Sleep Apnea in the Presumably Healthy Working Population—Revisited

Peretz Lavie, PhD

Sleep Laboratory, Faculty of Medicine, Technion—Israel Institute of Technology, Haifa, Israel

INTRODUCTION

Why Study the Prevalence of Sleep Apnea in the First Place?

THE REQUEST OF THE EDITOR OF *SLEEP* TO REVISIT MY 1983 PAPER ON THE "INCIDENCE OF SLEEP APNEA IN A PRESUMABLY HEALTHY WORKING POPULATION: A SIGNIFICANT RELATIONSHIP WITH EXCESSIVE DAYTIME SLEEPINESS"[1] has provided me with a unique opportunity to reexamine the reasons that led me to conduct this study more than 20 years ago, and to assess how the 1983 findings have stood the test of time. The main reason that led me to look for the prevalence of sleep apnea in the general population was my impression that there was a great discrepancy between the type of patients who spent their nights in the Technion Sleep Laboratory for clinical examinations, and the prevailing literature on the prevalence of sleep disorders. The literature on the prevalence of sleep disorders during the 60s and 70s almost exclusively focused on insomnia, and tended to ignore complaints related to excessive daytime sleepiness or chronic fatigue.[2-5] In fact, very little was known at that time about the prevalence of excessive daytime sleepiness. Bixler et al.[2] reported on a prevalence of 3.6% hypersomnia, and Karacan et al.,[3] who obtained information on sleep disorders from a random sample of 1645 individuals in Alachua County, Florida, reported that 0.5% complained of "too much sleep." Our experience in the clinical sleep laboratory, in which we started receiving patients on a regular basis in 1976, revealed a different picture. As soon as we started to see patients on a regular basis, we found that more than 50% of the people who were referred to our sleep laboratory complained of excessive daytime sleepiness, or morning and daytime fatigue, or of a combination of these complaints. In the majority, polysomnographic recordings revealed apneic events during sleep. Thus, our impression was that complaints related to daytime sleepiness, non-refreshing sleep, and chronic fatigue, and the laboratory finding of sleep apnea, were much more prevalent than would be expected based on the existing literature. These impressions were considerably strengthened by the results of a preliminary study in which we analysed a large data base of subjective complaints of 15,000 workers obtained during their annual medical checkup; 4.4% of the workers complained of excessive daytime sleepiness (EDS) during their medical interviews.

Based on these results, we decided to conduct a two-stage study to investigate the prevalence of sleep apnea in the general working population. Since the financial support for the study was obtained from a government agency responsible for safety at work, the study population consisted of "blue collar" industrial workers, and a great emphasis was placed on the interrelationships between safety at work and sleep complaints. In the first stage, a comprehensive survey on the prevalence of sleep-related complaints in the general working population with a major emphasis on excessive daytime sleepiness, was conducted. This was followed in the second stage by polysomnographic investigations of two selected groups of workers complaining of EDS and insomnia, and of noncomplaining controls.

The study was conducted during 1977-8, and the first report on the prevalence of sleep apnea was presented in the 20th annual meeting of the Association for the Psychophysiological Study of Sleep (APSS) which took place in Mexico City in 1980. The second presentation was made in a meeting organized by Lugaresi and Guilleminault (1981) in Bologna, which appeared as a chapter in a book in 1983.[6] The peer-reviewed papers appeared in *SLEEP* in 1981 and 1983.[1,7] Since the first stage of the study was the basis for the sleep laboratory investigation, I will provide a brief summary of this part before reviewing the accumulated literature on the prevalence of sleep apnea.

Excessive Daytime Sleepiness—A Prevalent Unrecognized Complaint

In the first stage of the study, 1502 industrial workers in more than 250 factories, were individually interviewed by trained medical students about their sleep habits and sleep complaints. The results of this survey confirmed our clinical impression that excessive daytime sleepiness is much more widespread than was previously considered. Fifteen percent of the workers reported that they needed to sleep during the day, 3.5% admitted to falling asleep during work breaks, and 2.6% confessed that they had to stop working in order to take a short nap. When asked how often they fell asleep during seven everyday situations (traveling, reading, watching TV, lectures, movies, plays and visiting friends), an approach later adopted by Johns in the Epworth Sleepiness Scale,[8] 119 workers reported falling asleep "always" or "many times" in at least two, and 35 workers reported falling asleep in at least three of the situations.

Workers complaining of EDS also complained significantly more of a large number of pre- and post-sleep symptoms, most notably snoring and excessive motility in sleep. Importantly, sleepy workers also had significantly more work accidents than the rest of the workers, and were less satisfied with their work conditions. Anticipating future findings, significantly more sleepy workers reported on hypertension and frequent headaches, and had a history of more hospitalizations. I concluded the discussion of that 1981 paper by saying:

"This cluster of pre- and post-sleep complaints, as well as the disturbing midsleep phenomena, shows remarkable resemblance to the type of complaints presented by patients complaining of

Address correspondence to: Peretz Lavie, Sleep Laboratory, Bruce Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Gutwirth Building, Haifa 32000, Israel; E-mail: plavie@tx.technion.ac.il

EDS due to breathing disorders in sleep. This close resemblance strongly implicates sleep-related breathing disorders as the main underlying etiology in the complaints of EDS among the workers studied here." (p.157). I should add, however, that at the time the discussion was written we already had preliminary results from the sleep laboratory stage of the study which pointed in the direction that many of the sleepy workers indeed had apneic events during sleep.

From EDS to Sleep Apnea

The results of the first stage confirming the impression that a relatively large segment of the adult, presumably healthy population, complained about EDS, and the observation that EDS is linked with a cluster of additional complaints and characteristics, led us to the second stage of the sleep laboratory study. Since this paper is printed side-by-side with the original paper, I will just summarize here its major findings in order to set the stage for the subsequent review and discussion of the literature. First, based on results of the sleep laboratory investigation, I estimated that the lower limit of the prevalence of a finding of at least 10 apneas per hour of sleep (Apnea Index, AI>10) in the industrial workers' population in Israel was 0.89%. Second, the occurrence of apneas in sleep was significantly associated with EDS, heavy snoring, frequent headaches, excessive motility in sleep, ear, nose, and throat (ENT) findings, and hypertension. This later finding linking apneas with hypertension was particularly impressive with five-fold more workers with AI>10 reporting hypertension, in comparison with workers with AI<10 (36.3% vs. 7.4%).

Limitations of the Study

Before examining some of these findings in light of the accumulated data since 1983, the limitations of the study should be recognized. Our sleep laboratory study suffered from several deficiencies. First, respiration during sleep was monitored by a nasal thermistor and a respiratory belt, which made the differentiation between central and obstructive apneas in some cases questionable. Second, there was no measurement of oxygen saturation. Third, since the importance of hypopneas was unrecognized at that time, only apneas were taken into consideration, which no doubt resulted in an underestimation of the true prevalence of breathing disorders in sleep. Fourth, since only one-third of the workers agreed to participate in the second stage of the study, it could have introduced some bias into the results. Fifth, since the study population consisted of presumably healthy individuals working in the industry, and the sleep laboratory study groups consisted of men only, the ability to generalize our results to the general population was limited.

I should also add that my choice of words for the title of the 1983 paper, "Incidence of Sleep Apnea in a Presumably Healthy Working Population" was wrong. The term "incidence" is reserved in epidemiological terminology to the rate at which new cases are discovered in a population, while the paper described the proportion of workers meeting the criterion of AI>10 at a particular point in time. Thus, the proper title should have been "Prevalence of Sleep Apnea in a Presumably Healthy Working Population." Unfortunately Hebrew does not differentiate between "incidence" and "prevalence."

It is rather gratifying that in spite of these limitations, comparison of the main results of the study to the findings on obstructive sleep apnea syndrome (OSAS) accumulated over the years reveals close similarities. Moreover, some of our observations have anticipated major future findings. I will examine now the results regarding the prevalence of sleep apnea, and the relationship between sleep apnea and hypertension, ENT findings and frequent headaches.

Apneas, Hypopneas, and the Prevalence of Sleep Apnea

It is very difficult to compare between the results of epidemiological studies investigating the prevalence of sleep apnea in the general population. The main reasons for that are the countless differences in the definition of the syndrome, particularly with respect to the use of apnea index (AI), or apnea-hypopnea index (AHI), the threshold used to define sleep apnea (e.g., AHI>5, AHI>10, AHI>15), and the reliance of the definition on the combination of apneas' frequency and subjective complaints, or on frequency of apneas alone. Other differences are in respect to the type of sleep study that was performed to identify apneas and hypopneas (e.g., attended PSG, unattended PSG, oximeter alone, etc.), the type of population studied, and the definitions used to select groups for sleep recordings (presumably healthy working population, hospitalized patients, snorers, sleepy patients, etc.) and the ethnic origins of the samples. Remarkably, in two studies using AI rather than AHI, one investigating all patients admitted during one year to a general hospital in Italy[9] and the other investigating sleep apnea in the general population in the Netherlands,[10] the estimated prevalence of OSAS was 1.0% and 0.9%, respectively, which is almost identical to the 0.89% observed in our study. Higher estimates ranging from 1.3% to 4.7% were reported in studies using AHI instead of AI.[11-14] Interestingly, using the criteria of AI>5 in combination with complaints about sleep (either insomnia or EDS), I estimated the prevalence of sleep apnea syndrome in the industrial workers' population to be in the neighborhood of 3.5%.[6]

The findings that 6/41 of the workers without any complaints had AI>5 (3/41 had AI>10), have been also supported by subsequent studies demonstrating that apneas in sleep is an occult finding among non-complaining individuals, particularly in elderly people.

Young et al.[13] reported that if symptoms are disregarded, 24% of male and 9% of female participants in the Wisconsin study had AHI>5. Similar findings were reported by others (see review[15]). The significance of these findings with respect to the definition of OSAS and its clinical significance is uncertain, an issue that will be discussed at the conclusion of this paper. I will examine now the findings linking apneas during sleep with hypertension, ENT findings, and headaches.

Hypertension and Sleep Apnea—The Holy Grail of Sleep Medicine

From a 20-year perspective, there is no doubt that the observation that workers with AI>10 suffered significantly more from hypertension than workers with AI<10, was of no less significance than the finding of the prevalence of sleep apnea itself. Although the association between sleep apnea and hypertension seen in many clinical cases has been recognized and discussed before 1983,[16] there was no evidence that this association extend-

ed beyond the obese, so-called Pickwickian syndrome patients, or the very OSAS patients.[17-19] As an immediate consequence of this unexpected finding, we decided to investigate the prevalence of apneas among a group of patients with essential hypertension.[20] In that study, which was the first to specifically address the possible association between sleep apnea and hypertension, we found that 16 out of 50 patients with essential hypertension who were randomly sampled at a hypertension clinic, had typical complaints of sleep apnea. Sleep laboratory recordings in these 16 patients, revealed that 13 (26% of the initial sample) had AI>5 and 11 (22% of the initial sample) had AI>10. Thus, the rate of patients with AI>10 among the patients with essential hypertension was approximately 20-fold higher than among the presumably healthy industrial workers. We concluded that paper by saying that: "The preponderant finding of Sleep Apnea Syndrome among patients with essential hypertension indicates that the possibility of sleep apnea syndrome should be taken into consideration when hypertensive patients are clinically evaluated. The most characteristic anamnestic features of EDS, loud snoring and restless sleep, which can be corroborated by the patient's bed partner, should alert the physician to this possibility." (pp. 376).

The relationship between hypertension and sleep apnea has become a major research area in subsequent years. It is gratifying to realize that our observations on a four-fold increase in the rate of hypertension in workers who had AI>10 and on the preponderant finding of sleep apnea among hypertensive patients, were fully confirmed by subsequent research. Our paper on sleep apnea in patients with essential hypertension was published in August 1984 in the *American Heart Journal;* in November of the same year, Kales et al.[21] reported that 30% of a group of essential hypertension patients had sleep apnea, and in 1985 two confirmatory studies were published by Williams et al.[22] and Fletcher et al.[23] So far, more than 50 studies have investigated the association between hypertension and obstructive sleep apnea; the majority of them have supported an independent association between OSA and hypertension (see review[24]). Particularly important is a series of studies that investigated exceptionally large populations of either sleep laboratory patients or randomly sampled populations, which allowed a careful control of all potential confounding variables. Three recent studies investigated the association between hypertension and breathing disorders in sleep in large random samples of the general population with wide age ranges. Young et al.[25] reported that in an unselected population of 1189 state employees in Wisconsin, breathing disorders in sleep were a risk factor for hypertension which was independent of age, BMI, or gender. Each apnea/hypopnea event per hour of sleep increased the hypertension risk in that population by approximately 4%. Importantly, their results show that the risk of hypertension was associated with RDI indices which were lower than the commonly employed cutoff point for OSAS of 5 or 10 respiratory events per hour. In a four-year follow-up study performed on a sub-sample of 709 of the original Wisconsin cohort,[26] the odds ratio for the presence of hypertension at follow-up (compared to an odds ratio of 1 for an RDI of 0) was 1.42 for an RDI of 0.1-4.9 at baseline, and 2.03 and 2.89 for RDIs of 5-14.9 and >15 respectively. This relationship was independent of known confounding factors. Neito et al.,[27] investigated 6132 subjects who were recruited from an ongoing population-based U.S. study (Sleep Heart Health Study—SHHS) aged>40 years. Sleep was studied by unattended home sleep recordings, and the association between RDI and hypertension was determined. They showed that after adjustment for confounding variables, the odds ratio for hypertension increased with escalating RDI categories in a graded dose-response fashion. Comparing the highest category of RDI (>30 per hour) with the lowest (<1.5 / hour) revealed an odds ratio of 1.37. Bixler et al.[28] investigated the relationship between hypertension and sleep disordered breathing in 1000 women and 741 men sampled from a much larger population, based on the presence of specific risk factors for sleep-disordered breathing. They reported an independent association between sleep-disordered breathing and hypertension that was strongest in young individuals, especially those who had normal weight. The association was not significant, or in the reverse direction, for the older individuals.

In addition to these large population studies, Davies et al.,[29] in a case controlled study of 24-hour ambulatory blood pressure measurements in 45 patients with OSAS and 45 normal matched controls, recently showed that the OSA patients had higher diastolic blood pressure during the day and night, and higher systolic blood pressures at night.

Similar results were reported for sleep laboratory populations. Lavie, Herer and Hoffstein[30] analyzed blood pressure data of 2677 patients recorded over several years in St. Michael's Hospital Sleep Laboratory in Toronto. They reported that the risk of hypertension rose with increasing OSA severity, as indicated by RDI or the level of nocturnal arterial oxygen desaturation. This relationship was independent of all potential confounding factors such as BMI, age, gender, or co-morbidity. There was a 1% increased risk for hypertension for each apnea/hypopnea event per hour of sleep. Grote et al.[31] similarly investigated 1190 consecutive patients referred for diagnosis of sleep-related breathing disorders and reported that the relative risk for hypertension was 4.15 for RDI >40 in comparison with RDI<5 after controlling for confounding variables.

Another line of evidence supporting the association between hypertension and sleep apnea comes from studies evaluating the effects of sleep apnea treatment on blood pressure. Mayer et al.[32] reported that six months of nasal Continuous Positive Airway Pressure (nCPAP) treatment significantly decreased blood pressure during sleep as well as during wakefulness in 12 patients with severe OSAS. This change could not be explained by a change in BMI. Suzuki et al.[33] performed ambulatory blood pressure monitoring for 48 hours in normotensive and hypertensive OSAS patients before and after CPAP treatment, and reported a significant decrease in daytime and nighttime blood pressure, but only in hypertensive patients. A possible selective effect of nCPAP treatment on OSAS patients was also reported by Engelman et al.[34] They showed a significant improvement in mean daytime arterial blood pressure only in a subgroup of patients defined as "non-dippers" under placebo treatment conditions. Others also reported that nCPAP treatment restored the normal circadian pattern of nocturnal "dipping" in OSAS patients.[35] Wilcox et al.[36] on the other hand showed a significant drop in mean 24 hour blood pressure in both normotensive and hypertensive patients after nCPAP treatment. Only diastolic blood pressure, however, was decreased during the day. Akashiba et al.[37] reported that two weeks of nCPAP treatment was sufficient to reduce both awake systolic and diastolic blood pressure in 31 OSAS patients. Minemura et al.[38] reported that the daytime and nighttime decrease in BP after nCPAP treatment was accompa-

nied by a significant decrease in daytime and nighttime levels of urinary noradrenaline. Interestingly, comparing the effects of nCPAP treatment with those of a nCPAP placebo (nCPAP administered at ineffective pressure) on 24 hour blood pressure in OSAS patients, Dimsdale et al.[39] reported that both treatments reduced daytime blood pressure levels to the same degree while only effective nCPAP treatment significantly reduced nighttime blood pressures. Voogel et al.[40] measured the blood pressure for 24 hours in OSA patients before and after three weeks of nCPAP treatment in a tightly controlled environment and with a control group. They showed that the treatment reduced the daytime and nighttime blood pressure, but only in the treated OSA group.

Perhaps the most convincing evidence that OSA can cause hypertension was found in animal models.[41] Phillipson's group in Toronto reported that producing OSA mechanically in dogs resulted in an increase in systemic blood pressure within a few weeks. When they stopped the OSA, the blood pressure fell back to normal again a few weeks later. Persistent hypertension could also be produced in rats by intermittent exposure to hypoxia for several days.[42]

Recently it was shown that sleep apnea is particularly important in patients with resistant hypertension. Isaksson and Svanborg[43] reported that the rate of sleep apnea syndrome in therapy resistant hypertensive patients was significantly higher compared to a control group of responders. Investigating 41 patients with drug-resistant hypertension by polysomnography, Logan et al.[44] reported that 83% of the patients had AHI>10. Lavie and Hoffstein[45] reported that hypertensive patients with sleep apnea whose blood pressure responds beneficially to treatment had lower RDIs than those patients whose blood pressure remained elevated despite anti-hypertensive therapy. Since neither obesity nor nocturnal hypoxemia appeared to be important determinants of ineffective treatment, frequent intermittent sympathetic stimulation appeared to be the most important factor. These findings are similar to those of Grote et al.,[46] who also found that patients with uncontrolled hypertension had significantly higher RDI than those whose blood pressure was well controlled.

ENT and Sleep Apnea—Rediscovering the Importance of the Nose in Sleep

The finding that 63.6% of the workers with AI>10 had some ENT findings, mostly in the form of allergic rhinitis and deviated nasal septum, also led us to examine this association in more specific studies. Confirming this observation, we documented breathing disorders in sleep in patients with allergic rhinitis.[47] These were mostly in the form of hypopneic episodes associated with microarousal from sleep, or K-alpha events. The conclusion of that paper anticipated the upper-airway resistance syndrome (UARS): "It is suggested that increased upper airway resistance and increased nasal discharge are responsible for the disordered breathing in sleep and for the 'microarousals.'" An historical investigation of the literature on the health consequences of obstructed nasal breathing revealed a wealth of evidence on deleterious effects on sleep quality and daytime behavior, some of it dating back to the 19th century.[48,49] The association between breathing disorders in sleep and obstructed nasal passages has been confirmed in large-scale studies, such as the Wisconsin cohort,[50,51] and in selected groups of patients with increased nasal resistance.[52] Furthermore, in a large series of patients referred for sleep evaluation because of snoring, daytime nasal resistance was found to be an independent risk factor for OSAS.[53] Treatment of nasal congestion by topical nasal corticosteroids appears to alleviate some of the daytime fatigue caused by the sleep fragmentation associated with the breathing disorder.[54]

The deleterious effects of mechanical nasal obstruction on breathing in sleep were first reported by Olsen et al.[55] and Lavie et al.[56] in normal young adults, and by Tassan et al.[57] in patients who had nasal packs after nasal surgery. In both normals and post-surgical patients obstructed nasal passages during sleep caused an increase in the number of disordered breathing events during sleep with concomitant sleep fragmentation. In a few of the subjects there was a dramatic appearance of full-blown OSAS. Carskadon et al.[58] later extended these findings to women. White et al.[59] anesthetized the nasal passages of 10 normal men during sleep and observed a fourfold increase in the number of breathing events during sleep which suggested that nasal receptors sensitive to air flow may be important in maintaining breathing rhythmicity during sleep. Furthermore, we[60] demonstrated that the effect of mechanical nasal obstruction on breathing during sleep was much more dramatic in children of OSAS patients. Without exception, all six children whose noses had been blocked suffered a large number of apneas during sleep. The average number of apneas increased tenfold with the obstruction, from one per hour to ten, whereas in the control group the increase was more moderate, from one apnea to three. Interestingly, their reaction to the experiment itself was dramatic. Patients' children reported that they had difficulty breathing through their mouths and two of them woke up in the middle with an alarming feeling of suffocation and asked to stop the experiment. The possible contribution of genetic factors in sleep apnea syndrome was later confirmed by Pillar and Lavie[61] and Redline et al.[62] Extensive reviews on the relationship between breathing disorders in sleep and nasal resistance can be found in.[63,64]

In spite of these findings, which point at the importance of proper nasal breathing during sleep, attempts to treat patients demonstrating breathing disorders in sleep by nasal surgery did not meet with great success in spite of an early impression.[65-68] It is possible though that a careful selection of patients using pre-surgical cephalometric evaluation, particularly in mild patients, may increase the success rate.[69] Likewise, popular devices used to dilate the anterior nares in patients without nasal pathology had a relatively weak effect on snoring and apneas.[70-72] External nasal dilation had also a very weak effect on patients with UARS, which represents the mildest form of breathing disorder in sleep.[73]

Headaches—A Non-Specific Symptom of Sleep-Disordered Patients

Evaluating the accumulated research on the relationship between OSA and headaches since the publication of the 1983 paper revealed a much more complicated picture. Although it is generally assumed that a complaint of headache upon waking up from sleep may indicate the possible existence of OSAS, this assumption was not uniformly supported by controlled research. There are some individual case reports documenting a relationship between cluster headaches and OSAS and some studies reporting on an association between morning headaches and OSA in comparison with normal controls.[74] Loh et al.[75] report-

ed that 23 out of 80 consecutive OSAS patients had awakening headaches. These headaches were of brief duration, and their occurrence and severity increased with increasing OSA severity. Treatment of OSA with continuous positive airway pressure or uvulopalatopharyngoplasty surgery reduced these headaches. Likewise, Ulfberg et al.[76] reported that the rate of morning headaches in patients with sleep apnea and in snorers was three-fold higher than in non-snorers.

But is this association specific to OSA, or perhaps a general finding in patients with sleep disorders? In a retrospective study, Poceta and Dalessio[77] showed that 24% of patients with OSAS had frequent morning headaches, which was not different from the patients with periodic leg movements and psychophysiological insomnia. Only in 30% of the sleep apnea patients did morning headaches improve after CPAP treatment. Similar findings were reported by Aldrich and Chauncey.[78] They reported that 18% of OSAS patients had frequent morning headaches compared with 21% to 38% in groups of patients with other sleep disorders. Paiva et al.[79] also reported that although headaches occurring during the night or early morning were often related to sleep disturbances, this was not specific to OSAS. Chervin et al.[80] questioned 36 subjects with cluster headaches about the times at which their headaches usually occurred and about several symptoms known to be predictive of OSA, and used logistic regression to determine whether occurrence of cluster headaches was associated with OSA symptoms. Although several OSA symptoms showed an association with cluster headaches' occurrence in the first half of the night, there was no general relationship with sleep-related symptoms.

Thus, it can be concluded that although subsequent studies confirmed the association between OSA and frequent headaches, frequent morning headaches is a nonspecific symptom in patients with sleep disorders but as a single symptom it is not a consistent and reliable symptom of OSAS.

Future Directions—Time to Target the Nonsleepy Patient?

Over the past 20 years, several types of abnormal obstructed breathing events during sleep have been described. Partial airway obstruction or hypopneas, first described by Kurtz and Krieger[81] were later shown to have the same consequences as apneas. Even more subtle breathing abnormalities have been described, such as progressive increases in respiratory effort, reflecting increasing upper-airway resistance, that terminate after an arousal.[82] To achieve some uniformity, The American Academy of Sleep Medicine proposed the following diagnostic criteria of breathing disorders in sleep.[83] These require that the individual must be found by overnight sleep laboratory monitoring to have five or more obstructed breathing events per hour during sleep. These events may include any combination of obstructive apneas/hypopneas or even respiratory effort-related arousals, plus having a complaint of excessive daytime sleepiness, or to have at least two of the following: choking or gasping during sleep, recurrent awakenings from sleep, unrefreshing sleep, daytime fatigue, or impaired concentration.

But are subjective complaints essential criteria for the diagnosis of breathing disorders in sleep? Although the vast majority of patients currently seen in diagnostic sleep laboratories are indeed examined because of daytime complaints, primarily excessive daytime sleepiness, it is not uncommon to find a large number of

apneic events during sleep in an otherwise asymptomatic individual, particularly in the elderly.[84] In some of these cases, the number of events would meet the diagnosis of severe OSAS if there were any of the above complaints. There is accumulated evidence that there is a critical frequency of disordered breathing events during sleep that is associated with long-term adverse health outcomes in individuals who otherwise do not qualify as having OSAS. The American Sleep Heart Health Study provided evidence that sleep-related breathing disorder has moderate effects on heterogenous manifestations of cardiovascular diseases within a wide range of AHI values that are considered normal, or only mildly elevated, regardless of any sleep-related symptom.[85] The values of AHI found to be associated with cardiovascular risk, 1-10 events per hour, are very common in the general asymptomatic population. Similar findings were reported with respect to hypertension.[25] Furthermore, Peker et al.[86] reported that coronary artery disease patients who also suffer from OSAS, defined solely by polysomnographic monitoring, had higher risk of cardiovascular mortality than patients without OSAS. Similar results were reported by Mooe et al.[87]

Thus, it appears that the mere finding of breathing disordered events during sleep confers a certain degree of risk, particularly in patients who are already at risk, regardless of any symptomatology. This was succinctly discussed by Hedner[88] in an editorial that accompanied the paper on the relation between AHI and cardiovascular risk in the SHHS study from which I borrowed the title for this section. Hedner pointed at the broad implications of the SHHS findings regarding the question of whether or not to treat asymptomatic patients with breathing disorders in sleep, and their significance with respect to the diagnostic efforts that should be invested in potential high-risk groups.

There is no doubt that currently only the daytime symptoms of OSAS patients are drawing medical attention. But if indeed the existence of breathing disorders in sleep is recognized as a risk factor for cardiovascular morbidity and mortality, regardless of any symptomatology, then a paradigm shift is needed in order to identify these individuals. Rather than waiting for symptomatic patients to come to sleep clinics, screening programs of high risk populations should be proactively initiated to identify individuals with breathing disorders in sleep, and this should be done at the youngest age possible.

There is accumulated evidence that age plays an important role in OSAS. For instance, the risk for hypertension in OSAS patients appears to be age-dependent and reaches a peak at the younger age groups of 30-50 years.[89,90] Likewise, excess mortality in OSAS patients appears to be restricted to patients younger than 50 years.[91-93] These consistent observations have been confirmed recently in a mortality analysis of more than 1100 patients conducted in our laboratory (paper in preparation).

These data may lead to the conclusion that for the majority of OSAS patients treatment of the syndrome starts too late. In most cases, a person comes for his first sleep laboratory diagnosis only when the symptoms of snoring and daytime sleepiness start bothering his or her partner. The average age of patients examined at sleep laboratories in different parts of the world is around 50, so we can state with a high degree of certainty that OSAS sufferers experience from breathing disorders in sleep for several years before they are diagnosed and treated. There is evidence that OSAS patients who are free of any overt cardiovascular morbidity, actually suffer from endothelial dysfunction which is a sub-

clinical state of atherosclerosis. This has been demonstrated by impaired vascular reactivity to vasodilating agents,[94,95] by increased concentrations of plasma homocystein,[96] by decreased levels of circulating nitric oxide,[97,98] and by increased rates of expression of adhesion molecules and indicators of oxidative stress.[99-101] It is entirely possible that the cumulative damage during the period between the syndrome's first appearance and its diagnosis may be irreversible.

Only large scale longitudinal Framingham-like studies such as the SHHS and the Wisconsin studies will be able to verify if the occurrence of breathing disorders in sleep even without any daytime symptomatology is related to long-term adverse health outcomes. It should be remembered, as noted by Littner and Shepard,[102] that the diagnostic criteria for hypertension and diabetes are based on quantitative measurements of blood pressure and fasting blood glucose regardless of any overt symptomatology. Perhaps in the future screening for breathing disorders in sleep will be done routinely as blood pressure measurements and plasma glucose levels.

Epilogue

I will end up this revisit of the 1983 paper on the prevalence (rather than incidence) of OSA with a vivid recollection from my first public presentation of these findings in the 20th APSS meeting in Mexico City in 1980. This will illustrate the change in zeitgeist with respect to the attitudes toward breathing disorders in sleep. At the conclusion of my presentation that there is an estimated 3.5% prevalence of OSA among presumably healthy industrial workers aged 40-60, one of the prominent sleep researchers of that time stood up and made the following comment "Either the prevalence of sleep apnea in Israel is for some reason unusually and unexpectedly high, or something is wrong with your data, it is impossible that there were so many sleep apneics in the population." I always wondered how this researcher reacted to Young et al.'s *New England Journal of Medicine* paper, which demonstrated that almost one out of four adult men have more than five breathing events per hour in sleep.

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