REVIEW SERIES

Sleep · 1: Obstructive sleep apnoea/hypopnoea syndrome: definitions, epidemiology, and natural history

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Thorax 2004;**59**:73–78. doi: 10.1136/thx.2003.007161

Arguments over the definition of obstructive sleep apnoea/hypopnoea syndrome (OSAHS) have still not been satisfactorily resolved. As a result, robust estimates of the prevalence of OSAHS are not possible. New approaches are needed to identify those who have ''CPAP responsive'' disease, enabling more accurate estimates to be made of the prevalence of the sleep apnoea syndrome in the community.

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The treatment of obstructive sleep apnoea/hypopnoea syndrome (OSAHS) has moved from relative certainty to a time of uncertainty over what really constitutes significant symptomatic disease. During the early years of OSAHS recognition, apnoeic events leading to abnormal sleep and consequential sleepiness seemed an easy scenario to understand. Furthermore, treating the apnoeas led to spectacular improvements in symptoms and there seemed little to argue about. Little by little these simple concepts have been whittled away so that we are no longer sure of how to relate the spectrum of upper airway narrowing at night to the impairment of health and thus treatment decisions.

DEFINITION

Problems first began to arise with the definition of sleep apnoeic events. In the early days the episodes of complete upper airway collapse with apnoea and subsequent arousal were easy to see and understand. Simple oronasal thermistors and chest/abdomen strain gauges identified hundreds of obstructive events,[1] and conventional epoch based sleep staging showed impairment of general sleep architecture with less slow wave sleep and more sleep stage changes.[1] Studies on unmatched (mainly young) normal subjects established an apparent narrow band of normality for numbers of apnoeas per hour of sleep, and the original definition of sleep apnoea (>5/h of >10 second apnoeas) rapidly became internationally accepted.[2]

Sleep induced upper airway narrowing

Unfortunately much has happened since then to expose how oversimplified this was. Upper airway narrowing with sleep onset is a normal phenomenon,[3] with various factors conspiring to accentuate it (such as obesity, craniofacial abnormalities, tonsillar enlargement, etc). These accentuating phenomena are not ''all or none'' in nature, and thus upper airway narrowing during sleep is a continuously variable phenomenon within a population and, indeed, to some extent across nights within an individual. The points along this continuum at which inspiratory resistance rises, snoring develops, hypoventilation ensues, or full apnoeas occur are fairly arbitrary but relatively easily identifiable. There is no obvious reason to expect onset of symptoms to be linked with the onset of these arbitrary points along the continuum. Thus, although there has been a replacement of apnoeas with ever more sensitive indices of disturbed breathing, these have not led to obviously better correlations with the patients' presenting symptoms and their management.

It was recognised early on that full obstructive apnoeas were not necessary to provoke arousals, and that obstructive hypopnoeas could do the same.[4] These were harder to define than apnoeas as the level of hypoventilation required to define an event was quite arbitrary—usually 50% reduced—and could vary considerably with the transducers and actual analysis algorithms used in the sleep study.[5 6] The addition of attendant hypoxic dipping was advocated to improve consistency, but again the threshold to define a dip was arbitrary and 2%, 3%, or 4% have been used with very different event rates resulting.[7]

Sleep fragmentation

With the appreciation that the dominant symptom of OSAHS—sleepiness—was due to sleep fragmentation, attention turned to defining respiratory related sleep fragmentation in the hope that this would better represent the disease activity. The finding that increases in upper airway resistance and resultant rises in inspiratory effort can lead to recurrent microarousals without evidence of apnoeas, hypopnoeas, or even hypoxia[8] led to the concept of respiratory related arousals (RERAs). This approach allows a variety of different respiratory events to be counted if they appear to lead to arousal. The so-called ''upper airway resistance syndrome'' is also included where increasing inspiratory effort alone (measured either with oesophageal manometry or by detecting inspiratory flow limitation) is an event as long as it seems to lead to an arousal. There is argument over the existence of such subtle respiratory abnormalities and whether the use of thermistors to record airflow led to under recognition in the first place.[9 10] This is likely to be part of the explanation, but there is no doubt that increased inspiratory effort alone can provoke an arousal, although the clinical importance of such events is not clear.[11] Hosselet *et al*[12] have investigated the best predictor of

''OSAH syndrome'' in 37 sleep clinic patients with OSAHS, some with no snoring or sleepiness and some with snoring and sleepiness. They found that counting apnoeas, hypopnoeas, and flow limitation events together best predicted sleepiness in a subsequent group of 103 patients, but only with a specificity and sensitivity of 60% and 71%, respectively.

Much effort has also been spent trying to define the minimum degree of sleep disturbance that might lead to daytime symptoms, and microarousals were originally defined as detectable lightening of the EEG for 3 seconds or more.[13] Reducing the length of EEG changes required to define a microarousal to 1.5 seconds (with EMG increases however small) was only minimally better at predicting daytime performance (simple reaction time).[14] On the other hand, the Edinburgh group have produced some evidence in normal subjects that one night of sleep fragmentation, insufficient to produce EEG changes but enough to cause transient rises in blood pressure (so called ''autonomic arousals''), can have small effects on daytime function.[15]

It was hoped that this increasing sophistication in measuring all the events consequent upon upper airway narrowing would improve our ability to correlate with, and predict, daytime symptoms. This, disappointingly, has not really been the case and a new gold standard to replace the apnoea/hypopnoea index (AHI), despite its clear limitations, has not evolved out of the enormous effort by many laboratories to try and measure *the* critical events. Our ability to correlate sleep study indices with daytime measures of sleepiness rarely rises above an *r* value of 0.4—that is, less than 20% of symptoms across a sleep clinic population appear explicable on the basis of the sleep study, our primary diagnostic tool.

Symptoms

The cause of our failure to correlate sleep studies to symptoms may also lie in our inability to measure the symptoms very well. Patients tell us they are sleepy, but sleepiness can be contributed to by many other problems from depression to the arrival of a new baby. There are many objective tests of sleepiness and vigilance that it was hoped would improve our ability to relate symptoms to the sleep study. These, too, have been disappointing with objective tests—for example, the multiple sleep latency test (MSLT), multiple wakefulness test, or driving simulators—appearing to correlate no better with sleep study indices than subjective scores such as the Epworth Sleepiness Scale (ESS).[16–18] Some of this poor correlation between sleep study indices and daytime function tests may be due not only to their poor measurement, but also to night to night variation in OSAHS severity and day to day variation in performance producing extra ''noise'' in the data.

Finally, inter-individual sensitivity is probably also an important factor with some individuals coping well with a degree of sleep fragmentation that renders another dangerously sleepy.[19 20] In addition, epidemiological surveys show a considerable spread of sleepiness (as measured with the ESS) within a population[21–23] and, perhaps, those already at the sleepy end of the spectrum are more likely to be troubled by additional sleep fragmentation

Cardiovascular aspects

To make matters worse, there is now increasing evidence that sleep fragmentation and sleepiness are not the only adverse consequences of OSAHS. For example, OSAHS produces rises in blood pressure,[24] both at night and during the day, and treatment of the OSAHS reduces it.[25 26] Much epidemiological work also suggests that there might be further cardiovascular consequences[27 28] although definitive interventional trials are unlikely to be possible, leaving a significant doubt as to the part played by confounders in cross sectional or case control studies. Therefore, in defining the disease and identifying patients for treatment, should hypertension as well as symptoms be included, as has been suggested in recent guidelines, despite the limitations of the data?[29] Unfortunately the correlation between sleep study indices and blood pressure is even worse than with sleepiness.[30]

In addition, there may be other effects of sleep apnoea—for example, on catecholamine levels,[31] insulin resistance,[32] leptin levels,[33] clotting factors,[34] and several other potential cardiovascular risk factors. However, the evidence for these remains at a circumstantial level with virtually no controlled intervention studies and more detailed studies sometimes reveal alternative explanations.[35] Finally, the part played by sleep induced upper airway narrowing and flow limitation and a consequential small rise in arterial carbon dioxide tension ($PaCO_2$) on the blood pressure in pre-eclampsia has been suggested by Connolly *et al*,[36] further expanding the ''syndrome'' of obstructive sleep apnoea.

There are now several large datasets correlating adverse outcomes with the AHI, such as the Wisconsin Cohort,[28 37 38] the Sleep Heart Health Study,[27 39] and the Pennsylvania study.[40] For historical reasons the AHI has been used as the predictor and perhaps a measure of hypoxia, such as time below a certain threshold. These studies have perpetuated the AHI as the measure of OSAHS, yet they do have the ability to explore the predictive value of other measures such as Sa_{O_2} dipping, microarousals, movement arousals, etc. Such detailed analysis would help the field enormously—either to establish that there is a clear ''best'' predictor or that simple alternative measures work just as well. This would allow the wider use of simpler and cheaper sleep studies to the considerable benefit of patients.

The failure of the specialty to harden up on its disease definitions, perhaps due to a level of intellectual rigour not always present in other areas and disorders, has led to significant problems with those who purchase health care.[41] It is unfortunate that arguments over precise definitions and outcomes have obscured the simple observation that very large numbers of patients with moderate to severe sleep apnoea have derived enormous benefit from the definitive treatment—nasal CPAP—an effect now clearly proven in robust placebo controlled trials[25 26] and meta-analyses.[42]

Given this depressing lack of correlation across populations between the supposed cause of OSAHS and its supposed symptoms, can we define accurately what sleep apnoea syndrome is, particularly when making clinical decisions? The answer is probably not, because we do not know how to pick out those individuals who have relevant symptoms and will respond to nasal CPAP and want to go on using it. This is arguably the end point of interest—that is, what is ''CPAP responsive disease'' since CPAP reverses the primary abnormality? This is rather similar to the state that interstitial lung disease was in a few years ago, when ultimately clinicians were forced to do a steroid trial regardless of the histological, lavage, or CT appearances as they were unhelpful in predicting therapeutic response or prognosis.

CPAP responsiveness

A recent study by Bennett *et al*[17] looked at predictors of CPAP response in a group of sleep clinic referrals with a wide range of OSAHS severity. When improvements in sleepiness (subjective or objective) were considered, simple sleep study derivatives such as >4% Sa_{O_2} dip rate and a body movement index proved the most predictive. Thus, in a sleep clinic population with symptoms compatible with OSAHS (snoring and sleepiness), the oxygen desaturation index was the best

and easiest means of defining the disease. Even so, the correlation was no better than 0.6, showing that less than 40% of the response to CPAP could be predicted from the sleep study. This has led to the suggestion that the sleep study is unhelpful and that a trial of CPAP is the only way to be sure of finding treatable disease, leading to the expression (attributed to Phil Westbrook) ''if in doubt, blow up the snout''. With modern auto-titrating machines such an approach is seductive. However, this would have several drawbacks. First, as shown in controlled trials,[25 26] there is an enormous placebo effect on subjective end points such as the ESS and SF36 score but not on objective tests of sleepiness such as the MWT. This implies that the proper assessment of a CPAP trial would need objective measures of sleepiness, greatly increasing the cost. Alternatively, one could work to try and reduce the placebo effect by explaining the possibility of little or no response to the patient, but perhaps running the risk of a real responder giving up in the early difficult days assuming that he/she was not going to benefit. Secondly, many patients present with compatible symptoms without anything remotely resembling OSAHS on a sleep study which would mean many unnecessary CPAP trials. In our experience such individuals have degrees of depression or poor sleep hygiene and also happen to snore. Furthermore, obesity alone is associated with sleepiness in the absence of OSAHS.[43] Some form of sleep study to raise the pre-test probability of a successful CPAP trial therefore seems necessary.

This has led to many sleep clinics adopting a highly pragmatic approach to the management of sleep apnoea—for example, using the sleep study merely as an identifier of some abnormality from heavy snoring through to frank OSAHS that might explain the patient's symptoms. The patient's symptoms are the more important part of this equation and there is good evidence that sleepiness and its resolution determines the success of CPAP more than the sleep study.[44–47] This means that counting events and setting thresholds becomes unhelpful: a severely symptomatic patient with only heavy snoring and increased arousals might warrant a trial of nasal CPAP, whereas an individual with few or no symptoms would need to demonstrate considerable amounts of OSAHS and hypoxic dipping to justify persuading him to have a trial of CPAP. A wide variety of sleep study technologies can be used to assess sleep apnoea to this level of precision.[48]

This is clearly a relatively unsatisfactory state of affairs, but there really is no evidence that greater precision in sleep studies leads to a greater precision in disease definition and management. Sleep specialists should not be embarrassed to function in this very clinical way. There are many areas of clinical medicine where the synthesis of experience and less than perfect tests determine treatment. Thus, for pragmatic reasons, the only current valid definition of OSA syndrome is ''sleep induced upper airway narrowing leading to symptomatic sleep disturbance''. Even this does not allow for the evolving area of cardiovascular complications perhaps being a reason to treat OSAHS, but as yet there is no evidence that treating OSAHS with CPAP reduces adverse cardiovascular outcomes better then conventional management of hypertension and other relevant risk factors which are often best addressed through simple lifestyle measures such as weight loss and dietary changes.

PREVALENCE OF OSAHS

It is clear from the above that the definition of relevant disease is not easy, hence making robust estimates of OSAHS prevalence is not possible. One can take the simple approach and base the prevalence estimates on sleep study indices alone. This has been done by many centres using very different technologies ranging from full polysomnography[49] to simple oximetry.[50] The results of many these studies have been reviewed in recent years.[51–53] Essentially, the prevalences vary depending on the definition of ''events'' and the population under study. If a tough definition is used—essentially identifying those individuals with moderate to severe disease who have clear sleepiness that would lead to a CPAP prescription if had they presented to a sleep clinic—then the prevalence is probably about 0.5% in a UK population of middle aged men (mean age 48.2 years) with a mean body mass index (BMI) of 24.9 and perhaps 1.5% in a similar population (mean age 52 years) but with a mean BMI of 27.1.[23 50]. If an all inclusive definition is used based entirely on polysomnographically defined apnoeas and hypopnoeas >5/hour and no symptoms, then the prevalence rises to 24% in a US male population with mean BMI of about 30.[49] In this latter study a more realistic prevalence estimate was attempted by defining ''OSAH syndrome'' as the combination of >5/hour apnoeas/hypopnoeas in conjunction with significant sleepiness (found in 10% of men and 12% of women). However, the overlap between these two states was actually no more common than would be expected by chance,[52] making the point that irregular breathing at night and sleepiness are both common and not necessarily related. The prevalence based on this combined definition was 4% in men and 2% in women.

Recent studies

More recent epidemiological studies[54–56] published since the last reviews in this journal have provided similar prevalence estimates which have not really advanced the situation much further and are unlikely to do so until we can better define the condition. Our recent attempt in this area tried to correlate sleepiness, using the validated sleepiness score ESS, with more sensitive measures of sleep fragmentation based on autonomic markers of arousal and measures of inspiratory effort overnight.[23] This also failed to improve the identification of a significant link between sleepiness and obstructed breathing, although the latter was weakly correlated with change in blood pressure overnight. Several other epidemiological studies have been performed on non-white groups[57–62] and have often found higher prevalences in Far Eastern and African populations, which are only partly explained by simple measures of body habitus but perhaps more by differences in craniofacial shape.[63]

Other more recent large studies have also failed to find a strong link between sleep apnoea activity and daytime measures of sleepiness and quality of life.[22] The large Sleep Heart Health Study (n = 5777) looked at sleepiness (ESS) across four grades of AHI severity and found that the mean value rose from 7.2 in those with an AHI of <5 to 9.3 in those with an AHI of ⩾30, only a 2.1 point rise in a scale ranging from 0 to 24. They also showed an independent effect of snoring, having allowed for the AHI, again demonstrating the limitations of a one night AHI measurement in defining symptomatic disease.[64] These results emphasise that ''sleep study OSAH'', as found in epidemiological studies, is not the same phenomenon as ''sleep clinic OSAH'' which presents usually because of significant symptoms. However, the Wisconsin Sleep Cohort Study did identify a correlation between sleep apnoea and multiple motor vehicle accidents, although correlation does not prove causation and the exact interpretation of these data has been questioned.[65] In this study an AHI of >15 versus no sleep disordered breathing or snoring increased the odds of having had multiple motor vehicle accidents by 7.3 (mainly in men) where the prevalence of such accident histories was 2.6% overall. Other epidemiological studies have also found poor or no correlation between AHI and symptoms or sleepiness.[66]

Sex differences

Other interesting epidemiological data have come from studying the prevalence of sleep apnoea in women aged 20–100 and the effects of the menopause. In a study from Pennsylvania and Madrid[67] the prevalence of OSAHS was estimated from a two stage process. Telephone interviews were used to assess pre-test probability based on conventional predictors that were shown to predict the prevalence of OSAHS to some degree (snoring, daytime sleepiness, obesity, hypertension, and menopause). The highest scoring groups were then relatively oversampled to provide a total of 1000 subjects who agreed to undergo sleep laboratory polysomnography studies. The definition of hypopnoea required a 4% fall in Sa_{O_2} and an AHI of ⩾10/h was their arbitrary cut off for defining OSAHS and symptoms were not required. These results were also compared with previous data from their laboratory on 741 men. Men had a prevalence of 3.9% and women 1.2% (ratio 3.3:1). However, in premenopausal women (and those on HRT) the rate was 0.6%, rising to 2.7% in postmenopausal women not on HRT. As would be predicted from all other studies, obesity also had a considerable effect in both sexes. These data were supported by similar effects on the prevalence of just snoring without OSAHS. Another interesting finding was that all the premenopausal women and those on HRT who had an AHI of ⩾15 had a BMI over 32. In contrast, in postmenopausal women without HRT who had an AHI of ⩾15 the prevalence of a BMI over 32 was less than 50% (similar to the men). This generates the hypothesis that the female sex hormones are perhaps protective to some extent against non-BMI related risk factors for OSAHS. Earlier studies had shown more severe OSAHS in postmenopausal women[68] and reductions in indices of sleep disordered breathing from HRT (oestrogen and progesterone) in healthy postmenopausal women.[69] Conversely, testosterone may provoke OSAHS, perhaps by effects on the upper airway.[70]

In conclusion, it is likely that symptomatic sleep apnoea in men worthy of CPAP treatment has a prevalence of 1–2%, depending on prevailing obesity, with the prevalence in women being perhaps one third of this. Supporting this at an anecdotal level, in a local Oxford general practice of 4500 patients (1840 aged 35–75 years) where awareness of OSAHS is high, there are seven patients (five men and two women) on CPAP with three others who have tried it but decided the hassles outweighed the advantages. This gives a prevalence of 0.6% men and 0.3% women currently on CPAP long term (unpublished observations). Much more impressively, Thoranin Gislason who runs the OSAHS service for the whole of Iceland with a population of about 250 000 has made a diagnosis of OSAHS in 2350 individuals between 1987 and 1999, of whom 886 were put on CPAP. There are about 51 000 Icelandic men aged between 35 and 65, of whom about 1.3% are on CPAP (personal communication).

EVOLUTION OF OSAHS

Most data on the evolution of OSAHS come from cross sectional surveys which assume that age related differences are due to the ageing process itself. Few studies have looked at individuals over a period of time and looked for evidence of progression and relevant risk factors for this. Cross sectional studies on prevalence do show effects of age, independent of the unfortunate propensity for a rising BMI with age. Some studies show an approximate doubling of AHI every 10 years or so,[54 71] although some have found a smaller rise with age.[49] If symptoms are included in the definition of OSAHS, then the prevalence seems to fall above the age of 60 or so (fig 1). This is the experience of most clinics looking after patients with OSAHS where the peak age of presentation is about 50 and the prevalence falls off quite steeply above this age. It is not clear if this is because older patients simply do not complain of their symptoms or because it genuinely does not have such adverse consequences as in younger patients. Bixler *et al*[54] have also shown that the nature of OSAHS in the elderly changes, with less severe falls in Sa_{O_2} with each apnoea than in younger patients, particularly in those with the highest AHI values, which were not explained by differences in BMI, for example.

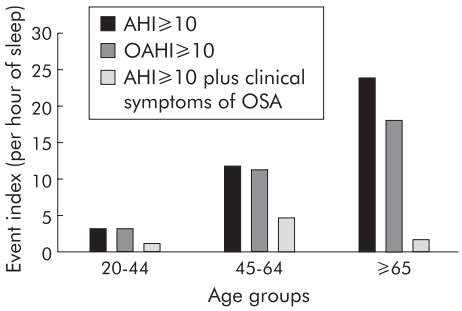

Figure 1 Mean sleep apnoea severity in ''young'', ''middle aged'', and ''older'' men from a community population. Three definitions of sleep apnoea are compared, a simple AHI (definition includes 4% Sa_{O_2} desaturation), an obstructive AHI (OAHI), and a combined sleep study (AHI ⩾10) + symptom based definition. Note that, although sleep study defined disease worsens with age, there is actually a fall in the group aged over 65 when the clinical definition including symptoms is used. Data from Bixler *et al*.[54]

The Wisconsin cohort study has looked at the same population on more than one occasion 4 years apart. A 10% weight gain predicted a 32% increase in AHI, whereas a 10% loss in weight predicted a 26% decrease in AHI.[72] This is similar to interventional data in patients with OSAHS where weight loss has considerable effects on OSAHS severity.[73 74] Clinical experience suggests that, before presentation, many patients with OSAHS have experienced a considerable and relatively sudden weight gain (fig 2). It is not clear whether this was the precipitant of their OSAHS or resulted from it. Lindberg *et al*[75] also showed in a questionnaire based epidemiology study in 2668 men that over 10 years snoring increased from 15% to 20% and that weight gain was an important predictor of this increased prevalence. In a subsample of this study, 38 subjects with symptoms of OSAHS who had undergone polysomnography 10 years previously were re-contacted. Of the 29 who had not received treatment originally, only four had an AHI of ⩾5 whereas 10 years later there were 13 ($p<0.01$), but there seemed to be no predictors of this decline.[76] In contrast, in a study from the Netherlands in which measurements were made 8 years apart, there was little change in thermistor defined AHI in a

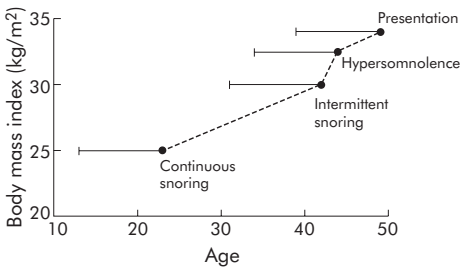

Figure 2 Evolution of sleep apnoea symptoms and body weight with age. Based on a retrospective assessment at time of presentation. Bars represent standard deviation. Note the long history of snoring before the development of OSAHS, and the sharper rise in body weight towards the time of eventual presentation. From Lugaresi *et al*.[81]

subgroup considered at higher risk of OSAHS, with some deteriorating and some improving.[77]

Pendlebury *et al*[78] restudied a group of sleep clinic attendees about 1 year after the initial presentation to see if their OSAHS had worsened or not. Unfortunately, this study group consisted only of those not put on CPAP because of less severe disease in the initial sleep study. Given that the mean AHI of the whole clinic population would have been higher at presentation (including those with more severe disease who did go onto CPAP), this apparent deterioration is probably an example of regression to the mean (of their population). Sforza *et al*[79] restudied after at least 5 years 32 patients with OSAHS who had refused treatment following diagnosis. On average there was no change in AHI, BMI, or indices of oxygenation, and most of the individual changes were explained by regression to the mean of the group. There was no correlation between change in BMI and change in AHI. In addition, there were no changes in blood pressure or objective sleepiness using the MSLT. There is thus conflicting evidence as to whether OSAHS inevitably worsens in the absence of weight gain, although it probably does if weight does rise. Once again, different populations and clinical patients versus epidemiological studies may explain some of the conflicts in the data.

In conclusion, recent work has added little to the reviews of epidemiological studies in this journal written some seven years ago.[51 80] It is more widely recognised that AHI poorly defines the syndrome resulting from upper airway narrowing during sleep, and this has made life much more difficult for those seeking to estimate the so far unrecognised health burden of OSAHS. It is hoped that new approaches will begin to identify those who have ''CPAP responsive'' disease or significant cardiovascular risk. We will then be in a better position to make true estimates of sleep apnoea syndrome in the community.

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