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Obstructive Sleep Apnoea: From pathogenesis to treatment: Current controversies and future directions

Peter R. Eastwood[1,2], **Atul Malhotra**[3], **Lyle J. Palmer**[4], **Eric J. Kezirian**[5], **Richard L. Horner**[6], **Mary S. Ip**[7], **Robert Thurnheer**[8], **Nick A. Antic**[9], and **David R. Hillman**[10]

[1]West Australian Sleep Disorders Research Institute, Department of Pulmonary Physiology, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia [2]School of Anatomy and Human Biology, University of Western Australia, Perth, Western Australia, Australia [3]Harvard Medical School Medical Director Sleep Disorders Research Program, Brigham and Women's Hospital, Boston, Massachusetts, USA [4]Centre for Genetic Epidemiology and Biostatistics, University of Western Australia, Perth, Western Australia, Australia [5]Division of Sleep Surgery, Otolaryngology—Head and Neck Surgery, University of California, San Francisco, California, USA [6]Departments of Medicine and Physiology, University of Toronto, Toronto, Ontario, Canada [7]Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong, China [8]Kantonsspital Münsterlingen, Münsterlingen, Switzerland [9]Adelaide Institute for Sleep Health and Flinders Medical Centre, Adelaide, South Australia, Australia [10]West Australian Sleep Disorders Research Institute, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia

Abstract

Obstructive sleep apnoea (OSA) is a common disease, recognized as an independent risk factor for a range of clinical conditions, such as hypertension, stroke, depression and diabetes. Despite extensive research over the past two decades, the mechanistic links between OSA and other associated clinical conditions, including metabolic disorders and cardiovascular disease, remain unclear. Indeed, the pathogenesis of OSA itself remains incompletely understood. This review provides opinions from a number of leading experts on issues related to OSA and its pathogenesis,

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Correspondence: Peter R. Eastwood, Department of Pulmonary Physiology, Sir Charles Gairdner Hospital, Hospital Avenue, Nedlands, WA 6009, Australia. peter.eastwood@health.wa.gov.au.

P.E. is a National Health and Medical Research Council (Australia) Senior Research Fellow at the West Australian Sleep Disorders Research Institute, Sir Charles Gairdner Hospital and Professor at the School of Anatomy and Human Biology, University of Western Australia. A.M. is a Pulmonary Intensivist and Sleep Specialist who is an Associate Professor of Medicine at Harvard Medical School and is Medical Director of the Sleep Disorders Research Program and Clinical Chief of Sleep Medicine at Brigham and Women's Hospital in Boston. L.P. holds the Winthrop Chair in Genetic Epidemiology and is Director of the Centre for Genetic Epidemiology and Biostatistics at the University of Western Australia. E.K. is Director of the Division of Sleep Surgery in the Department of Otolaryngology—Head and Neck Surgery at the University of California, San Francisco. R.H. is currently a Tier 1 Canada Research Chair in Sleep and Respiratory Neurobiology and Associate Professor of Medicine and Physiology at the University of Toronto, performing research in the control of sleep and breathing. M.I. is Mok Hing Yiu Endowed Chair Professor of Respiratory Medicine and Associate Dean in Education at the Li Ka Shing Faculty of Medicine, The University of Hong Kong. R.T. is Head of the outpatient clinic at the Kantonsspital Münsterlingen, Switzerland and Associate Professor of Respiratory Medicine at the University of Zurich, Switzerland. N.A. is a Senior Staff Specialist in Respiratory and Sleep Medicine at the Adelaide Institute for Sleep Health and Flinders Medical Centre. He is Clinical Director of the Adelaide Institute for Sleep Health. D.H. is Director of the West Australian Sleep Disorders Research Institute and Head of the Department of Pulmonary Physiology at Sir Charles Gairdner Hospital and Clinical Professor at the University of Western Australia.

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interaction with anaesthesia, metabolic consequences and comorbidities, cardiovascular disease, genetics, measurement and diagnosis, surgical treatment and pharmacotherapeutic targets.

Keywords

pathogenesis; treatment; sleep apnoea syndrome

INTRODUCTION AND SUMMARY OF CONTRIBUTIONS

Peter Eastwood

Obstructive sleep apnoea (OSA) is characterized by episodes of partial or complete pharyngeal collapse associated with reductions or total absence of airflow during sleep. OSA affects up to 20% of the population, with approximately 5% experiencing excessive daytime sleepiness.[1] It is associated with increased accident risk and is an independent risk factor for a range of clinical conditions, such as hypertension, stroke, depression and diabetes. The total economic burden of OSA (health costs, lost productivity, accidents, loss of life quality) is substantial, accounting for billions of dollars per year,[2,3] and is expected to increase.

Despite a marked increase in the number of annual research publications on OSA over the past 10 years, from 255 in 1998 to 1198 in 2008 (PubMed search), the mechanistic links between OSA and other associated clinical conditions, including metabolic disorders and cardiovascular disease, remain unclear.[4] Indeed, the pathogenesis of OSA itself remains incompletely understood, although it is now widely accepted that it is multifactorial in nature, involving anatomical, neuromuscular, chemical and mechanical factors.[5]

This review provides expert opinions from a number of scientists on contemporary issues relevant to solving important pathophysiologic, diagnostic and treatment dilemmas posed by OSA. Each scientist was asked independently of the others to comment on where their field should be heading, not necessarily where it is heading. It is notable therefore that the need to more precisely define OSA phenotypes is a common theme.

More precise phenotypic characterization would allow better targeting of an individual patient's therapeutic options, whether they be surgical, mechanical or pharmacological, to optimize outcomes. Such improved characterization would also help define patients who may be suitable for assessment using portable monitoring as part of a simplified clinical algorithm for the diagnosis of OSA.[6,7] From a population health perspective, better phenotypic classification is essential for improved accuracy of large-scale epidemiological or genetic association studies. Thus the need to better define OSA phenotypes and to standardize and develop simple techniques to do so should be considered as priorities for future research into OSA.

But an even more fundamental immediate priority for OSA research should be the development of a global consensus on the criteria used to define OSA severity. When a historical comparison with a normal population is required, the Wisconsin study of middle-aged adults[8] is most commonly referred to. However, we are currently in the absurd position in which an AHI cut-off of 5/h used to define sleep-disordered breathing in the Wisconsin

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study[8] is the approximate equivalent of an AHI of 15/h using the 'Chicago' definition[9] and 10/h using the alternative 2007 American Academy of Sleep Medicine definition.[10,11] This absence of standardization has numerous implications including its impacts on disease identification, severity grading and comparability of results between different laboratories and research studies and their design.[11,12] The lack of standardization may also affect treatment decisions, treatment funding by third parties, OSA prevalence estimates, estimates of the public health impact of OSA and the establishment of links between OSA and comorbidities. Determining the most appropriate definition for OSA severity, whether by AHI or other means, requires studies comparing alternative definitions in terms of their association with relevant outcomes, such as hypertension, cardiovascular disease, sleepiness, impaired quality of life or accidents.[11] An immediate priority for the global sleep community should be an inclusive discussion by relevant international organizations of the most appropriate criteria.[13] Despite the recognized limitations of the AHI,[14] it is perhaps the best OSA metric we have at the moment and it may be time to accept this and take steps to agree on the measurement principles defining it.

PATHOGENESIS

Atul Malhotra

The pathogenesis of OSA is traditionally thought to involve a complex interaction of pharyngeal anatomical compromise with state-dependent upper airway dilator muscle dysfunction.[5] Important roles for unstable ventilatory control (high loop gain, i.e. increased propensity for periodic breathing or cyclical output from the central pattern generator), end-expiratory lung volume and possibly upper airway oedema have more recently been suggested.[15] Emerging evidence suggests that OSA mechanisms are variable with some pathophysiological factors having major roles in some patients more than others. For example, some patients may have OSA primarily due to anatomical compromise at the velopharynx (amenable to uvulopalatopharyngoplasty), whereas others may have primarily high loop gain (amenable to oxygen) and still others may have a combination of abnormalities (requiring a multifaceted therapeutic approach).[16] The following three concepts are proposed to advance our knowledge of OSA pathogenesis.

First, the assessment of variables in isolation is unlikely to be illuminating as the complex interplay of various physiological variables is critical to the presence or absence of disease, for example, a high arousal threshold may be deleterious if profound hypoxaemia and hypercapnia develop prior to arousal, but a high arousal threshold may be beneficial if the accumulation of respiratory stimuli prior to arousal is sufficient to activate pharyngeal dilator muscles and stabilize the upper airway.[17,18] Thus, experiments designed to assess one isolated variable (such as arousal threshold) are unlikely to yield a complete picture. Methods to integrate multiple variables using computational models[19] or multivariate statistical models will ultimately need to evolve and mature.

Second, less cumbersome methods are needed to delineate mechanisms underlying apnoea without requiring investigator-attended overnight experiments to acquire quality data. Clearly, simplification or automation will be required to achieve the eventual goal of providing equipment to patients, sending them home and having the test results allow clear

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understanding of why apnoea is or is not occurring. Another approach would be to find predictive variables (e.g. demographic, blood gases, polysomnography (PSG) characteristics, biomarkers, etc.) that may predict pathophysiological variables with sufficient accuracy to allow patient classifications based on underlying mechanisms. Regardless of how this sub-classification is accomplished, the field needs to eventually move beyond the AHI to identify genetic markers in large-scale studies or to stratify which patients to include in sophisticated therapeutic studies.

Third, therapeutic strategies will need to be targeted based on underlying mechanism, to move us beyond CPAP. A single drug or combination of drugs is unlikely to fix apnoea using a 'one-size fits all' approach. However, individualized therapy based on the specific patient's underlying pathophysiology is likely to be fruitful. For example, a theoretical agent to raise hypoglossal output is unlikely to eliminate apnoea in all patients.[20,21] Some patients may respond well to such an agent if the primary abnormality was upper airway muscle dysfunction; however, upper airway dilation may actually be deleterious in patients with unstable ventilatory control if hypocapnia was induced.[22,23]

Further progress is likely to result from a more comprehensive analysis of multiple pathophysiological variables to identify mechanisms underlying apnoea in large patient cohorts and then targeting these variables using a mechanistic approach.

ANAESTHESIA

David Hillman

'Sleep' is a commonly used metaphor for anaesthesia. Indeed both states are related with a common narcotic switch thought to be responsible for unconsciousness in each.[24] It is with the transition to unconsciousness during sleep onset[25] or anaesthetic induction[26] that upper airway (and other) muscle activation markedly diminishes and vulnerability to upper airway obstruction first becomes apparent in structurally predisposed individuals. Vulnerability to obstruction in either state is related.[27] This relationship has several implications for future practice in both sleep medicine and anaesthesia.

First, current methods for determining vulnerability of the upper airway to collapse and the site of this collapse in patients with suspected OSA are costly and imprecise. Separating the predisposing structural component of OSA pathogenesis from the permissive role of sleep-related reduction in airway dilator muscle activity is not a simple matter, as sleep is not a homogenous or easily standardized state. The degree of muscle relaxation varies with sleep stage and its effects with posture, including whole body posture, neck position and mouth opening. Furthermore sleep does not allow intrusive investigations to be simply carried out because of their arousing effects. Unconscious sedation or anaesthesia addresses these problems: it allows the influence of the structural and neurogenic components of upper airway function to be separated by suppressing the latter component. The nature and site of the predisposing structural abnormality can then be defined under steady state conditions while the accompanying inhibition of arousal responses permits invasive investigations to be undertaken. Such precision is likely to be vital in the development of specific OSA treatment methods, including planning dental and surgical interventions, as we continue to look for

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alternatives to globally applied positive airway pressure therapies. Drug-induced ‘sleep’ endoscopy is in its nascent stages as an investigative tool and better defined methods that include consideration of the nature and depth of sedation will be developed.[26]With appropriate clinical evaluation, it is possible that such methods could allow sleep studies to be dispensed with when investigating OSA, at least in patients with probable surgically correctable abnormalities, because vulnerability to collapse can be defined by measurement of closing pressure under unconscious sedation and its site determined contemporaneously by endoscopic methods.

Second, the relationship between upper airway behaviour during sleep and anaesthesia suggests that observations during anaesthesia could be much more systematically used as a method for screening for the possibility of OSA than is currently the case. A substantial proportion of the population, approximately 10% in Australia, have general anaesthesia each year. This greatly exceeds the incident rate of sleep apnoea. Clinical observation of airway patency during anaesthetic induction and emergence alone provides useful pointers to the vulnerability to collapse, as does the necessity for artificial aids to maintain airway patency and degree of difficulty of tracheal intubation.[28] So much the better if upper airway collapsibility was formally assessed during the anaesthetic procedure, for example, as could readily be accomplished by measurement of pharyngeal critical closing pressure.[27]

Third (and conversely), vulnerability to obstruction during sleep should be routinely considered during preoperative evaluation of patients as this indicates increased likelihood of airway management difficulties under anaesthesia.[26–28] Implications include safer use of preoperative medication, highlighting possible difficulty with airway maintenance and/or tracheal intubation following anaesthetic induction and ensuring airway patency during emergence and postoperatively when under the influence of sedating drugs.

METABOLIC CONSEQUENCES AND COMORBIDITIES

Mary Ip

A strong association between OSA and a range of metabolic disorders is expected due to the common risk factor of obesity. To define the independent contribution of OSA towards metabolic derangements, above and beyond that of comorbid presence, meticulous attention has been given to control and adjust for body fat. Adipose tissue is now established as an active endocrine organ,[29] and this knowledge should lead us to view adiposity not merely as a ‘confounder’, but as an ‘active partner in crime’, when evaluating the impact of OSA on metabolic derangements. Elevated levels of some mediators of cardiometabolic derangements, known to come predominantly from fat cells, have been demonstrated in OSA,[30,31] and it is postulated that intermittent hypoxia or neurohumoral changes in OSA may have modulated their expression and/or release from adipose tissues.

If this hypothesis is correct, for the same severity of OSA, adverse metabolic effects would depend on the amount of fat in an individual. In such a case, are lean OSA subjects exonerated from detrimental metabolic consequences? First, it is clear that many non-fat-dependent aetiologic mechanisms are at play in various metabolic disorders. Second, although intermediary mechanisms common to various metabolic disorders have been

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proposed in OSA,[32] they would inevitably differ in their contribution for each disorder. There is little evidence of differential effect of blood pressure response in OSA subjects due to different body habitus, but recent epidemiological data raised the suggestion that sleep-disordered breathing may predict future hypertension more so among less obese persons.[33] On the other hand, there is little data to suggest a differential effect of blood pressure response in OSA subjects of different body habitus.[34] On the other hand, one can speculate that body fat would be most influential in the modulation of OSA effects on glucose metabolism, due to its pivotal role in the latter—diabesity. Indeed, clinical data on the impact of OSA and insulin sensitivity in relation to obesity have been conflicting, fuelling this possibility.[35] Recent studies suggest that OSA may impair insulin secretion, a factor usually present for the precipitation of glucose intolerance or diabetes in the insulin-resistant state, and which has little to do with obesity.[36] Hence, lean OSA subjects probably still suffer from metabolic consequences, as supported by some clinical studies,[32] but it appears logical to postulate that any detrimental effects may be mitigated for disorders that are heavily obesity-dependent. At the other end of the obesity spectrum, it is plausible that progressive obesity may overwhelm any less impressive adverse effect of OSA, but one can also speculate that it may allow escalating amplification of detrimental effects. In brief, the partnership of OSA and adiposity does not necessarily run a linear constant along the range of body fat mass and is widely open to research.

Most health problems that afflict humans are governed by both the environment and genetics. The potential importance of dietary factors on the clinical outcomes in OSA has been highlighted in recent animal studies. Intermittent exposure to hypoxia in mice promotes lipid peroxidation, dyslipidemia or insulin resistance,[37] but only a high-cholesterol diet combined with intermittent hypoxia results in atherosclerotic lesions compared with either factor alone.[38] Such findings have immense implications for the global cardiometabolic outcomes that OSA subjects may suffer from, as many of them have multiple risk factors.

Finally, although suggesting at the outset that a comorbid existence of OSA and metabolic disorders is not unexpected, physician awareness is still suboptimal, especially among those who do not work in sleep medicine. While much remains to be learnt from rigorous research regarding the relationship between OSA and metabolic disorders, it is the immediate task of every clinician to be highly vigilant of their common coexistence and address the patient's problems in a holistic manner.

CARDIOVASCULAR DISEASE

Robert Thurnheer

OSA has been identified as an independent risk factor for the onset of arterial hypertension. A clear dose effect has been demonstrated: the more apnoeas per hour of sleep, the higher the chance for becoming hypertensive.[39] Cardiovascular morbidities, such as stroke, coronary artery disease and heart failure,[40] are major health risks for OSA patients. It is unclear whether these associations are independent of hypertension. It may be that OSA independently drives atherogenesis through inflammatory processes that have emerged as critical in the pathogenesis of atherosclerosis. In support of this, CPAP is likely to reduce some inflammatory markers in OSA patients.[41]

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How do we investigate these mechanisms systematically? One controlled but not randomized landmark study has shown risk reduction close to that of a normal population when patients with OSA are effectively treated.[42] Have we seen too much success with treatment of symptomatic OSA and its beneficial effects on cardiovascular disease for us to now ethically undertake randomized controlled trials (RCT) involving withholding effective OSA treatment? How can we deal with this dilemma?

As hypertension, an important risk factor for cardiovascular disease, is associated with OSA, we are justified in screening hypertensive patients for OSA. Such screening would be likely to identify asymptomatic OSA patients in whom a prospective RCT could then be performed to determine the magnitude of cardiovascular risk reduction with CPAP and its likely mechanism. Studies, such as this, would help to answer whether it is reduction of sleepiness, normalization of night-time breathing or influence on inflammation or coagulation, which accounts for the cardiovascular risk reduction. This is important as we have seen blood pressure reduction merely with treatment in sleepy OSA patients[43] but not equally in those with elevated AHI and normal daytime vigilance.[44] By focussing our primary treatment target on ‘vigilance’, ‘inflammation’ and ‘vascular tone’ instead of ‘sleepdisordered breathing’ we could open the field for combined pharmacological treatment together with CPAP.

Cross-sectional studies looking for associations between cardiovascular risk factors and OSA appear less likely to help to solve the pivotal questions. Prospective interventional studies are needed to look at cause and effects in cardiovascular risk reduction in patients with night-time breathing disorders. These studies are difficult to perform, time-consuming and expensive, and need long-term follow up. They could be easier to do if we were able to target surrogate markers for cardiovascular diseases, where measurable changes like oxidative stress, systemic inflammation, endothelial dysfunction or arterial stiffness may be found, as these occur long before patients experience major cardiovascular events. Hitherto, studies have produced conflicting results. One recent RCT has been disappointing in this respect by showing no beneficial effect of acute CPAP on blood markers of inflammation, including CRP, IL-6, IFN-γ and anti-inflammatory adiponectin,[45] whereas other studies have been able to demonstrate a beneficial effect on serum cardiovascular risk markers.[46–48] As not all investigations have assessed CPAP compliance, unequal use of treatment might explain these equivocal results. Thus, objective data on adherence are mandatory for further studies of any effects of treatment. Moreover, acute CPAP results in beneficial changes in other surrogate markers like urinary catecholamine excretion, baroreflex sensitivity and arterial stiffness.[49] If these effects could be translated into a reduction in end-points, such as stroke or myocardial infarction in other than OSA population studies, one could even justify doing large-scale RCTs on surrogate markers with symptomatic sleep apnoea patients. While RCTs for the clinically relevant end-points could be done in countries where CPAP therapy is not generally available, this raises ethical dilemmas that may make it the least attractive of these options.

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GENETICS

Lyle Palmer

OSA is a genetically complex disease under a substantial degree of genetic control that most likely results from multiple interacting genetic and environmental factors; these factors are poorly defined.[50,51] The only published genome-wide linkage scans for OSA within families did not produce strong evidence of linkage to OSA phenotypes.[52,53] With the exception of these linkage scans and a small number of genetic association studies[54–57] the molecular genetics of OSA in humans remains largely unexplored.

A major limitation to current progress in understanding the genetics of OSA is that there have are few large epidemiological or genetic studies available internationally.[50] We therefore have a critical current need for large and comprehensive clinical resources linked to biospecimen banks. It has become increasingly recognized that the use of undersized populations has resulted in false positive and inconsistent results in studying diseases that are likely to be multigenic in origin and where individual genetic variation may contribute at most a few per cent of the phenotypic variation. A related need is for improved phenotyping of OSA; the AHI is at best a very crude phenotype for genetic analysis. A further related need is for an international consortium of well-phenotyped OSA cases with DNA available; replication remains the gold standard for genome-wide association studies (GWAS) findings. OSA remains one of the few chronic diseases for which no such consortium currently exists.

A GWAS for OSA holds the potential for enormous scientific and, ultimately, clinical benefits[50,58] The ultimate goal of such research is the improvement of biological understanding, prevention, diagnostic tools and treatment.[59] While the strength of association of any identified individual genetic variants and phenotypes are likely to be modest, combinations of multiple variants may allow the identification of subgroups at high disease risk for whom early and targeted intervention is appropriate.[60] The discovery of aetiological sleep loci may also assist in the definition of key modifiable environmental aetiological factors using methods, such as ‘Mendelian Randomization’.[61] There has not yet been a GWAS for OSA in a well-powered case–control study; OSA is one of the few remaining common, chronic diseases for which this is true.

Within OSA cases, there has been little work on genetic pathways that offer potential solutions for prevention or treatment.[50] Both gene : environment interactions and pharmacogenetics are areas of growing interest in complex disease genetics.[62] The reasons for the widely reported variable clinical tolerance of CPAP therapy among OSA patients[63] are unknown, but may well include genetic mechanisms. Collection of DNA from intervention trials and RCT is therefore important.

The use of ‘universal’ general population controls are proving to be a powerful strategy for gene discovery in GWAS,[64] and are increasingly being used worldwide. The question of what constitutes a ‘control’ in the setting a GWAS for OSA is interesting. While a general population sample that had undergone overnight PSG to exclude OSA would be the ideal, no such resource of sufficient size currently exists internationally. Instead, comparison with

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both ‘universal controls’ and general population samples screened for sleep disorders using questionnaires and/or home sleep studies are the only currently feasible options. Careful attention will need to be paid to the potentially complicating interrelationships with obesity in any GWAS for OSA.

MEASUREMENT AND DIAGNOSIS

Nick Antic

OSA is a prevalent disease and long waiting lists for diagnosis and treatment are inevitable.[65] Clinical sleep laboratories were first seen in the 1970s in the USA, evolving from neurology or psychiatric services or research programmes.[66] Sleep measurement was precise, with an encephalogram (EEG) focus. However, it became apparent that OSA was the most common sleep disorder presenting for investigation and the discovery of a highly effective treatment, CPAP, markedly accelerated referrals.[67] While the gold standard for OSA diagnosis remains attended laboratory PSG, it is notable that in the developing world there may be no sleep laboratory access at all. An important unanswered question is whether the level of complexity required of an attended laboratory PSG is needed for routine OSA diagnosis.

Polysomnographies are complicated to set up and analyse. Sleep measurements using EEG, electrooculograms and electromyograms are a large reason for this complexity. EEG measurement during sleep can be important, for example, for detection of nocturnal seizure disorders,[68] however, the vast bulk of PSG are performed to assess OSA. Do EEG, electromyogram and electrooculogram measurements add complexity, costs and limit availability of OSA assessment without providing much useful additional diagnostic information?

The justification for performing full laboratory PSG is challenged when considering the imperfections in our current ‘gold standard’ test:

1. Patients potentially altering OSA with different behaviour in the laboratory to home (e.g. alcohol consumption, body position, sleep quality, etc.).
2. Variability in AHI measures from different sleep technicians using the same scoring techniques.
3. At least three scoring systems for scoring respiration during sleep exist, the ‘Chicago’ criteria as well as the 2007 American Academy of Sleep Medicine recommended and alternative criteria.[9,10] The different scoring criteria produce markedly different AHI results on the same patient.[11]

These observations lead to the question: can simpler diagnostic methods (e.g. nasal flow measurement and/or oxygen dips during sleep) be used in a more available and cost-effective way? If these simpler techniques incorporated a simple ambulatory automated EEG with the respiratory measurements, the diagnostic techniques would be more robust. The technology already exists to do this. Simple automated sleep/wake differentiation may suffice. Respiratory measurements at home are limited by the inability to identify when patients are asleep except using crude patient estimates. Given OSA is a sleep-specific

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disease, this leads to dilution of recordings by wakefulness that can lead to false negative results. But does this matter? If patient outcomes using simplified diagnostic techniques are non-inferior to 'best clinical practice' but are simpler, more widely available and cost-effective, shouldn't we be using them?[69,70] It should be noted, however, that these outcome studies have used highly selected patient groups. Any simplified model of diagnosis must be backed by an understanding of the limitations of the simplified test, the patient population being tested and careful consideration of the clinical issues of the patient by a health professional trained in sleep medicine.

If our gold standard technique is imperfect can we remain wedded to it? Whatever we do we must immediately fix this confusion around scoring techniques. We need attended laboratory PSG for more complex patients with complicated disorders of sleep (e.g. seizures, sleep hypoventilation, Cheyne-Stokes respiration) but given the complexity and disease prevalence we need to continue to evolve simpler techniques for diagnosing OSA that are accurate and lead to good patient outcomes. After all, diabetes is a disease with a similar prevalence to OSA, yet not every patient has an oral glucose tolerance test.

SURGICAL TREATMENT

Eric Kezirian

Although tracheotomy offered effective treatment in the early years after the description of OSA, the surgical procedures more commonly used today have greater acceptance but generally less effective treatment outcomes. The challenges in sleep surgery are shared by other surgical fields, and developments in three key areas will contribute substantially to advancing the field.

First, improvements in characterizing surgical candidates are essential. Surgery inherently treats anatomic abnormalities, and there is substantial evidence suggesting that surgical outcomes depend on the pattern of upper airway obstruction.[71,72] In general, incorporating surgical procedures to treat regions or structures responsible for obstruction in an individual patient improves outcomes. Unfortunately, there is no gold standard evaluation. Most available techniques are limited by being static examinations and/or performed during wakefulness; they have not proven adequate for characterizing sleep-related patterns of obstruction for most patients. Drug-induced sleep endoscopy is a promising technique because it defines dynamic airway examination under sedation (albeit not natural sleep),[73] but this technique is not well understood and has its own limitations including cost. Also unclear are the associations between surgical results and patient traits, such as age, gender, race/ethnicity and BMI. Emerging evidence concerning OSA pathogenesis and phenotypes only adds to the matrix of factors that likely influence surgical outcomes.[15] Overall, improving the characterization of patients will enhance our understanding of what predicts surgical success.

Second, more effective utilization of available procedures and the development of new surgical and non-surgical treatments will need to occur in parallel with developments in characterizing patients. Outcomes after specific procedures treating the same structure and performed on what appear to be largely similar patients are heterogeneous.[74] Accurate and

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precise characterization of patients will undoubtedly explain some of this variation, clarify the shortcomings of available interventions and pave the way for the development of new procedures.

Finally, higher-level evidence, with outcome measures that evaluate treatment effectiveness, will be essential in order to advance the field. Most sleep surgery literature consists of case series, although there are multiple randomized surgical trials and cohort studies. There are numerous challenges in the design of higher-level sleep surgery studies, including those concerning ethics, feasibility and study design. Nevertheless, multi-institutional surgical trials can provide generalizable, higher-level evidence superior to those obtained with case series studies. These trials must include not only the traditional measure of surgical outcomes, comparison of preoperative and postoperative sleep studies, but also objective measures describing the health-related and functional adverse consequences of OSA. Just as Hb A1c is used to monitor glucose control in diabetes mellitus management because it is closely associated with complications,[75] so too may biomarkers, such as CRP[76,77] (to cite one example) be more associated with cardiovascular complications than OSA severity. These intermediate outcomes may be valuable in monitoring effectiveness of all treatments, as some treatments, such as positive airway pressure, have high efficacy but effectiveness limited by compliance and other treatments, such as surgery, have variable efficacy, albeit equal to effectiveness because there are no issues of compliance.[78]

PHARMACOTHERAPEUTIC TARGETS

Richard Horner

The rationale for the notion that OSA may be amenable to pharmacotherapy is simple: identification of the critical sleep state-dependent mechanisms that ultimately produce upper airway closure should lead to identification of rational mechanistic targets, effective manipulation of which should prevent OSA. One key initial problem with this scenario, however, is identifying the critical mechanistic targets. This is a particular problem for OSA because different individuals have OSA for different reasons, that is different combinations of factors contribute to pathogenesis and severity to varying degrees within and between subjects.[5,79] Such factors include: (i) anatomical predisposition to obstruction; (ii) sleep state-dependent neural compensatory mechanisms to prevent obstruction; (iii) loop gain affecting respiratory control instability; (iv) arousal threshold, with arousals from sleep destabilizing breathing; (v) lung volume influences on upper airway size (exacerbated by obesity); and (vi) rostral fluid shifts when supine altering airway collapsibility. Many of these factors are amenable to creative pharmacological manipulation now or in the future. However, given that the involvement of these factors in OSA pathogenesis can vary within and between patients, including across the night and between sleep states, there will almost certainly not be one ‘critical mechanism’ to target for pharmacotherapy, and any such ‘one target’ approach will almost certainly fail. The challenge therefore is to devise simple and effective ways to identify the physiological phenotype of each patient and target the relevant mechanisms in each individual.

The next key challenges to any OSA pharmacotherapy are significant and involve identifying a strategy to effectively administer a therapy that selectively targets the critical

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mechanisms at the required times (i.e. the sleeping period) with minimal side-effects. There are several reviews of attempted pharmacotherapy for OSA, these highlight the lack of effectively reliable interventions.[20,80–84] Unfortunately, this literature also indicates that although the basic science research underpinning the field of sleep and breathing is growing, there are too many examples of premature clinical studies with small samples in unselected patients, with little sound physiological rationale for most of the agents being tested or their proposed targets.[20,80–84] Even once potentially viable targets for pharmacotherapy are identified, however, barriers to efficacy are: (i) the agent not getting to the desired target sites to exert its beneficial effect (a delivery problem); (ii) the agent acting at other sites to obscure, or oppose, the beneficial response (specificity problem); (iii) efficacy being obscured by unwanted side-effects (concentration-dependent, receptor-targeting and/or sensitivity problems); (iv) different responses occurring in rapid eye movement sleep versus non-rapid eye movement sleep (a neurobiology problem); and (v) the actual sites of obstruction varying within and between patients across sleep states and body positions,[85] such that the pharmacotherapy may be effective at some times and not others. At present the field is not sufficiently mature or large enough to have the solid basic science foundation and personnel to overcome these challenges. Increasing research interest and career opportunities in sleep, with effective transdisciplinary collaborative and translational research, are required to overcome these challenges, as they have been in other more established fields.

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