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Occult sleep apnea: the dilemma of negative polysomnography in symptomatic patients

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Abstract

Background and purpose: To determine the benefit of repeat polysomnography with/without esophageal pressure (PES) monitoring to diagnose sleep apnea syndrome (SAS) in patients with symptoms of sleep apnea who have had a 'negative', single-night polysomnogram (PSG).

Patients and methods: This is a retrospective investigation of 1187 patients seen in our sleep lab from January to December 2001, of which 709 were adults suspected of having sleep apnea. Following a single PSG, 588 patients were diagnosed with sleep apnea and 121 had negative PSGs (an apnea–hypopnea index <5 events per hour). Of the 121 patients, 92 continued to complain of unexplained sleepiness, loud snoring, or apnea, symptoms which were also documented on their initial evaluation (PSG or multiple sleep latency testing). The remaining 29 patients had no further complaints, or another medical cause of their sleepiness was established (i.e. asthma) following the single-night PSG. Of the 92 patients, 28 underwent additional screening with both repeat PSG and PES monitoring within the following 6 months.

Results: With repeat PSG and PES monitoring, 18 of the 28 patients with previous, negative PSGs were diagnosed with sleep apnea. The sensitivity of a single-night PSG fell to 97%, with a false negative rate of 3%. Only 12 of the 28 would have been positive based on polysomnographic criteria alone, without the additional PES monitoring. On the other hand, 10 of the 28 remained negative and further evaluation revealed other, underlying medical problems (i.e. nocturnal asthma) that explained their symptoms.

Conclusions: There is a clear benefit of repeat PSG, with or without PES monitoring, for patients with a prior negative PSG and continued symptoms suspected of having SAS.

Keywords: Obstructive apnea; Upper airway resistance; Second night; Esophageal pressure monitoring; Negative polysomnography; Snoring; Sleepiness

1. Introduction

Patients, in general, will not seek medical attention unless they are prompted by a bothersome symptom. In the case of sleep apnea, it is usually snoring, witnessed apnea, or excessive daytime somnolence (EDS). It is the task of the sleep physician and laboratory to identify patients with sleep apnea and to initiate therapy. The current practice standard is predicated on one-night polysomnography. If it is negative (apnea–hypopnea index (AHI) <5 events per hour), the diagnosis of sleep apnea is usually discarded. However, a significant group of these patients remain symptomatic despite negative testing. If the clinical suspicion for obstructive sleep apnea (OSA) exists, and polysomnography is negative, the physician faces a true dilemma with regards to further patient management. Untreated, sleep apnea may lead to an increased risk of hypertension, stroke, myocardial infarction and even death (1). Patient complaints should not be dismissed, especially after effective treatment for

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sleep apnea that may alter associated cardiovascular outcomes and the effects of excessive daytime tiredness on the patient's quality of life.

The variability with which sleep apnea occurs on a night-to-night basis has been suggested (2), but its clinical significance has not yet been fully elucidated. When patients are tested in the laboratory, they do not always meet the diagnostic threshold for OSA (AHI >5 events per hour) with one night of polysomnography. Regardless of this, it is clearly recognized that increased nocturnal respiratory effort subsequently leads to EDS. The purpose of our study was to evaluate patients with symptoms of sleep apnea who had a negative polysomnogram (PSG) and no other diagnosis to explain their symptoms.

2. Methods

2.1. Selection criteria

Following Institutional Review Board approval, 1187 PSG studies performed at the Sleep-Wake Center at Hackensack University Medical Center from January to December 2001 were reviewed retrospectively. Informed consent for PSG was obtained. Of the 1187 patients initially identified, 478 were excluded from analysis (due to a previously established diagnosis, or age <18 years) and 709 remained.

Patients were not excluded on the basis of race, sex, body mass index (BMI), or comorbidities (Fig. 1). To control for confounding factors, patients were excluded if their repeat PSG occurred more than 6 months from the initial evaluation, if increased upper airway resistance syndrome (UARS) was suspected, and/or esophageal pressure (PES) monitoring was used with their initial PSG evaluation. The Center for Medicare and Medicaid Services has standardized the diagnosis of sleep apnea syndrome (SAS) as an AHI of 15 events per hour without symptoms, and five events per hour when combined with EDS, impaired cognition, mood disorders, insomnia, hypertension, ischemic heart disease or history of stroke (3).

A PSG study was labeled positive when these criteria were met. Excluded patient studies numbered: 298 performed for titration of continuous positive airway pressure (CPAP) ventilation, 67 for bilevel positive airway pressure (BiPAP) titration and 14 for evaluation of residual sleep apnea following uvulopalatoplasty or institution of a mandibular advancement device. One study was excluded because only the Maintenance of Wakefulness Test was performed, eight because of lack of a comparison study within 6 months of a PSG with PES monitoring (usually due to suspected increased UARS) and nine because they were performed for pediatric patients. Finally, 78 were excluded because of incomplete information.

2.2. Polysomnography

PSG and multiple sleep latency testing (MSLT) were performed in an accredited sleep laboratory associated with a tertiary university hospital. PSG was performed with continuous monitoring of electroencephalography, electro-oculography, chin electromyography, respiratory effort (thoracoabdominal impedance plethmysthography), airflow via nasal thermistor, electrocardiography, oximetry and anterior tibialis electromyography. MSLT, having four 20-min nap opportunities with continued PSG monitoring, was performed at the discretion of a board certified sleep physician for patients with complaints of daytime tiredness or sleepiness.

2.3. Esophageal pressure monitoring

Esophageal pressure probes (Ackrad; Cranford, NJ) were calibrated and placed in the retrocardiac position (4). Each catheter balloon was inflated with 1 ml of air, calibrated using a 10 cm graduated cylinder of water and then stiffened in ice water prior to placement; the patient received local anesthesia with topical lidocaine or benzocaine. To achieve the retrocardiac position, the distance of catheter advancement was calculated by multiplying 0.288 by the height of the patient in centimeters. Positioning was confirmed by obtaining maximum cardiogenic oscillation and Valsalva maneuver (negative pressure swings are not seen if the balloon is located in the abdomen). All patients had baseline values <-5 cmH_2O. A RespSponse III transducer (Medtronics, Minneapolis, MN) and Sandman Software were used for these esophageal pressure probes.

Studies were scored by a registered polysomnographer, and reviewed and interpreted by board certified sleep physicians. Continuous PES monitoring recorded the nadir in each epoch. Nadirs, by definition, represent a decrescendo–crescendo pattern. Events per hour with a nadir >-10 cmH_2O were recorded as an PES index. An index >10 events per hour was a positive study.

2.4. Polysomnographic scoring

Staging was performed according to the Rechtschaffen and Kales scoring manual (5). Apneas were defined as the complete cessation of airflow for a minimum of 10 s. Hypopneas were defined using the following criteria: (1) a 50% decrease in airflow during sleep, (2) a 20% decrease in airflow associated with a 3% drop in oxygen saturation, and/or terminated by an arousal, and (3) the event lasts 10 s or longer (6,7).

2.5. Patient analysis and classification

All 709 patients who complained of tiredness, snoring or sleepiness underwent an initial PSG, with or without MSLT (Fig. 1). Five-hundred eighty-eight patients with an AHI ≥ 5

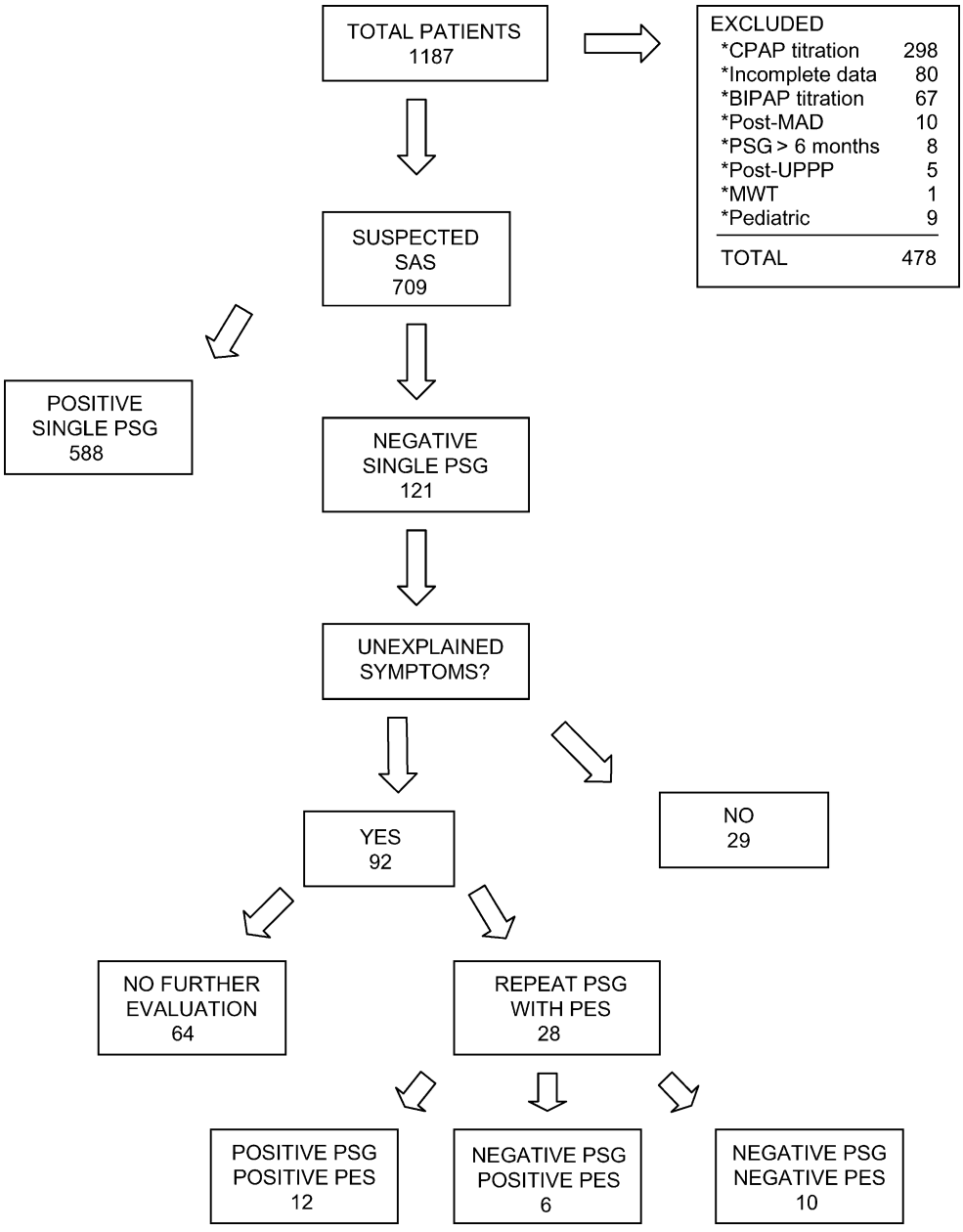

Fig. 1. Patient classification.

events per hour were diagnosed with sleep apnea and offered treatment. One hundred twenty-one patients having an AHI <5 events per hour were negative studies. However, these patients had clinical complaints and at least two of the following at the time of their first PSG: moderate–heavy snoring, desaturation ($\geq 3\%$), apneas and hypopneas (albeit <5 events per hour). Daytime sleepiness was also evidenced (MSLT <10 min). These 121 patients were divided into two groups: 29 who received a diagnosis other than sleep apnea to explain their sleepiness (i.e. nocturnal asthma) and 92 whose symptoms were unexplained.

Of these 92, 28 agreed to repeat PSG with PES monitoring and 64 declined further evaluation. Of the latter, the majority desired further testing but were unable to obtain insurance approval and/or funding for a second study; the rest chose instead to receive empiric therapy with stimulants, continuous positive pressure ventilation or mandibular advancement devices.

Among the remaining 28 patients, the repeat PSG was considered positive if the AHI was ≥ 5 events per hour and/or the PES index was >10 events per hour with a nadir > -10 cmH_2O. Positive patients ($N=18$) were diagnosed with sleep apnea and offered treatment. The results were used to calculate the increased diagnostic sensitivity of a repeat PSG compared to a single-night study.

Table 1
Confirmation of patient symptoms on polysomnography and MSLT

Apneas and or hypopneas present, with an AHI <5 events per hour
Moderate–heavy snoring
EDS: (a mean sleep latency on MSLT of <10 min, Epworth sleepiness score >10, or severe symptoms (i.e. sleepiness while driving))
Desaturation (drop in oxygen saturation by at least 3% on pulse oximetry)

2.6. Data analysis

All statistics were performed by a biomedical statistician. Bayesian statistics were used to calculate the sensitivity and false negative rate. The χ^2-test and Wilcoxon Rank test were used to compare the distribution of snoring, desaturation, apneas/hypopneas, and EDS among the groups via SAS software (SAS Institute, Cary, NC).

3. Results

Of 709 patients who underwent PSG for suspected sleep apnea (Fig. 1), 588 were diagnosed with sleep apnea with a single-night PSG and 121 had a negative initial study. Of these, 29 had their sleepiness readily explained by a condition other than sleep apnea (i.e. narcolepsy, congestive heart failure, nocturnal asthma, etc.). Ninety-two patients continued to have unexplained symptoms.

Of these 92, 64 declined further evaluation and 28 underwent repeat PSG with PES monitoring. There was no statistically significant difference in clinical characteristics and symptoms between those who had further evaluation and those who did not; there was equivalent, moderate/heavy snoring ($P=0.25$), desaturation ($P=1.17$), AHI ($P=0.34$) and mean sleep latency on MSLT ($P=0.94$). Of the patients with negative initial PSGs, approximately two-thirds (18/28) were subsequently diagnosed with SAS via repeat PSG and PES monitoring (Fig. 1, Tables 1 and 2). Interestingly, 12 of the 18 would have been diagnosed with sleep apnea with the data from the repeat PSG alone, without including the data from PES monitoring. These patients had an average age of 41 years, BMI of 33 kg/m^2, and were mostly men. Ten patients had negative repeat studies. This group was unique in that most of their apneas and hypopneas occurred during REM sleep (Tables 2); however this did not reach statistical significance. The sleep architecture and arousal patterns were not significantly different among the three groups.

According to our data, a single-night PSG does not have 100% sensitivity for diagnosing OSA in symptomatic patients. In fact, when repeat PSG with PES monitoring are used, the sensitivity of a single-night PSG drops to 97%, with a false negative rate of 3%. If our sample had included the entire cohort of symptomatic negative patients (92), rather than only 28, the sensitivity of a single PSG could have been as low as 90%.

The majority of the 28 patients who underwent repeat PSG with PES monitoring chose to undergo at least one form of treatment; 13 were titrated with CPAP with complete resolution of their apneas and desaturations, six chose to have a mandibular advancement device, and five were placed on modafinil for hypersomnolence. At follow-up evaluation all of these patients stated that they had an improvement and/or resolution of their symptoms. Two patients from this group were diagnosed with simple snoring, and two patients chose sleep hygiene, weight reduction and observation.

Many of the 64 symptomatic patients with negative initial PSGs, who refused further evaluation, also chose to undergo at least one empiric treatment. Twenty-nine had various other sleep disorders. Eighteen patients were lost to follow-up.

4. Discussion

OSA is a clinical diagnosis, confirmed by polysomnography. Only 83% of our patients (588/709) with clinically suspected OSA were diagnosed by single-night PSG. The main focus of our study was to determine whether further evaluation with repeat PSG and PES monitoring would reveal additional cases of OSA. PSG diagnosis (as opposed to clinical criteria alone) is beneficial in confirming the diagnosis of OSA while excluding other

Table 2
Mean values for symptomatic group following repeat PSG with esophageal pressure monitoring

Number of patients	Oxygen saturation (%)	Sleep latency (min)	AHI total		Pes-10 index[a]
			1st Study (REM only)	2nd Study	
Positive standard PSG 12 ± positive PES	92	6:39	3 (7)	10	37
Negative standard PSG 6 + positive PES	91	8:31	1 (4)	3	44
Negative standard PSG 10 + negative PES	90	5:21	3 (8)	2	4

Mean values reported. All patients had moderate–heavy snoring. Standard PSG, repeated standard polysomnography; PES, esophageal pressure monitoring; AHI, apnea–hypopnea index; REM, rapid eye movement; -10, nadir more than negative 10 cmH_2O.

[a] All indices reported in events per hour.

causes of sleepiness, and also enables patients to seek reimbursement from insurance providers (i.e. Medicare and Medicaid) who require a positive PSG study prior to supplying noninvasive positive pressure ventilation devices.

Our data clearly show that repeat PSG, with or without PES monitoring, can provide substantial, physiologic and quantifiable reconciliation of the discrepancy between a strong clinical suspicion of OSA and an initial, negative PSG. There are, however, two important caveats regarding the interpretation of our data and its general application to sleep disorders. The fact that only 28 of the 92 symptomatic patients with unexplained sleepiness and a negative PSG underwent further evaluation may indicate some selection bias, either based on patient preference or insurance carrier (i.e. patients who were more symptomatic continued testing). However, we were unable to detect such a bias using standard statistical methods, possibly because it was limited by the retrospective nature of our study.

A second issue is that, although the use of PES probes has been established for the diagnosis of UARS, this is not the case for OSA. However, increased esophageal pressure has been clearly associated with partial and/or complete upper airway obstruction. While nasal pressure monitoring is available, we chose PES monitoring because the results are easily quantifiable as pressure nadirs recorded as absolute numbers, which can be duplicated and compared from laboratory to laboratory and do not affect sleep architecture (8,9). PES nadirs, by definition, imply a crescendo–decrescendo pattern, which has been repeatedly associated with airway obstruction (10) and which did not have to be further identified for scoring in our study. Like an AHI, the PES index was used for comparing patients with different total sleep times. An index of 10 events per hour (with or without arousals) was used as an indication of sleep fragmentation and disruption due to increased airway obstruction and increased negative esophageal pressure. As previously noted, a value of > -10 cm of water is markedly abnormal (11), and seemed a reasonable, albeit arbitrary, cutoff point. Pressure transducers and EEG arousals, on the other hand, are dependent on subjective assessment, are semi-quantitative (12,13), and allow for more variability of interpretation. Thermistors are not quantitative and can lead to inadequate scoring (1,6,14–16).

Arousals, while included in the diagnosis of UARS, are important but not necessary for the diagnosis of OSA; we found the PES index to be easily quantifiable, efficient, and comparable. While some may argue that patients with negative PSG and PES index (10/28) had UARS, the physical characteristics of our cohort (age, sex, race, BMI (Table 2)) are clearly different from the population described by Guilleminault et al., where there is a reported tendency for patients with UARS to be younger, female, with lower BMI and a lower arousal threshold measured by esophageal pressure (12). Our symptomatic patients who underwent repeat PSG and PES monitoring were mainly middle-aged, obese men, a subpopulation more typical for OSA than UARS.

In our study, the degree of change in esophageal pressure did not match the severity of obstruction or the number of apneas, as was similarly reported by Wantanabe et al. (17). In fact, it takes more negative pressure to cause an arousal in a patient with UARS than in normal controls (18). The difference in effort and esophageal pressure between those with sleep apnea and those with UARS may represent either a fundamental difference in these conditions or in patient responses to the same physiologic problem. However, we had a small number of patients, and this difference may not persist in a larger study. In our study, there was no statistical difference in the apneas, hypopneas, desaturation, snoring, EDS and arousals between patients with positive repeat PSGs and those with negative repeat PSGs and positive PES studies. No study was terminated early due to intolerance of PES monitoring, confirming previous reports of patients' acceptance of this modality.

Finally, the variability in the AHI on the PSGs of patients with sleep apnea has been clearly seen in other epidemiological studies (2,11,19,20), although its cause is still unknown. It is this natural variation that makes the upper airway so difficult to model mathematically. One proposed explanation is the Starling resistor theory, where the upper airway is viewed as a collapsible tube (21). However, in practice, the collapsibility of the tube is difficult to predict and can vary temporally and mechanically (17,18,22). This may be a further argument for the inclusion of a second-night PSG for the diagnosis of sleep apnea.

True variability (as opposed to change in the results due to change in patient characteristics) can be seen in these patients. The fact that all of our repeat studies were performed within 6 months of the initial evaluation may have decreased, but not completely eliminated, possible changes in physical characteristics (there were no significant weight changes in our population), alcohol or medication use, or comorbidities that may have confounded previous studies. A large number of patients with negative initial PSGs sought further treatment for their clinical complaints.

The treatment of patients with low AHIs is supported in the literature. It has been demonstrated that, untreated, even a minimally increased number of apneas and hypopneas (less than 5 events per hour), simple snoring or EDS can lead to the development of hypertension, ischemic heart disease, and stroke (23). Patients may be inappropriately medicated with stimulants or diagnosed as having hypersomnolence, depression, etc.

One interesting finding is that the majority of patients suspected of having sleep apnea based on our clinical criteria, and who tested negative with repeat PSG/PES monitoring, often had increased REM-associated arousals. This has been seen in other studies (22,24), and may be a result of the decreased muscle tone in REM sleep, with a subsequently decreased respiratory effort. If this is the case,

then these may be false negative patients for whom PES monitoring would not be helpful.

Currently, patients with mild sleep apnea/increased UARS may choose 'no therapy', weight reduction, mandibular advancement devices, uvulopalatoplasty, or nocturnal CPAP. The specific benefits of these modalities have not yet been clearly compared. Because of its potential for long term morbidity and mortality, sleepiness is a symptom requiring immediate and aggressive evaluation. Many of the patients in our study, who did not qualify for CPAP following single-night PSG, nevertheless requested treatment for their sleepiness, and some were successfully titrated on CPAP with complete resolution of the events. This highlights the importance of quality of life to the patient. While CPAP may offer immediate relief for the patient, the long term effects remain to be seen.

In conclusion, this study suggests that the further clinical evaluation of patients with signs and symptoms of sleep apnea, and who have had a negative initial PSG, may be a guide for treatment. Considering the documented increase in morbidity and mortality associated with OSA, it seems prudent to actively pursue such treatment for these patients. Further studies may be done to validate and exploit the potential use of PES monitoring as a quantifiable method of evaluating upper airway obstruction and/or resistance in patients with partial or minimal upper airway obstruction. Perhaps, with these tools, effective treatments may be offered to patients whose symptoms would otherwise be summarily dismissed, regardless of the consequences to their quality of life and general health.

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