Review article

UDC: 616.24-008.4:612.821.7
doi:10.5633/amm.2022.0408

PERSONALIZED TREATMENT OF OBSTRUCTIVE SLEEP APNEA: IS IT STILL A LONG WAY OFF?

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The combination of sleep fragmentation, intermittent hypoxia exposure and circadian rhythm misalignment is crucial to represent multiple obstructive sleep apnea (OSA) clinical scenarios. Treatment of OSA has traditionally been directed to anatomical component treatment, implying the application of continuous positive airway pressure (CPAP) therapy, oral devices, upper airways surgery, weight loss, and positional therapy. These therapeutic approaches may be frustrating, especially in patients who fail to tolerate CPAP therapy, they may require personal engagement and are hardly maintained, or they have variable and hardly predictable efficacy. So, new treatment approaches aiming at specific, treatable, phenotype characteristics of OSA are needed as alternative therapeutic options.

Acta Medica Medianae 2022;61(4):54-62.

Key words: *OSA phenotypes, personalized treatment of OSA*

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Introduction

Obstructive sleep apnea (OSA) is life-threatening disease that causes significant economic burden if untreated, and it is characterized by intermittent hypoxia, sleep fragmentation and sleep deprivation. Benjafield et al. estimate that 936 million people aged 30-69 years may have mild to severe OSA (1). When not treated, OSA is linked with long-term, health-related consequences, but also decreased work productivity and work-related accidents and motor vehicle accidents (2). The results of eighteen-year follow-up of the Wisconsin Sleep Cohort study show that severe OSA is associated with a 3-fold increase in total mortality risk ($p < 0.0008$), in-dependent of age, sex, body mass index (BMI), but after exclusion of patients who reported using a continuous positive airway pressure (CPAP) therapy at night, this association was even higher, 3.8-fold increase in total mortality (3).

The gold standard for diagnosing sleep breathing disorders is polysomnography (PSG) under controlled conditions. It is demanding, time-consuming and expensive test. Although there are many neurophysiological signals obtained during PSG, the treatment decision is greatly based on the apnea-hypopnea index (AHI), which represents number of cessations in breathing – apneas and periods of reduction in airflow – hypopnea longer than 10 seconds per hour of sleep, causing a drop in oxygen saturation (SATO2) or arousal, which shows some limitations. For example, patients in whom respiratory events last longer may have significant hypoxemia with relatively low AHI, and vice versa, shorter events and significantly higher AHI with minimal exposure to hypoxemia and its negative impact. Recent studies have shown that apnea during REM sleep may be significant for the development of insulin resistance and cardiovascular side effects of OSA (4, 5). It is becoming clear that OSA involves a clinical spectrum that greatly surpasses classic manifestations regarding male, obese and sleepy patients (6). Lack of drowsiness does not exclude the presence of significant breathing disturbances in sleep, 25% moderate OSA patients are not sleepy at all. Up to 50% OSA patients are not obese (7, 8).

OSA pathogenesis

Just like heterogeneity in clinical presentation, OSA pathogenesis is diverse too. Certain degree of anatomic impairment (narrow, collapsible)

of the upper airways is of crucial importance. Since the obstruction occurs only during sleep, dynamic, non-anatomical factors (insufficient or reduced pharyngeal dilatator muscle activity during sleep, low respiratory cortical arousals threshold, unstable respiratory control system – high 'loop gain') present in about 70% of OSA patients, play an important role in mediating the presence or absence of OSA (9, 10).

Anatomical causes of OSA are generally heterogeneous ones, with potential multi-level obstruction of the upper airways. Only 25% of patients have one-level obstruction, while 75% have multilevel obstruction sites (11). The structures that may contribute to upper airway narrowing and collapse include soft palate, tongue size and position, epiglottis and lateral pharyngeal walls, pharyngeal dilator muscle, primarily m. genioglossus, hyoid bone position, and upper airways surface tension. The severity of OSA is independently associated with increased expiratory tracheal collapse (12). Obesity is an important risk factor. Pharyngeal fat deposits cause a reduction in pharyngeal volume. Neck circumference has routinely been used as a risk predictor of OSA. Although PSG is a gold standard for OSA diagnosis, it does not provide information on obstruction localization. Several other diagnostic modalities have been demonstrated to usefully supplement physical examination: lateral cephalogram, 3-dimensional computed tomographic scan, drug-induced sleep endoscopy (DISE), dynamic magnetic resonance imaging (cine-MRI). The last two modalities are promising since they evaluate static and dynamic aspects of the upper airways during sleep and in sleep-like state. Restrictions on clinical use include:

1) awake static imaging does not provide an insight into dynamic characteristics of upper airways during sleep;

2) lack of clear imaging protocols; and

3) high costs (13, 14).

The best measure to describe functional anatomy of upper airways during sleep is pharyngeal critical closing pressure (Pcrit) (15). Pcrit values of OSA patients are usually similar to the values of atmospheric pressure, showing that obstruction of their airway is at or near 0 cmH2O during sleep. Pcrit may vary from: -5 to >5 cmH2O. Pcrit value +5 cmH2O or close shows that airways are highly collapsible, while a sub-atmospheric Pcrit indicates relatively stable upper airways, since suction pressure is required for an airway to be closed during sleep. The values of sub-atmospheric range in this group (0 to -5 cmH2O) are important because of overlapping in Pcrit between healthy and affected individuals. Near 20% of OSA patients have Pcrit like healthy population. This group of patients, in whom the pathogenesis is dominated by a mild anatomical predisposition in combination with one or more non-anatomical causes of OSA, is more likely to benefit from non-CPAP targeted therapies than those who have high Pcrit (16). Considering that current technique of measuring Pcrit is invasive, technically complex, needs CPAP utilization and pharyngeal pressure catheter, a simpler Pcrit measuring would be of great importance for making decisions on targeted treatment (17). There are some innovative and effective methods for determining the level of anatomical damage in OSA patients, including a method for assessing expiratory flow limits in individuals with chronic obstructive lung disease using an existing methodology; Genta et al. have revealed that analyzing the shape of the inspiratory flow curve during constrained airflow during sleep, as well as the degree of negative effort dependence, might reveal the location of obstruction; simple quantifying of peak flow during PSG showed association with active Pcrit (a measure including upper airways collapsibility and neuromuscular compensation); additionally, during routine CPAP titration, the prescribed level of CPAP pressure is linked to Pcrit and may be useful in discriminating between patients with mild and extremely collapsible airways: therapeutic level of CPAP ≤ 8.0 cmH2O showed sensitivity of 89% and specificity of 84% for detecting mild collapsibility, but after independent validation the specificity was 91%, but sensitivity was reduced to 75% (18-21).

Traditional therapeutic approach

Treatment of OSA has traditionally been directed to anatomical component treatment, implying the application of CPAP therapy, oral devices, upper airways surgery, weight loss, and positional therapy. Currently, CPAP therapy is the gold standard, especially in severe OSA cases. The mechanism of action provides pneumatic splint to maintain patency of upper airways. CPAP therapy also stabilizes the upper airway by increasing expiratory reserve lung volume. Advancement in CPAP technology and optimal choice of masks may improve comfort and tolerance, but poor adherence rate is often high (> 50% in some countries). About 5 million, 85% of diagnosed OSA patients in the United States of America, receive the positive airway pressure (PAP) treatment, whether it is CPAP, AutoPAP or Bilevel PAP, but only 3 million, 60%, will adhere to treatment in the long terms. Although daytime sleepiness was minimal, a minimum average use of CPAP therapy was only 3.3 hours per night, as reported by a large randomized trial on CPAP therapy. This level of adherence has no cardiovascular benefit. Long-term CPAP therapy adherence is significantly associated with younger age, female gender and increased sleepiness, but not with OSA severity (22-24). Oral devices are used as a backup to CPAP therapy or as a first-line treatment if CPAP therapy fails. The overall response rate (AHI 5) varies between 21% and 71%. About 25% of individuals with severe OSA are included in this response rate. The partial response rate (> 50% reduction in AHI) varies between 6% and 63% (25). Clinical success of surgical treatment is defined as a reduction in AHI from greater than 50% to less than 20%, with rates ranging from 5% to 78%. Changes in pharyngeal morphology and upper airway muscle activity during waking or sleeping periods may be major determinants of therapy response rate (26, 27). Weight loss reduces the severity of OSA, although in different range, by dietary modifications (3%-18% body weight reduction reduces AHI from 3% to 62%),

and after bariatric surgery (12%-37% body weight reduction reduces AHI from 48%-90%). Variability is also influenced by baseline BMI and adipose tissue distribution (28).

These treatments can be annoying, especially for patients who are unable to tolerate CPAP therapy; they may necessitate personal engagement and are difficult to sustain (weight loss); or they may have variable and unpredictable efficacy (oral devices, upper airways surgery, positional therapy). As a result, instead of 'one-size-fits-all,' novel treatment approaches aimed at specific, curable phenotypic traits are required as alternative therapeutic options (29).

New therapeutic options

The pharyngeal muscles are crucial for maintaining the patency of the upper airways. They receive complex signals synchronized with inspiration from respiratory tract neurons to strengthen and dilate airways and prevent inspiratory collapse. They also get reflex signals from pressure-sensitive mechanoreceptors in the airways and chemoreceptors that detect CO2 or O2 changes. An major component to OSA pathogenesis is a reduction or loss of central and reflex stimulation to the upper airways during sleep (30). The relation between upper airway muscles activation and stimuli (measured via Pcrit) is known as muscle responsiveness (31). Some OSA patients have a high threshold to stimuli during sleep that cannot be reached without waking up, while others can recover airflow during sleep through pharyngeal muscle activation without waking up. High upper airways muscles responsiveness may be a protection against OSA development despite anatomical predisposition. The upper airway contains over 20 muscles. They help in speech, swallowing, and chewing, in addition to maintaining airway patency. In the pathophysiology of OSA, m. genioglossus is the largest and most studied pharyngeal dilator muscle. M. genioglossus response to airway narrowing during sleep is low in about 30% of OSA patients (32, 33).

Hypoglossal nerve stimulation with an implanted neurotransmitter is a method for activating upper airway muscles while sleeping. Electrical stimulation has been tested to treat OSA since the 1980s, with a variety of techniques, invasive ones, as described in STAR trial, and non-invasive, as studied in TESLA trial. Improvements in subjective drowsiness, as well as significant reductions in AHI and oxygen desaturation index, have been reported in recent research (ODI). It is difficult to select potential patients who could benefit from this treatment, what can be related to individual Pcrit (anatomical pharyngeal configuration and the site of the collapse). Endoscopy was employed in the STAR study as a screening tool to rule out individuals with concentric upper airway collapse, which could improve therapeutic response rates. However, one-third of patients were classified as those without improvement. This treatment strategy may play a role in patients with moderate to severe OSA in whom CPAP therapy failed, with BMI < 32 kg/m^2, and without significant collapse during DISE (34-39).

The results of nine studies, included 120 adult patients with OSA, showed that oropharyngeal exercises reduced AHI by about 50% and increased lowest SATO2 > 2.5%, improved subjective sleepiness about 45% (> 6 points reduction according to the Epworth Sleepiness Scale), and reduced snoring (40).

There is no approved pharmacotherapy for OSA yet, but various attempts have been made and are still being made to find one (41).

There have been recent advancements in understanding pharmacological measures for improving upper airway muscles. The introduction of potassium channel blockers into the pigs' nostrils activated mechano-receptors, which increased pharyngeal muscle activity and reduced upper airway collapsibility. In healthy adults without OSA, a recent research using 10mg 4-aminopyridine orally, a very strong potassium channel blocker, only slightly increased m. genioglossus activity in the REM phase but not in non-REM sleep (42, 43). Desipramine, a tricyclic antidepressant with strong noradrenergic, mild serotonergic, and mild antimuscarinic effects, reduces collapsibility of upper airways and OSA severity, preventing sleep-induced reduction of m. genioglossus activity, especially in patients with minimal muscle responsiveness (44). It is interesting that hypnotic zolpidem has the potential of increasing pharyngeal muscle responsiveness during airway narrowing without compromising other important OSA causes (45). In REM sleep, muscarinic receptors antagonists exhibited a particularly strong restorative effect on m. genioglossus activity. In a preliminary proof-of-concept research, these findings were recently applied to humans. The m. genioglossus reactivity to negative esophageal pressure swings was increased near threefold with atomoxetine combined with oxybutynin, and the AHI was reduced by 63% in both REM and NREM sleep, and oxygen saturation parameters improved as well.

Since the majority of obstructive events are related to cortical arousal, respiratory cortical arousals were considered crucial for airway reopening after an obstructive event in OSA patients. About 20% of obstructive events, however, end without respiratory cortical arousal, and another 20% occur after the upper airway is already reopened and airflow is established. So, airway reopening may be restored without arousal (46). When an increase in negative intrathoracic pressure reaches a particular degree of respiratory arousal threshold, respiratory cortical arousals from sleep during an obstructive event occur (47). The gold standard for determining the respiratory cortical arousals threshold is to use a PSG and an epiglottic or esophageal pressure catheter. The negative pressure just before cortical arousal is the respiratory cortical arousal threshold. Patients with OSA who require a considerable change in intrathoracic pressure to trigger respiratory cortical arousal (high respiratory arousal threshold 25 cmH2O) frequently have extended respiratory events, particularly if they also have poor upper airway muscle response (47). On the other hand, 30%-50% of OSA patients (> 85% of non-obese

patients) wake up too easily to modest changes in intrathoracic pressure (between 0 and -15 cm H2O), which may impede proper responsiveness of upper airway muscles as compensation mechanisms to stabilize breathing (48, 49). Frequent arousals cause sleep fragmentation, change sleep architecture by preventing deeper stages of sleep and enhancing sleep instability. So, strategy in reducing respiratory cortical arousals in these patients may stabilize breathing during sleep. Having in mind the aforementioned facts, the potential therapeutic role of hypnotic drugs in treating OSA patients with a low respiratory cortical arousals threshold phenotype has been a field of interest in a lot of studies. An increase in respiratory cortical arousals threshold must be without decreasing pharyngeal muscles activity. Simultaneously, hypnotic use in patients with a high respiratory cortical arousal threshold may prolong respiratory episodes and aggravate hypoxemia, particularly in obese individuals with advanced illness. Standard doses of trazodone (100 mg), zopiclone (7.5 mg) and eszopiclone (3 mg) raise the respiratory cortical arousal threshold and may lower AHI by 25% to 50% without affecting pharyngeal muscle response or increasing hypoxemia levels. However, high doses, especially in patients with severe OSA may prolog obstructive events and worsen hypoxemia. Paradoxically, zolpidem increases m. genioglossus activity almost three-fold both in healthy and in OSA patients (50, 51). These findings highlight hypnotics' therapeutic potential in carefully selected patients (those with a low respiratory cortical arousal threshold and SATO2 > 70%) (52, 53). The current method for determining respiratory cortical arousal threshold is inconvenient for routine clinical usage since it is time-consuming, expensive, and unpleasant (requires an airway pressure catheter). Based on three variables obtained by standard PSG (AHI, lowest SATO2, and apnea/hypopnea ratio), Edwards et al. developed a simple method for estimating respiratory cortical arousal threshold with high sensitivity and specificity that could be used in clinical practice after additional tests were completed (49).

'Loop gain' describes the sensitivity of the negative feedback loop that controls ventilation, which is utilized to keep blood gas tension levels within determined limits (41). Namely, during sleep, PaCO2 precisely regulates ventilation by chemoreceptors afferent feedback information. The ratio between ventilator response and ventilator disturbance is known as 'loop gain' in respiratory physiology. It consists of three components:

1) tissue (tissue, blood and lungs with CO2)

2) release in circulation (time needed for a change in CO2 concentration to mix with existing blood, to come and be detected by chemoreceptors), and

3) sensitivity to CO2 concentration change (chemosensitivity).

Any medical condition that alters one or more of the aforementioned components (for example, heart failure) alters 'loop gain'. Respiratory control can also be affected by intermittent hypoxia (54, 55). Elevated 'loop gain' shows unstable ventilation control. People with high 'loop gain' have exaggerating ventilator response to minimal changes in CO2 concentration. This can lead to hypocapnia and respiratory drive reduction, and may result in repetitive upper airway collapse. About 30% of OSA patients have high 'loop gain' (less than -5) which shows an increase in ventilation for over 5 l/minute in response to reduction in minute ventilation of 1 l/minute. More negative number reflects higher 'loop gain'. High 'loop gain' in combination with even a moderate collapsibility of upper airways may initiate OSA pathogenesis. On the other hand, hypoventilation commonly occurs during sleep in those with extremely low 'loop gain', such as those with obese hypoventilation syndrome. 'Loop gain' can be measured utilizing transitory pressure drops in CPAP during sleep until obstructive events occur, then quick reintroduction of CPAP with a breathing mask and pneumotachograph to determine 'loop gain' (33, 56-58). This method requires well trained staff and complicated data analysis. Terrill et al developed a method for evaluating 'loop gain' that employs the nasal pressure data from a typical PSG (59).

Because oxygen possesses ventilatory stabilizing qualities, primarily due to a decrease in peripheral chemosensitivity, it might theoretically be a therapy option for OSA patients with higher-than-normal loop gain (41). In OSA patients with high loop gain, oxygen therapy reduces loop gain and lowers AHI by nearly half (60). However, all of the studies that have looked into this issue so far have had varying initial hypoxia and normoxia levels, as well as an emphasis on monitoring various outcomes with varying quantities of supplemental oxygen for a maximum of three months. Patients with OSA who have intermittent hypoxia and have a SATO2 reduction of 94% to 85% differ significantly from those who have a SATO2 reduction of 95% to 91%. Trials aimed at determining the phenotypes and endotypes of OSA have concentrated on a small number of patients selected among thousands of OSA patients. The suppression of hypoxic respiratory stimulation, with simultaneous increase in hypercapnia and acidosis development, has not been fully understood yet, even without associated respiratory pathologies. Maybe in future, with the development of better and more simple methods for identifying different OSA phenotypes, application of oxygen therapy alone, or in combination with other therapeutic approaches, may be justifiable in appropriately selected patients (increased loop gain, or patients with higher nocturnal intermittent hypoxia), but not in others. Currently, we still have a long way to go before its routine application in the treatment of these patients (61, 62). Acetazolamide (500 mg twice daily for one week) is a carbonic anhydrase inhibitor that reduces loop gain in OSA patients by roughly 40% (63). Zonisamide, also having carbonic anhydrase inhibitory features, reduces AHI in obese patients with severe OSA (64). Unwanted side-effects reported by patients (dizziness, taste changes, dry mouth) may limit long-term tolerance for carbonic anhydrase inhibitors. Aminophylline, theophylline, and caffeine are xanthines that improve diaphragm contractility by antagonizing adenosine in the central nervous system. While xanthines have shown to be useful in reducing central

apneas in premature infants and patients with heart failure and periodic breathing, they have had mixed outcomes in individuals with OSA. Donepezil is a reversible acetylcholinesterase inhibitor that boosts cholinergic transmission to muscarinic and nicotinic receptors. Donepezil was first tested on OSA severity in a group of 11 patients with Alzheimer's disease and compared to placebo (N = 12) in a parallel arm trial by Moraes et al., based on the involvement of cholinergic systems in ventilatory control during sleep and evidence that reduced thalamic cholinergic activity was associated with OSA severity in patients with multisystem atrophy. In this population, Donepezil 10 mg resulted in a 50% reduction in AHI after three months of treatment. Sukys-Claudino et al tested the same medicine in 11 OSA patients without Alzheimer's disease for one month and found a 23% reduction in AHI from baseline and a 39% reduction compared to placebo. Oxygen saturation and drowsiness improved as well, however sleep efficiency was lowered on the medicine (41).

Recent studies have highlighted a potential for combining different therapeutic approaches as an effective alternative to single therapeutic options in many OSA patients. For example, by combining two therapeutic options targeting anatomical features, such as positional therapy and hearing aids, AHI reduces by about 75% in comparison to a reduction of about 50% when they are used alone. A targeted phenotypic approach combined with non-CPAP therapy (including hypocaloric diet) and pharmacological agents (trazodone and/or acetazolamide) decreases symptoms by 65%. In a small group of patients, combining oxygen therapy to diminish loop gain with a hypnotic to raise cortical arousals threshold reduces AHI by 95% (65-67).

Pcrit, respiratory cortical arousals threshold, loop gain and muscle responsiveness−PALM approach of targeted therapy has been developed according to the phenotype concepts as an addition to already present clinical determinants (symptoms, AHI, comorbidities) to facilitate overall personalized approach for OSA treatment. Briefly, having in mind that anatomical component is a key force in OSA, it is highlighted that this feature is the most important determinant in treatment decision. OSA patients with only mild anatomical impairment (Pcrit < -2 cmH2O), about 19%, have, as a rule, significant impairment of a non-anatomical component. It is estimated that the application of therapies targeting non-anatomical causes will solve OSA in these patients. Moderate anatomical impairment (Pcrit -2 to 2 cmH2O) affects about 58% of OSA patients. Non-anatomical mechanisms are present in approximately two-thirds of these patients. These patients are expected to benefit the most from a combination of targeted anatomical and non-anatomical interventions (e.g. oral devices and oxygen therapy). The remaining third of patients with moderate anatomical impairment who do not have a significant contribution from non-anatomical causes will most likely require one or more anatomical problem-specific therapies (positional therapy, CPAP therapy, surgical interventions). Twenty-three percent of OSA patients have severe anatomical impairment (Pcrit > 2 cmH2O), so they require a therapy targeted at its treatment (CPAP therapy) (68).

A European Respiratory Association research seminar titled 'Defining harmful effects of sleep disturbances and disorders' was held in Dublin in 2019. It was the first step in promoting scientific cooperation and building a critical mass of European research consortiums. The ability to identify illness risk at an individual level, understanding biological mechanisms responsible for disease development and comorbidity onset, and early start in applying individualized therapies are all important aspects of the future of medicine, according to the seminar's conclusion. Prerequisites for achieving these personalized medicine goals in OSA include:

1. definition of relevant phenotypes using real-world data from well-selected cohorts;
2. the combination of sleep fragmentation, intermittent hypoxia exposure and circadian rhythm misalignment is crucial to represent multiple OSA clinical scenarios;
3. cell cultures of animal and human models in intermittent exposure to hypoxia should be technically improved by including hypercapnia as an associated stimulus;
4. activities of the disease should be viewed through the prism of the onset and progression of comorbidities in OSA patients, with initiation of early personalized interventions;
5. application of innovation in clinical research methods to decrease costs and increase productivity;
6. artificial intelligence will be crucial in monitoring dynamics and heterogeneity of OSA longitudinal studies. This will also be the case with new techniques for identifying abnormal respiratory events during sleep or new methods for analyzing sleep electroencephalogram (69).

Conclusion

Recent identification of various OSA phenotypes has created a basis for applying targeted therapy. Development of simplified approaches to identify certain phenotypes is crucial in well-selected groups of patients. Further well-designed studies are needed to define risks/benefits of such a treatment approach.

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Pregledni rad **UDC: 616.24-008.4:612.821.7**
doi:10.5633/amm.2022.0408

PERSONALIZOVANA TERAPIJA OPSTRUKTIVNE SLEEP APNEJE – KOLIKO SMO DALEKO?

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Kombinacija fragmentacije sna, povremene izloženosti hipoksiji i neusklađenosti cirkardijalnog ritma presudna je za ispoljavanje višestrukih kliničkih scenarija opstruktivne sleep apneje (OSA). Lečenje OSA tradicionalno je usmereno na lečenje anatomske komponente i podrazumeva primenu terapije kontinuiranim pozitivnim pritiskom (CPAP) tokom sna, primenu oralnih aparata, operacije gornjih disajnih puteva, gubitak težine i pozicionu terapiju. Ovakav pristup lečenju može biti frustrirajući, posebno za bolesnike, koji ne tolerišu CPAP terapiju, zahteva veliko lično angažovanje i teško je održiv ili ima promenljivu i teško predvidljivu efikasnost. Dakle, novi terapijski pristupi, koji ciljaju specifične, lečive, fenotipske karakteristike OSA, neophodni su kao alternativa.

Acta Medica Medianae 2022;61(4):54-62.

Ključne reči: *OSA fenotipovi, personalizovana terapija OSA-e*