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Endotypes and phenotypes in obstructive sleep apnea

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Abstract

Purpose of review—The purpose of this review is to describe the variability of obstructive sleep apnea (OSA), both from a standpoint of underlying mechanisms and in terms of clinical manifestations.

Recent findings—Recent data suggest that not all patients with sleep apnea get their disease for the same reason. As such, no one variable is effective at defining which patients do or do not have sleep apnea. Identifying the mechanism(s) underlying OSA for an individual is helpful as it can help to determine whether personalized therapy could be developed based on an individual's characteristics. In addition, these underlying mechanisms may be helpful in predicting response to therapy and prognosticating regarding future complications.

Summary—OSA is a heterogeneous disease with highly varying underlying mechanisms. OSA has variable clinical manifestations with definable subsets having risk of particular complications. Future studies will be helpful to identify mechanisms underlying OSA using clinically accessible tools and then using these data to focus individualized treatment approaches.

Keywords

airway; apnea; lung; sleep; ventilation

INTRODUCTION

Obstructive sleep apnea (OSA) affects nearly one billion people worldwide, with substantial associated morbidity, mortality, and financial and social costs [1]. OSA is a disease characterized by repetitive pharyngeal collapse during sleep [2]. This intermittent collapse results in reduced airflow which has two sets of consequences: arousal from sleep to resume airflow, and gas exchange disturbances from hypopneas (reductions in breathing) or apneas (cessations of breathing) [3]. The recurrent arousals in OSA lead to neurocognitive consequences including diminished memory consolidation, daytime sleepiness, and reduced quality of life [4]. Hypoxemia and hypercapnia with resulting catecholamine surges, oxidative stress, and low-grade inflammation are thought to underlie the cardio-metabolic consequences of OSA [5]. However, the mechanisms contributing to these adverse health outcomes of OSA are complex and incompletely understood.

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Recent studies have suggested that OSA is a heterogeneous disease both from the standpoint of underlying mechanisms (endotypes) and in its clinical expression (phenotypes) [6–8]. Disease heterogeneity has been long recognized in the cancer field, but more recently has been discussed in other respiratory disorders such as asthma (e.g. allergic, occupational, exercise-induced, cough-variant), chronic obstructive pulmonary disease (e.g. pink puffers and blue bloaters, but also small airways fibrosis and other manifestations), acute respiratory distress syndrome (hypo-inflammatory, hyper inflammatory, variable lung compliance, and response to positive pressure ventilation) [9]. The recognition of this heterogeneity in disease states is potentially helpful because therapy can sometimes be personalized based on individual characteristics [6]. Other biological insights such as predictive models and genetic susceptibility are more likely to be fruitful if homogeneous patient groups can be identified rather than searching in broad groups of disease e.g. analogous to searching for a single ‘cancer’ gene for all types of cancers.

Although individuals with OSA are generally categorized under the same universal diagnosis, the diagnosis of OSA carries with it variable and complex underlying mechanisms and various clinical and polysomnographic features. The OSA diagnosis is usually defined by a single data point captured by polysomnography or polygraphy, the apnea-hypopnea index, but recent studies have demonstrated that this simplistic approach has the potential to underestimate the complex heterogeneity of OSA. Determining individual risks and anticipating treatment responses (both in routine practice and for designing clinical trials) requires a better characterization of the disease complexity. There is growing evidence that a new delineation of specific OSA subgroups is the prerequisite for the development of precision and personalized medicine in this field. [10,11,12,13]

Obstructive sleep apnea endotypes

The pathogenesis of OSA is generally accepted to be highly variable. The underlying endotypes include anatomical compromise, impaired pharyngeal dilator muscle function, unstable ventilatory control (elevated loop gain), and low arousal threshold (being predisposed to wake up with respiratory disturbances) [14,15]. Other factors such as end expiratory lung volume, arousal intensity, and redistribution of body fluid, are also likely important [16–18]. The studies on anatomical compromise have consisted of imaging and sophisticated measures of mechanics under passive conditions [19,20]. In general, patients with OSA have anatomical compromise as compared to matched controls, but considerable overlap exists since pharyngeal anatomy explains only a portion of the variance in the occurrence and severity of OSA [21,22]. Thus, anatomy is not the whole story, perhaps explaining the variable benefits seen with surgical interventions directed primarily at anatomical compromise.

Pharyngeal dilator muscle function is also important, because patients with OSA have been shown to have increased activity in the major dilator muscles during wakefulness as compared to matched controls [23]. Compensatory reflexes exist during wakefulness which increase the activity of these muscles; however, with the onset of sleep there is a loss of protective reflexes which yields a fall in pharyngeal dilator muscle activity, resulting in collapse in those who are anatomically susceptible [24]. The negative pressure reflex (NPR)

refers to the robust activation of the pharyngeal dilator muscles in response to a collapsing (subatmospheric) perturbation. The NPR has been shown to be highly variable both during wakefulness and during sleep, implying that a therapy to augment this reflex would also be predicted to have variable efficacy [25]. Of note, muscle activation, as assessed by EMG, is an important component of muscle activity but abnormalities of electrical–mechanical coupling have also been reported in some OSA studies [26–28]. The importance of these upper airway muscles and reflexes is emphasized by the observation that these muscles are both necessary and sufficient to stabilize breathing if adequate respiratory stimuli (negative pressure, carbon dioxide) can accumulate with sufficient magnitude and for adequate duration [29]. For example, some very obese patients do not have OSA, because of robust upper airway muscle responses [30].

Regarding unstable ventilatory control, engineers use the concept of ‘loop gain’, which is a term that has been adapted into the medical literature. An elevated loop gain refers to a system which is unstable with perturbation, whereas a low loop gain system describes one that is intrinsically stable [17,31]. An analogy to room temperature is often helpful when considering the factors that can lead to instability in negative feedback control. Although the human body generally tries to maintain a PaCO₂ of roughly 40 mmHg, the temperature in a room is generally set to roughly 20°C. The temperature in a room might be prone to oscillation if the thermostat were too sensitive. That is, if a change to 19.998°C were enough to turn on a furnace, the temperature in the room would likely overshoot and the result would be fluctuations in room temperature [32]. By analogy, if an individual had robust chemosensitivity (high loop gain), such that for a minor change in PaCO₂ there resulted a major change in ventilation, there would similarly be fluctuations in PaCO₂ [33]. Another analogy would be a furnace that was too powerful, such that a temperature fall to 19°C led to a major output of the furnace to 70°C, there would clearly be risk of major fluctuations in room temperature. By analogy, if an individual were to wake up from sleep with a PaCO₂ of 45 mmHg, and the ventilatory response led to a fall in a PaCO₂ down to 10 mmHg (below the chemical apnea threshold), there would clearly be an unstable control system and marked fluctuations in PaCO₂ would be predictable [34].

The classic breathing pattern defined by high loop gain is Cheyne–Stokes breathing, or periodic breathing, as seen at high altitude [35]. Elevated loop gain, however, is also thought to be important in OSA, and several classic studies have showed an important role of high loop gain in OSA [17,31]. Fluctuations in output from the central pattern generator in the brainstem affect the activity of both the diaphragm and the upper airway dilator muscles. As a result, the upper airway may be vulnerable to collapse when output to the upper airway dilator muscles is at its nadir, particularly in those who are anatomically susceptible. High loop gain is important particularly in a subset of individuals in whom anatomical factors are not the predominant mechanism underlying the presence or absence of OSA [36]. High loop gain has also been shown to predict failure of upper airway surgery, presumably because the surgery does not address the underlying abnormalities in control of breathing [37]. Efforts to lower loop gain using either oxygen or acetazolamide have been helpful, although these studies have also emphasized the complexity of the situation given the multiple interacting variables [38].

Some patients with OSA have a propensity to wake up readily in response to respiratory disturbance; this inclination to easy arousal from sleep is termed low arousal threshold. Several points deserve emphasis:

A low arousal threshold has been demonstrated in roughly one-third of patients with OSA [15].

Premature awakening from sleep, as occurs with low arousal threshold, might lead to insufficient accumulation of respiratory stimuli to activate the pharyngeal dilator muscles. As such, repetitive apnea may result [39].

Agents which raise the arousal threshold, such as hypnotic agents like trazodone or eszopiclone, may have a role to allow more accumulation of respiratory stimuli and thus activate dilator muscles which could stabilize breathing. Some physiological studies have shown potential benefits although hard outcome data are lacking [40].

The arousal threshold interacts in complex ways with other pathophysiological traits, because the stimulus to arouse from sleep is thought to be negative intrathoracic pressure. Thus, factors that affect control of breathing can impact the time to arousal, depending on ventilatory drive and prevailing mechanics [16].

OSA endotypes are worth consideration for several reasons (see Fig. 1). First, as stated, the endo types may guide individualized therapies to allow interventions to be guided based on underlying mechanism. In some cases, with multiple underlying mechanisms, combination therapies may be needed to yield an acceptable result [38]. Second, underlying endotypes of OSA may be related to risk factors for disease. For example, posttraumatic stress disorder is a known risk factor for OSA, which may reflect a low arousal threshold seen in some of these patients [41]. Moreover, patients with neuro muscular disease commonly have OSA, perhaps as a result of underlying upper airway dilator muscle dysfunction. Third, the endotypes of OSA may be important predictors of therapeutic response to clinical interventions. For instance, a high loop gain is predictive of treatment-emergent central sleep apnea (complex sleep apnea). High loop gain and low arousal threshold can also predict failure of uvulopalatopharyngoplasty surgery. Moreover, patients with low arousal threshold are reported to have decreased adherence to positive airway pressure (PAP) therapy compared to those with normal arousal threshold [42]. Fourth, the recognition for the variability in clinical expression of OSA (phenotypes) has led to the assertion that OSA endotypes may predict disease complications. These findings amplify the potential importance of OSA pathogenesis in guiding clinical management. Nonetheless, these concepts have not been widely adopted into clinical practice because of rigorous outcome data remain sparse, and simplified methods to identify the various pathophysiological traits clinically are still evolving. [43].

Obstructive sleep apnea phenotypes

Ye et al. was one of the first teams to perform cluster analyses on a cohort of patients with OSA [7], defining three distinct groups: sleepiness with cardiovascular risk [8], disrupted sleep with insomnia, and asymptomatic patients. Further work by these authors has shown

little symptomatic improvement in those ‘asymptomatic’ patients, whereas sleepy patients who adhere to PAP therapy become less somnolent. In addition, sleepy patients are apparently those patients with OSA at greatest cardiovascular risk [44,45].

OSA phenotypes have been principally identified through different methodologies of cluster analysis such as latent class analysis, hierarchical ascending clustering, or K-means clustering. The goal of these efforts has been to identify clearly distinct subgroups of OSA with minimal differences between two individuals within a same phenotype and clear differences between two individuals having distinct phenotypes. Across previous studies, anywhere from three to seven clusters have been identified in such analyses, the number depending on the clustering method employed, and the different selections and combinations of variables included in the clustering analyses. Some studies have been based on the anatomic and/or craniofacial characteristics of OSA patients, others on symptoms, polysomnographic indices, or comorbidities. A combination of comorbidities and symptoms has been mostly used. Few studies have included extensive combinations of lifestyle, clinical, polysomnographic, and comorbidity variables. The majority of studies have been based on local or national databases whereas geographical factors, lifestyle, behaviors and genetic background might also impact OSA phenotypes [46].

The importance of these phenotypic clusters has drawn increasing attention in part because of the failure of some large multicenter trials to improve cardiovascular risk of OSA [47]. Given that only a subset of patients appear to be at OSA-related cardiovascular risk [8], the finding that a large group of patients with OSA does not derive cardiovascular benefit from OSA treatment is perhaps not surprising [48]. Major efforts are underway to identify those patients who are likely to be at high cardiovascular risk so that such patients can be identified prospectively in designing interventional trials.

Several approaches may be viable to identify patients with OSA who may be at high cardiovascular risk:

Certain endotypes may be important in predicting cardiovascular risk. For example, short respiratory events, perhaps associated with high loop gain and low arousal threshold, have been associated with cardiovascular risk [49]. Short respiratory events compared to longer events are typically those with minimal desaturation. In contrast, hypoxic burden, based on the area under the hypoxia curve, is predictive of cardiovascular risk. Marked hypoxemia can be a marker of high arousal threshold [15,50]. Thus, the data are not consistent regarding the epidemiological findings, emphasizing the need for further mechanistic research.

Cardiovascular biomarkers, or panels of biomarkers, may be useful in predicting cardiovascular risk [51]. hsCRP is a robust marker of cardiovascular risk but has been inconsistent in its association with OSA versus obesity. A panel of biomarkers could assess sympathoexcitation (e.g. muscle sympathetic nerve activity, heart rate variability), oxidative stress (e.g. lipid peroxidation), and inflammatory pathways (interleukin-6, hsCRP), and may be useful to optimize the prediction of OSA-associated cardiovascular risk [51–53].

Novel biomarkers such as microRNAs, the air way or gut microbiome, metabolomics, exosomes, and other techniques are now being assessed in the context of OSA-associated cardiovascular risk. Trimethylamine N-oxide (TMAO) is a cardiovascular biomarker which has been shown to be released by gut bacteria; antibiotics have been shown to suppress TMAO in humans. Recurrent hypoxia from OSA may lead to changes in gut bacteria which could release metabolites affecting cardiovascular risk. In theory, drug targets could block the impact of the metabolites thereby diminishing cardiovascular risk. Studies in rodents have shown proof of concept although human interventional data with hard outcomes are lacking [54–56].

The use of exosomes is being increasingly examined whereby extracellular vesicles acquired from humans can be examined in vitro to assess their impact on endothelial cell function and barrier permeability. Bhattacharjee et al. [57] have shown endothelial dysfunction induced by exosomes from humans with obesity hypoventilation syndrome; these abnormalities largely resolved after the patients were treated with PAP. Such approaches could be used in clinical trials since patients who had high cardiovascular risk could ostensibly be defined based on in vitro analyses of the participant's exosomes.

A subset of patients with OSA do not respond well to PAP. Some individuals have treatment emergent central sleep apnea, which in some cases can persist in the long term (treatment persistent central sleep apnea) [58]. The natural history of these patients is unclear, but long-term adherence and cardiovascular protection may well be compromised. Individuals with high loop gain are those thought to be at risk of reduced PAP efficacy, and thus their disease may be particularly amenable to interventions targeting this endotype (e.g. acetazolamide or oxygen).

Adaptive trial designs are being used such that the outcomes and interventions in studies can be changed on an ongoing basis depending on response to therapies. Such studies have been used in the oncology world but are increasingly being applied to trials in sepsis, asthma, and other respiratory diseases. One example would be to enroll patients and, prior to randomization, determine for which outcomes a particular patient is at risk. In theory some patients could be enrolled to assess Alzheimer's risk (perhaps based on impaired memory or ApoE status), whereas others could be enrolled examining cardiovascular outcomes (perhaps based on endothelial dysfunction or other biomarkers), and yet others may be likely to remain asymptomatic and thus treatment benefits would be difficult to demonstrate [52,53,59,60,61].

CONCLUSION

Major progress has been made in the OSA field via recognition of the heterogeneity of this disease, both in terms of its pathogenesis (endotypes) and its expression (phenotypes). Only through further mechanistic and multidisciplinary clinical translational and basic research are new therapeutic targets and approaches likely to emerge. Further research is also needed for recognizing sex-based phenotypes and the impact of these subtypes on treatment prescription. The majority of the relevant studies have been cross-sectional and the impact

on treatment adherence or prognosis of these clusters remains to be studied ideally by combining existing databases in large international consortia.

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KEY POINTS

- OSA is a heterogeneous disease with multiple underlying mechanisms.
- The mechanism underlying OSA might affect clinical manifestations.
- The clinical presentation of OSA is highly variable with some patients asymptomatic and others at major cardiovascular risk.
- Further research regarding OSA endotypes and phenotypes is imperative.

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| <p>Pertinent history 65 year-old man History of hypertension and atherosclerosis High alcohol intake BMI 42, enlarged neck circumference Severe OSA</p> <p>Possible endotype Anatomic occlusion</p> <p>Possible phenotypes Excessive daytime sleepiness</p> <p>Therapeutic options Nasal CPAP Weight reduction</p> | <p>Pertinent history 35 year-old man History of type 2 myotonic dystrophy BMI 21, mild weakness in hands Mild restriction and reduced supine FVC on pulmonary function testing Moderate mixed sleep apnea</p> <p>Possible endotypes Reduced pharyngeal dilator function High loop gain</p> <p>Possible phenotypes Daytime fatigue Sleep maintenance insomnia</p> <p>Therapeutic options NIPPV Acetazolamide, oxygen</p> | <p>Pertinent history 55 year-old woman History of type 2 diabetes Diagnosed with RLS BMI 33, trace extremity edema Moderate OSA</p> <p>Possible endotypes Low arousal threshold</p> <p>Possible phenotypes Low energy, tiredness Sleep maintenance insomnia</p> <p>Therapeutic options Nasal CPAP Weight reduction Hypnotic agent / CBT-I</p> |
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FIGURE 1. Three factitious patients to illustrate the potential variability in underlying mechanisms and clinical manifestations of obstructive sleep apnea (BMI, body mass index; CBTI, cognitive behavioral therapy for insomnia; CPAP, continuous positive airway pressure; NIPPV, noninvasive positive pressure ventilation; OSA, obstructive sleep apnea; RLS, restless legs syndrome).