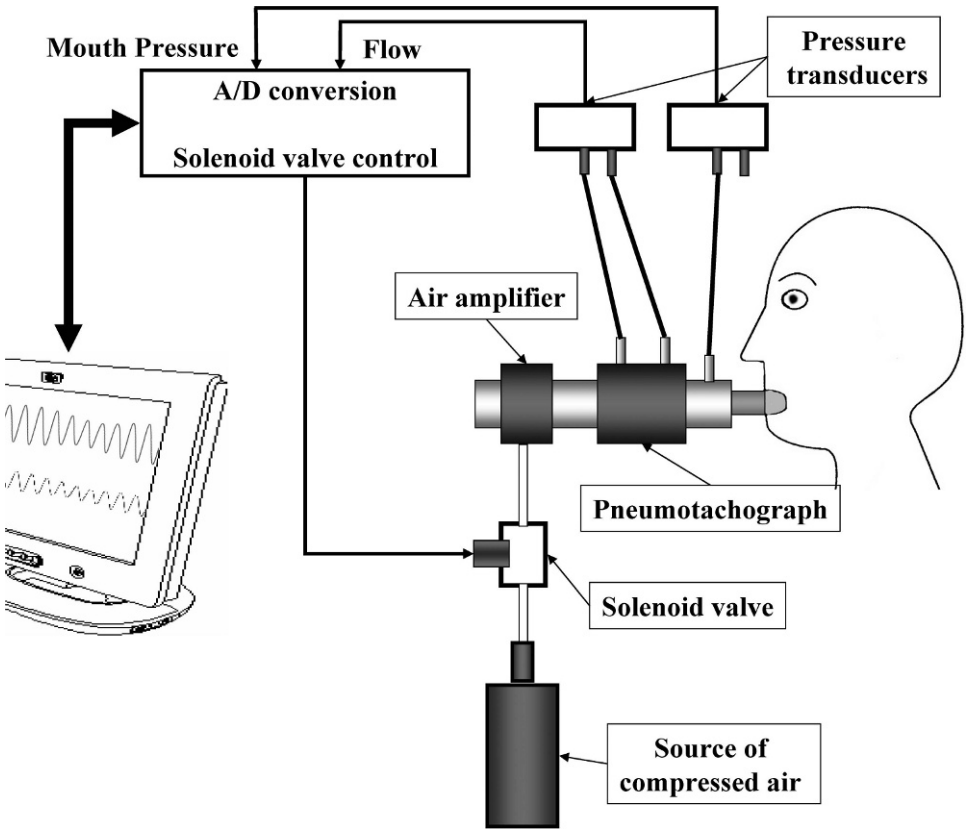

Figure 1 - Schematic representation of the negative expiratory pressure apparatus.

voluntary reactions to the NEP stimulus.[25] Values of $\Delta\dot{V}$ (%) were calculated as the maximum of seven measurements. Upper airway collapsibility was also evaluated by measuring the expired volume at 0.2 s ($V_{0.2}$) immediately after NEP application (Fig. 2). These values were expressed as a percent of the mean inspiratory volume of three breaths taken before NEP application. Measured volumes were accepted only when differences between inspiration and expiration for each of the three breaths were less than 10%. Values of $V_{0.2}$ were calculated as the mean of seven measurements.

Statistical analysis

Logistic regression was used to analyze the continuous factors with categorical responses. Receiver operating characteristic (ROC) curves were constructed to determine the probability of a positive result or sensitivity (true positive rate) versus the probability of a false positive result (false positive rate) at various levels of the measured $\Delta\dot{V}$ (%) and $V_{0.2}$ (%) values. These curves were used to identify the cut-off value that yielded the largest number of correctly classified patients (Table 2). The differences between subjects were evaluated using the Mann-Whitney test. Data are reported as mean $\pm$ SD, and a p-value <0.05 was considered statistically significant. Statistical analysis was performed using a commercially available software package (JMP 8.0, SAS Institute Inc; Cary, NC, USA).

RESULTS

The anthropometric and respiratory characteristics of the OSA and normal subjects are shown in Table 1. $\Delta\dot{V}$ (%) and $V_{0.2}$ (%) values were statistically different ($p<0.0001$) between normal and severe OSA subjects (Fig. 3). Patients with severe OSA had a greater decrease in flow compared to normal subjects. In addition, severe OSA patients exhaled during the first 0.2 s of the NEP application, which was an average of 11.2% of the inspired volume, compared to 34.2% for the normal subjects.

Given that OSA and normal subjects differed in age and pulmonary function tests (FVC-forced vital capacity and FEV_1-forced expiratory volume first second), multiple logistic regressions were performed. In these regressions, the OSA and normal subjects were the dependent variables, and the model age, FVC, FEV_1 and the NEP parameters [$\Delta\dot{V}$ (%) and $V_{0.2}$ (%), one for each regression] were also included. Both multiple logistic regressions showed that the NEP parameters were not influenced by variables that were not completely matched.

ROC curve analysis was performed to evaluate the predictive effectiveness of $\Delta\dot{V}$ (%) and $V_{0.2}$ (%) for severe OSA identification (Fig. 4). Areas under the ROC curves showed that $V_{0.2}$ (%) and $\Delta\dot{V}$ (%) could very accurately identify severe OSA subjects (0.99 and 0.97, respectively). For $V_{0.2}$ (%), its optimal ROC curve cut-off value was 22.2%, with a sensitivity of 95.8% and a specificity of 95.8%, whereas the optimal cut-off of $\Delta\dot{V}$ (%) was 70%, with a sensitivity of 91.7% and a specificity of 91.7% (Table 2).

DISCUSSION

The current study verified the efficacy of measuring an expired volume at 0.2 s and flow drop during NEP application for identifying severe OSA subjects. The main

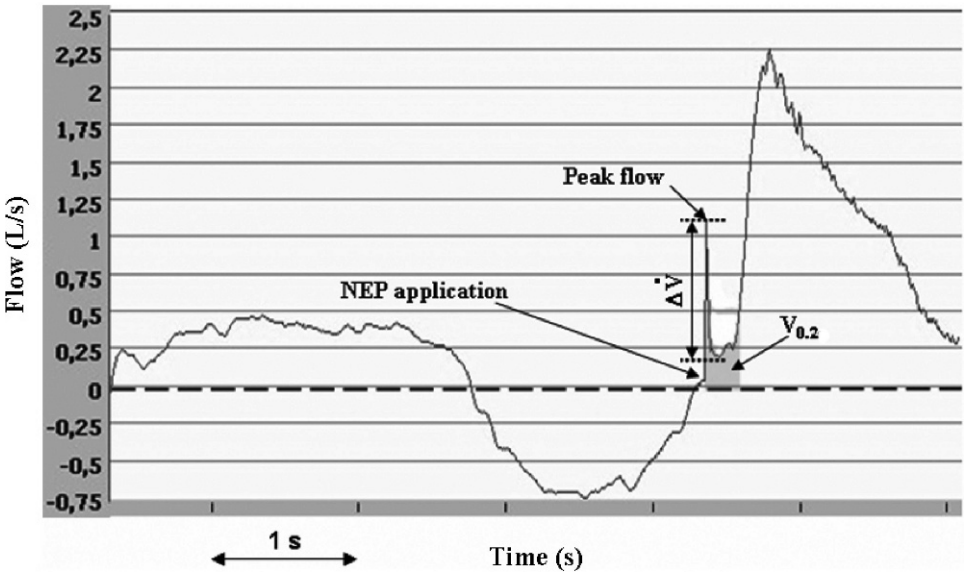

Figure 2 - Measurement techniques for upper airway collapsibility evaluated as expiratory volume in 0.2 s (percent of the mean inspiratory volume of the three breaths preceding NEP application) and as the flow drop ($\Delta\dot{V}$; expressed as the percent of the peak flow).

finding was that upper airway collapsibility, which was measured by an expired volume at 0.2 s and a flow drop during NEP, is a valuable predictor for severe OSA.

Obesity and increased upper airway collapsibility are considered among the most important determinants for OSA. Previous studies on obese male subjects have shown that at least 40% are affected with OSA.[26-27] Given that obesity is considered a major cause of OSA, we performed the ROC curve analysis on the $V_{0.2}$ and flow drop induced by NEP in severe OSA and normal subjects matched for BMI (body mass index). These results are consistent with collapsibility being the main mechanism of upper airway obstruction during sleep and BMI being a major factor to precipitate upper airway collapsibility. Higher collapsibility was associated with severe OSA, whereas lower collapsibility was characteristic for normal subjects. Our data show that upper airway collapsibility could be a useful tool to predict severe OSA when evaluated by the NEP measurements $\Delta\dot{V}$ and $V_{0.2}$.

Previous studies have evaluated the flow limitation induced by NEP during wakefulness by different methods to assess upper airway collapsibility in OSA and non-OSA subjects.[16-21] Some studies have applied methods similar to those adopted for evaluating flow limitation in patients with bronchial obstruction;[15] however, other studies have performed new methods for quantifying upper airway obstruction.[16-21] The different methods have shown a role for NEP in identifying upper airway collapsibility. Van Meerhaeghe et al.[18] expressed the expiratory flow limitation as the percentage of the expired tidal volume over which the NEP-induced flow did not exceed spontaneous flow. The authors concluded that NEP might be useful in predicting OSA with an

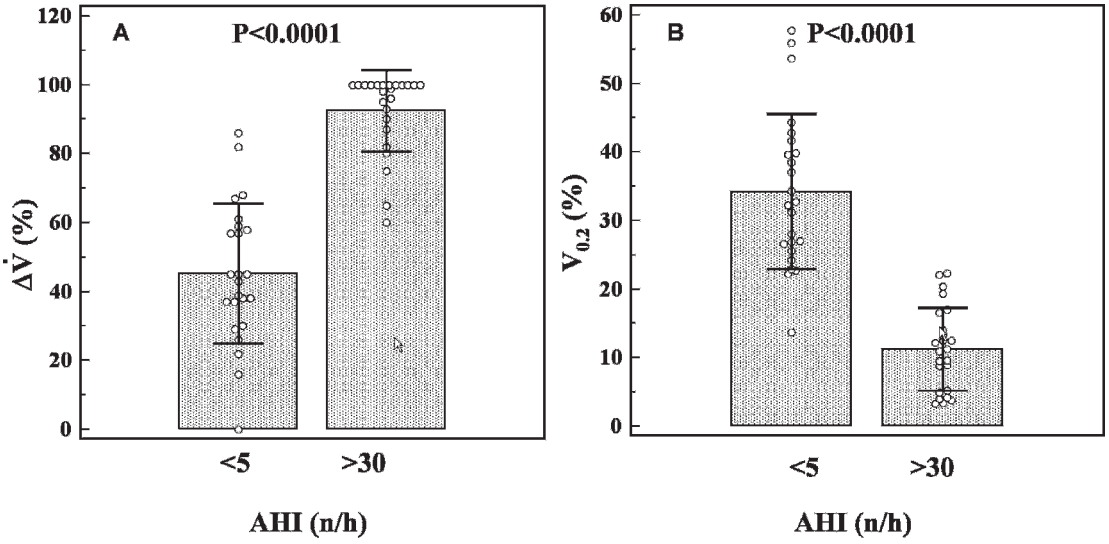

Figure 3 - Comparison of the (A) flow drop percent of the peak flow $\Delta\dot{V}$ (%) and (B) the expiratory volume at 0.2 s [the percent of the mean inspiratory volume $V_{0.2}$ (%)] between normal and severe OSA subjects.

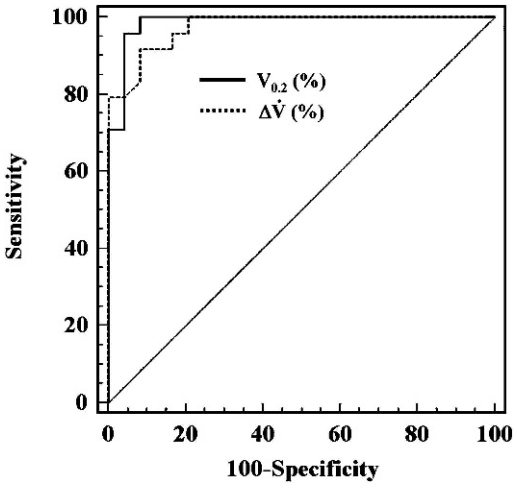

Figure 4 - Receiver-Operating Characteristic (ROC) curves of the measured upper airway collapsibility. The curves were evaluated as the expiratory volume at 0.2 s [$V_{0.2}$; the percent of the mean inspiratory volume of three breaths preceding NEP application (continuous line)] and as flow drop [$\Delta\dot{V}$; the percent of the peak flow (dashed line)], which were induced by negative expiratory pressure for classifying normal subjects and patients with severe OSA (AHI >30/h).

AHI ≥15 in a clinic-based population with a sensitivity of 81.9% and a specificity of 69.1%. Tamisier et al.[21] applied a ratio of the areas under the curve for the NEP flow-volume loop to the spontaneous flow-volume loop. They reported a quantitative index that was higher in healthy subjects compared to patients with any type of SDB with a reliable, predictive positive value of 96.6% and a predictive negative value of 76.9%. Given that sleep disorders of breathing (SDB) and normal subjects show significant differences, there is a trend of a lower quantitative index in severe patients who express more highly collapsible upper airway. In our study, we applied expiratory measurements ($\Delta\dot{V}$ and $V_{0.2}$) at the very beginning of expiration, showing suitable results useful to detect upper airway obstruction.

A limitation in this study was that patients and controls were not perfectly matched. Using multiple logistic regression analysis, however, we showed that NEP parameters were not influenced by variables that were not completely matched. Another limitation of this investigation was that the population studied consisted of subjects attending a sleep laboratory, and only severe OSA subjects were included. This procedure was performed to better evaluate the effectiveness of the NEP test in detecting marked upper airway collapsibility. Further investigations on the whole spectrum of disease severity are needed to better detect how the NEP test could be useful in detecting mild and moderate OSA in subjects.

OSA has been increasingly recognized as a serious health problem worldwide. Untreated OSA in the general adult population is significantly related to psychomotor[8] and memory[28] deficits, reduced cognitive function, depressed mood and altered quality of life in areas related to vitality, social functioning, and mental health.[9] In addition, OSA is believed to be an independent risk factor for cardiovascular diseases.[4] Special emphasis is given to recognizing the patient with cardiovascular disease who has coexisting sleep apnea, which may contribute to the progression of the cardiovascular condition. This finding may explain, at least in part, the increased mortality rate.[29]

Numerous studies have found a 2- to 7-fold increase in the risk of OSA subjects being involved in motor vehicle crashes. The risk is more relevant for commercial motor vehicle operators due to the weight and size of the vehicles they drive and/or the number of passengers they transport.[5] It has also been shown that snoring and daytime sleepiness, which are characteristics of OSA, are tightly associated with occupational injuries.[6-7] OSA is a treatable risk factor, and therefore, determining its existence is important.

With increasing diagnoses of OSA, there is an increase in the number of people on the waiting lists for the small number of sleep laboratories capable of clinically and properly treating these patients. In addition, the current diagnostic procedures are time consuming and expensive. To address this critical issue, it is necessary to identify reliable and inexpensive screening systems to detect subjects at risk for the disease.

The NEP test evaluates upper airway collapsibility and provides a rapid and objective assessment that can be widely used to identify patients with severe OSA. Interesting applications of this measurement could be in assessing the fitness of drivers for specific categories, such as commercial drivers, or identifying the perioperative period of undiagnosed OSA patients who are known to have a higher incidence of difficult intubations, postoperative complications, increased intensive care unit admissions, and an increased hospital stay. Another field of interest could be workers with jobs who are at an increased risk for accidents. It is important to heighten public awareness of the potential hazards and health risks that surround undiagnosed sleep apnea; therefore, diagnosing and treating sleep apnea are important medical and social issues.

CONCLUSIONS

In conclusion, we found that upper airway collapsibility can be evaluated by $\Delta\dot{V}$ and $V_{0.2}$ during the NEP test, and these measurements are valuable to detect severe OSA subjects. During wakefulness, the pharyngeal collapsibility measurement using NEP is predictive of collapsibility during sleep. The NEP test is fast and could be adopted as a screening test for evaluating suspected, severe OSA patients because it appears to be a very reliable diurnal test that objectively predicts this respiratory disorder. It could be even more powerful in association with anamnestic data, such as snoring and hypersomnolence. Further analysis using a more heterogeneous population could also be useful.

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