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Authors

Light, Matthew
Owens, Robert L
Schmickl, Christopher N
et al.

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Precision Medicine for Obstructive Sleep Apnea

Matthew Light, MD[*], **Robert L. Owens, MD**, **Christopher N. Schmickl, MD, PhD**, **Atul Malhotra, MD**

Division of Pulmonary, Critical Care and Sleep Medicine, University of California San Diego, 9300 Campus Point Drive #7381, La Jolla, CA 92037-7381, USA

Keywords

Arousal threshold; Loop gain; Obstructive sleep apnea; OSA Treatment; Precision medicine

GENERAL CONSIDERATIONS

Obstructive sleep apnea (OSA) is a common condition with major neurocognitive and cardiovascular sequelae.[1] The disease is characterized by repetitive collapse of the pharyngeal airway during sleep yielding repetitive hypoxemia and hypercapnia with associated catecholamine surges. This breathing pattern leads to sleep fragmentation and autonomic changes that predispose to associated disease consequences.[2] Although commonly thought to be purely a result of upper airway crowding (frequently attributed to obesity), obstructive apneas do not occur during wakefulness.[3] In addition, there is considerable overlap in airway collapsibility (as measured by passive critical closing pressure or Pcrit technique) between patients with OSA and controls such that clearly other mechanisms are involved.[4] Recent studies have emphasized the variability in OSA both from the standpoint of mechanisms underlying disease (ie, endotypes) as well as from sequelae of disease (ie, phenotypes).[5,6] As a result of this variability, OSA is being considered a disease amenable to precision medicine from the standpoint of diagnosis, treatment, as well as prognostication.[7]

PATHOGENESIS AND ENDOTYPES

Anatomic compromise at the level of the pharyngeal airway is necessary, although not always sufficient, for the development of OSA.[8,9] Based on imaging as well as assessment of mechanics, patients with OSA are at risk of pharyngeal collapse as compared with matched controls.[10] The patency of the pharyngeal airway is maintained during wakefulness ostensibly through protective pharyngeal reflexes that increase pharyngeal dilator muscle activity and prevent upper airway collapse.[11] As one example, the genioglossus muscle has phasic activity (bursts with each inspiration) and is state-dependent (has higher activity during wakefulness than during sleep) and has been extensively studied in this context.[12]

[*]Corresponding author. mlight@ucsd.edu.

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The decrease in activity of the genioglossus muscle (and other upper airway dilators) at the onset of sleep may lead to pharyngeal collapse in those who are anatomically predisposed.[13]

Control of breathing may also be important in OSA pathogenesis.[14–16] Loop gain is an engineering term used to define the stability or instability in a feedback control system. A system with high loop gain is one which is prone to instability, whereas a system with low loop gain is intrinsically stable. A high loop gain system may develop oscillations with minor perturbations, whereas a system with low loop gain is one that will remain stable even with marked perturbations. Fluctuations in output from the respiratory central pattern generator in the brainstem lead to oscillations in activity of both the diaphragm and the upper airway dilator muscles. Thus, patients with high loop gain (and an anatomic predisposition) may develop upper airway collapse and obstruction when output to the upper airway dilator muscles is at its nadir.[17]

The ability to tolerate reductions in ventilation—the respiratory arousal threshold—is often variable between people and has also received recent attention.[18–20] Some patients have a low arousal threshold (wake up easily), whereas others have a high arousal threshold (sleep soundly).[21] Evidence suggests that most patients with OSA have some periods of stable breathing that occur spontaneously and are thought to result from activation of upper airway dilator muscles by endogenous stimuli (eg, CO_2, negative intrapharyngeal pressure).[22,23] In patients with a high arousal threshold, the accumulation of these respiratory stimuli can lead to activation of pharyngeal dilator muscles and thus periods of stable breathing. In contrast, patients with a low arousal threshold may have repetitive apneas. In this setting recurrent arousals from sleep reduce the period for sufficient accumulation of respiratory stimuli such that pharyngeal protective reflexes are not engaged.

Although the abovementioned factors are reasonably well established, recent emphasis has been placed on individual variability in each of these traits (endotypes). Some patients have primarily an anatomic problem predisposing them to pharyngeal collapse, whereas others have dysfunction in the upper airway dilator muscles, and still others have unstable ventilatory control (high loop gain) predisposing to pharyngeal collapse. It is not uncommon for patients to have multiple abnormalities that may be underlying OSA.[24,25]

Most of the concepts described earlier treat the upper airway as a collapsible tube with uniform collapsibility (ie, Starling resistor). One of the features of the Starling resistor is flow limitation such that increasing respiratory effort will not lead to increased flow. However, in practice a variety of flow patterns are observed across patients, which suggest that upper airway behavior is more complex.[26] Moreover, Azarbarzin and colleagues[27] have recently suggested that the different flow pattern “signatures” can be used to predict the variable sites of airway collapse. At least, in theory, 2 patients with the same collapsibility (as measured by passive Pcrit) might have very different anatomy and may respond differently to the same therapy aimed at improving anatomy, such as an oral appliance.

The personalized medicine approach to treating OSA involves recognition of this individual variability. Different interventions are available to influence each of these traits and may be effective strategies to treat OSA at least in select individuals and especially in

those patients intolerant of continuous positive airway pressure (CPAP). For example, uvulopalatopharyngoplasty may be a useful strategy for patients who have OSA as a result of anatomic compromise at the level of the velopharynx.[28,29] Similarly, implantable hypoglossal nerve stimulators are effective in a subset of patients with OSA, although there are substantial barriers to this modality including cost, the need for multiple invasive procedures, and the inability to accurately predict responders.[30–32] On the other hand, surgical interventions may ineffective in patients who primarily have an issue with unstable ventilatory control.[33] Another example is the use of oxygen or acetazolamide, which are 2 strategies to lower loop gain and have been shown to be effective in a subset of patients with OSA.[34] Similarly, nonmyorelaxant hypnotic agents (eg, trazodone or eszopiclone) have been shown to increase the arousal threshold and may be useful in reducing sleep-disordered breathing events in select patients with a low arousal threshold predisposing to OSA.[35,36] In contrast, hypnotics may be ineffective or even deleterious in patients who have other underlying OSA mechanisms. Combination interventions have also been tried with some success to treat OSA in patients with multiple endotypes.[25]

DETERMINING THE OBSTRUCTIVE SLEEP APNEA ENDOTYPE

The challenge of determining the mechanisms underlying OSA has been the subject of extensive investigation.[37] Traditional assessment of the OSA endotype required multiple overnight experiments conducted by an MD or PhD to assess patients' physiology and to determine the magnitude of the variables (eg, pharyngeal collapsibility, loop gain, arousal threshold). However, recent emphasis has been placed on making these techniques more accessible to clinicians such that pathophysiologic traits could be estimated without the need for complex experiments. Several approaches have been used. First, Sands and colleagues[38] have recently used signal processing techniques to analyze standard polysomnography to make estimates of the various endotypes underlying OSA.[39] Orr and colleagues[40] have extended some of these findings to allow the assessment of some traits using home sleep testing. Further work will be required to validate these techniques and to determine their clinical utility. Second, Edwards and colleagues[20] have developed a regression equation to determine the arousal threshold using variables derived from standard polysomnography. For example, using the apnea-hypopnea index (AHI), the nadir saturation, and the presence of hypopneas and apneas, the investigators were able to define greater than 60% of the variance in the arousal threshold. Such efforts may allow the clinician to classify patients without the need for sophisticated physiologic testing that may be burdensome and limit willingness to participate in the diagnostic process. Third, technological innovations are allowing acquisition of data using wearable technologies or using blood biomarkers to help to draw conclusions. For example, technologies are being developed to assess sleep stages and oxygen levels in individuals, which may allow the assessment of pathophysiologic traits. Shin and colleagues have also reported in abstract form the ability to predict the arousal threshold using serum biomarkers such as high-sensitivity C-reactive protein and fasting blood glucose. Ongoing metabolomics research may further these efforts as well.[41] More work is required, but the realization that OSA is more than just an anatomic disease has opened the door to a personalized medicine approach to sleep apnea treatment.

OBSTRUCTIVE SLEEP APNEA PHENOTYPES

Although endotypes have been extensively studied, the variable OSA phenotypes have received less attention. Phenotypes have been described using various techniques. For example, Ye and colleagues[6] performed cluster analyses on large cohorts and found that patients with OSA have varying symptoms. Some have daytime sleepiness, others have difficulty sleeping at night, and there are those who remain relatively asymptomatic. These observations have been extended to other cohorts that have also demonstrated that symptoms change with CPAP treatment according to the original cluster.[6,42,43] Zinchuk and colleagues[44] also used cluster analysis and were able to risk stratify patients with OSA more effectively based on polysomnographic variables than with the AHI alone. The realization that not all patients with OSA are at risk of the same complications has several implications. First, further mechanistic research is imperative to determine why some patients with OSA get some complications, whereas others seem relatively protected. Secondly, with respect to clinical trials, a “one size fits all” strategy of trying to prevent a partiular OSA consequence (eg, cardiovascular disease) by giving all patients with OSA nasal CPAP may be ineffective if only a subset is at risk. Finally, these findings also have clinical implications because interventions may be tailored to reduce the risk of a particular complication in a patient with a specific predisposition.

SUMMARY: WHY ENDOPHENOTYPES MATTER

There are several reasons why understanding OSA mechanisms on an individualized basis may facilitate a personalized medicine approach to therapy:

a. Endotype predicts phenotype. As stated, the mechanisms underlying OSA are highly variable as are the disease manifestations. In theory, OSA from a particular underlying mechanism may have different disease consequences than OSA caused by a different mechanism. As one example, OSA in the elderly seems to be more a function of upper airway anatomy and less an issue with loop gain as compared with younger patients with OSA.[45–47] The authors and other investigators have hypothesized that the mechanisms underlying OSA in the elderly may explain the lack of observed complications in these patients in some large epidemiologic cohorts.[48,49] On the other hand, younger patients with OSA tend to have higher loop gain, which may increase risk of cardiovascular disease, as large, negative pleural pressure excursions can adversely affect cardiac loading conditions and ventricular wall stress.

b. Endotype determines response to therapy. Nasal CPAP therapy is highly efficacious but not always well tolerated. Stanchina and colleagues[50] observed that patients with OSA with high loop gain might be at risk of developing treatment-emergent central apneas on therapy (ie, complex OSA) and thus may not tolerate CPAP as well as other patients with OSA.[51] Such findings have implications for individual patient management, because patients likely to have an inadequate response to CPAP would ideally be identified *a priori* such that other interventions could be considered. Another example, which the authors and other investigators have recently observed, is that patients with unstable

ventilatory control (high loop gain) are more likely to fail upper airway surgery with OSA as compared with matched individuals with low loop gain.[33,52] These findings may be helpful to stratify which patients are likely to benefit (or not) from a particular surgical intervention.

c. Diseases associated with OSA may predispose based on specific endotypes. Several studies have suggested that patients with posttraumatic stress disorder are at risk of OSA although the mechanisms are unclear.[53,54] Based on available data, the authors have speculated that such individuals may have a low arousal threshold and thus may be at risk of developing OSA on this basis. Similarly, certain patients with neuromuscular disease are known to be at risk of OSA, perhaps due to impairment in upper airway dilator muscle function.

d. Endotype may define individualized interventional strategies. The use of oxygen and/or hypnotics is likely to be beneficial for some patients with OSA but not for others, depending on underlying mechanisms.

Based on the conceptual framework discussed earlier, the authors believe that OSA endophenotypes have essential implications for advancing OSA management. They may soon be used in the clinic to deliver a precision medicine-style approach to patient care (Fig. 1), and ultimately they may drive the future success of OSA clinical trials such that efforts will focus on high-risk patients who are most likely to benefit from a particular intervention (Fig. 2).[55]

SUMMARY AND FUTURE DIRECTIONS

New insights into OSA have opened the door to personalized medicine whereby individual patient characteristics can help guide management. However, many questions remain unanswered:

a. How should endotype be best determined in the clinic and should these assessments change management? Ultimately the answer to this question will likely involve sophisticated analyses of physiologic signals (eg, from polysomnogram, home sleep testing, or wearable technology) combined with plasma biomarkers.

b. Should patients with OSA known to be at risk of various disease complications be treated in an individualized manner, for example, should an otherwise healthy patient with OSA predicted to be at high risk of OSA-induced cardiovascular complications receive statin therapy and aggressive lifestyle modification? Such decisions may be guided by underlying OSA mechanisms and by risk stratification using novel techniques.

c. How should new biomarkers be best discovered in the OSA field? Advances have been made using exosomes, microRNAs and metabolomics/lipidomics that have allowed discovery of new potential causal pathways to disease.[56,57] Recent insights into the microbiome have added the possibility that OSA affects gut bacteria, which in turn alter the associated metabolites important in the pathogenesis of atherosclerosis.[58]

d. How can positive airway pressure (PAP) adherence be best optimized using new technology? Recent publications have shown potential benefits to patient engagement and interactive educational devices.[59,60] Our clinical experience suggests that ultimately different patients will respond to varying strategies, for example, intensive support versus real-time patient feedback versus monetary incentives or other approaches.[61,62]

e. How will wearable technology affect OSA diagnosis and treatment in the future? Technological advances may well allow OSA diagnosis and some sleep assessment to occur on an ongoing basis. Such data may be helpful diagnostically and may motivate behavioral changes such as improving sleep hygiene, and increasing PAP use. As the capability of wearable devices improve, the 3 pillars of health (diet, exercise, and sleep) could be managed more comprehensively. Big Data approaches derived from wearable devices will allow more robust conclusions over time.

OSA is an exciting field due to the tremendous progress that has been made in our understanding over recent years. The future looks bright because patients are yet to fully realize the benefits from fresh insights into sleep science and recent advancements in technology that are ongoing. OSA endophenotypes, an expanded array of OSA biomarkers, and a new wearable technology are 3 key elements that are currently leaping bench to bedside and are likely to have a significant impact on the substantial burden of disease-facing society.

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KEY POINTS

- The mechanisms underlying obstructive sleep apnea (OSA) are highly variable given that any single factor explains only a portion of the variance in OSA occurrence.
- The apnea-hypopnea index (AHI) is an imperfect metric of disease severity, because various complications are predicted by different sleep-disordered breathing variables, for example, 4% desaturation predicts hypertension, whereas 2% desaturation predicts insulin resistance. Similarly, arousal frequency predicts memory consolidation, and the duration of oxyhemoglobin saturation less than 90% predicts platelet aggregation. Thus, the optimal AHI definition may vary with the outcome of interest.
- Not all patients with OSA are at risk of the same complications. Cluster analyses and clinical trials suggest that some patients with OSA are at risk of cardiovascular complications, whereas others may be at risk of neurocognitive sequelae, and still others may remain asymptomatic.
- Although continuous positive airway pressure (CPAP) remains the treatment of choice for OSA, personalized medicine approaches are being used to optimize adherence to therapy. Examples include wearable technology with real-time patient feedback, which may help engage motivated patients and encourage CPAP use.
- Different interventions are now being tried to treat OSA based on endotypes (mechanisms) underlying the disease. Oxygen or acetazolamide may be effective for patients with unstable ventilatory control (high loop gain), whereas palatal surgery may be effective for patients with primarily an anatomic problem at the level of the velopharynx.

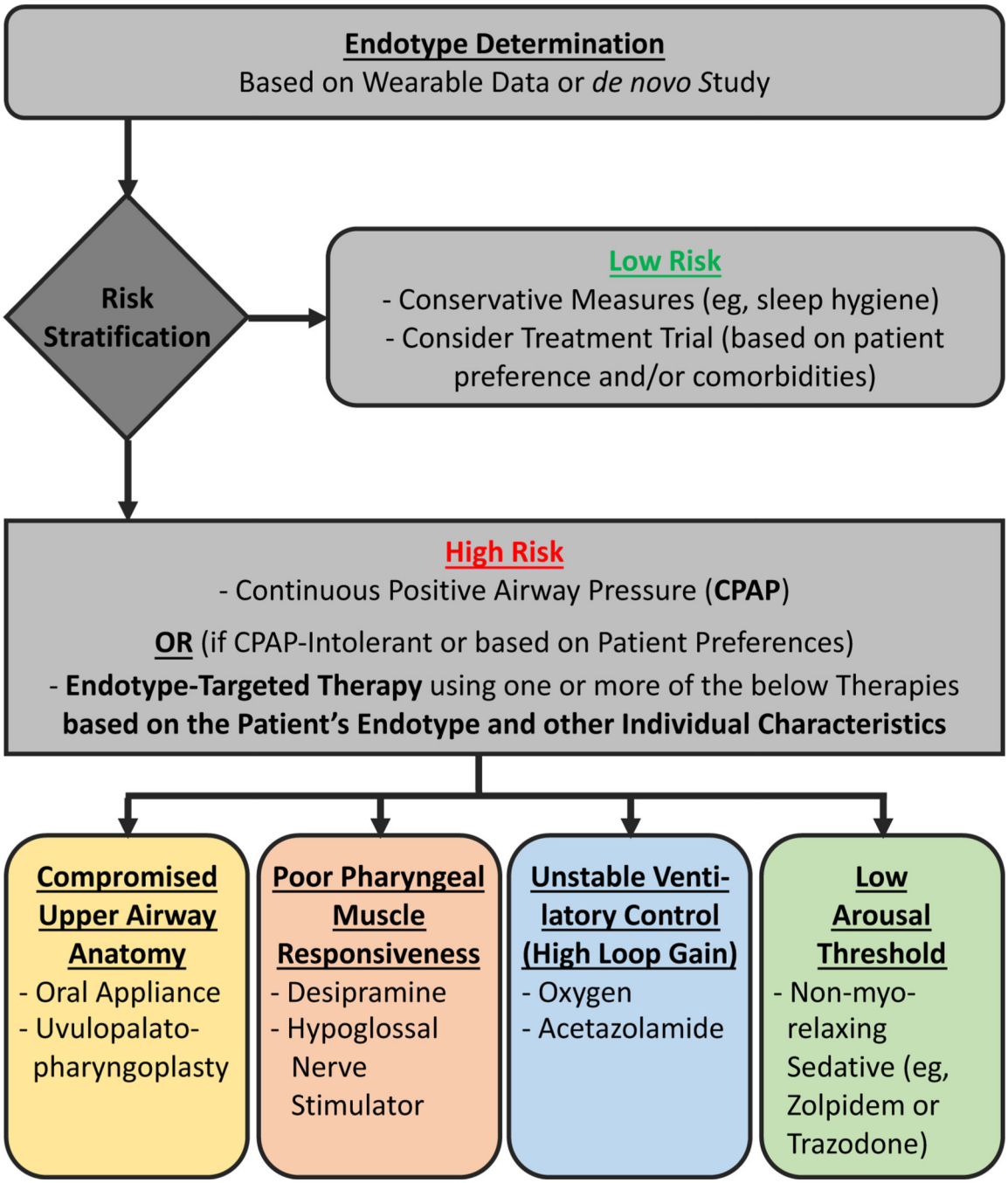

Fig. 1.

Personalized medicine approach in clinical practice based on endotypes. Determination of an individual's endotype could be used for risk stratification to help decide *whether* (aggressive) treatment is indicated. In highrisk patients who are CPAP intolerant, this information could further be used to tailor therapy toward the individual's underlying sleep apnea causes. Note that in a given individual sleep apnea may potentially be due to multiple traits, thus requiring combination therapy; for example, a patient may have sleep apnea due

to both high loop gain and low arousal threshold and may thus require both oxygen and a sedative in order to achieve stable breathing at night.

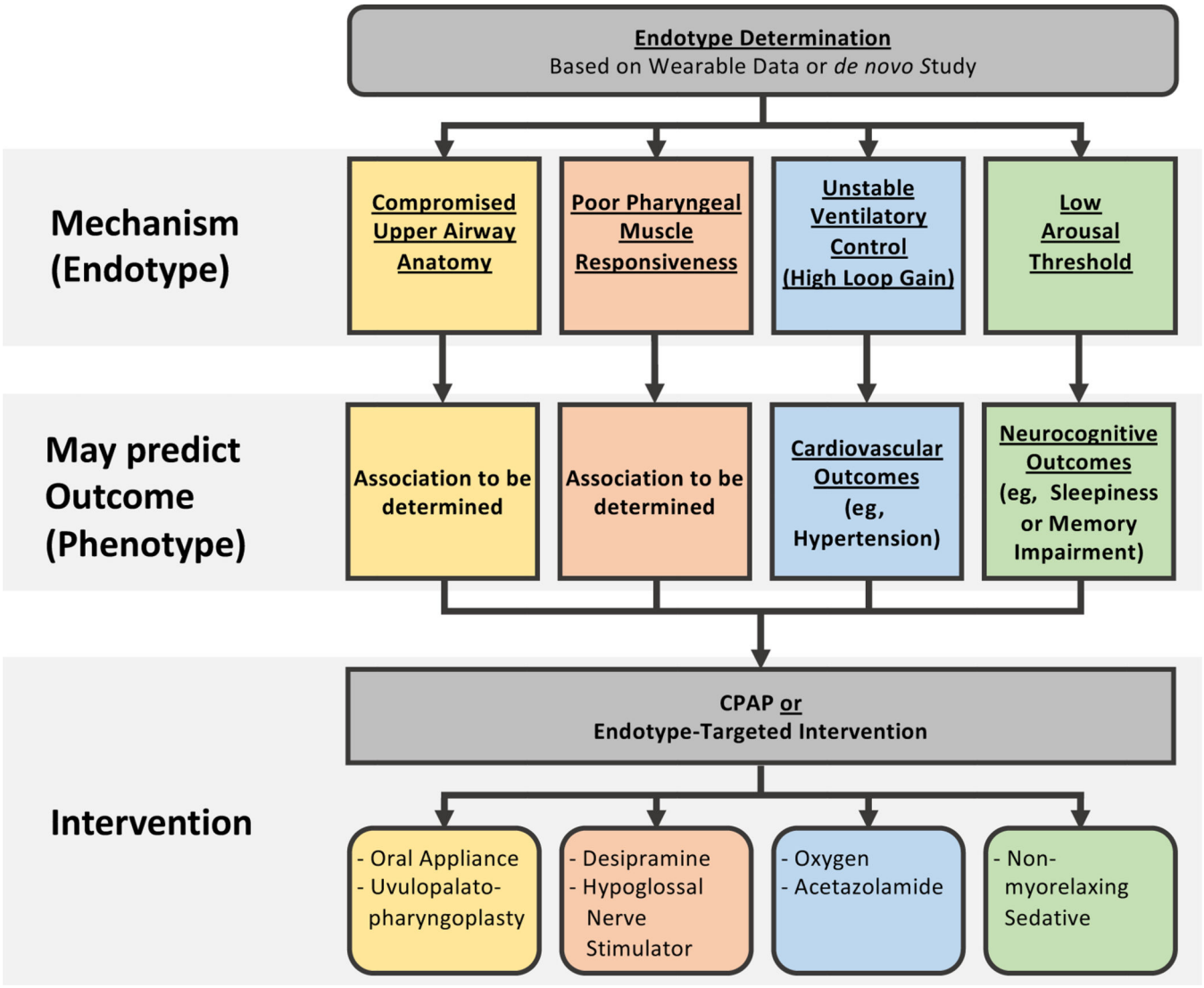

Fig. 2.

Personalized medicine approach in clinical trial design based on endotypes. As discussed in the text, the authors speculate that an individual's sleep apnea endotype may predict which adverse health outcomes this person is at risk for; it certainly is predictive of which interventions other than CPAP may be efficacious. In this para-digm, a trial seeking to improve hypertension would maximize its power (ie, chance of success) by enrolling primarily patients with OSA due to high loop gain using CPAP (or potentially oxygen) as the intervention. Note that in a given individual sleep apnea may be due to more than one trait, thus increasing the risk of several adverse health outcomes; for example, a patient with OSA from high loop gain and low arousal threshold may be at risk of both hypertension and impaired memory and thus be a good candidate for trials focusing on either outcome.