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THEORETICAL REVIEW

Non-continuous positive airway pressure treatment options in obstructive sleep apnoea: A pathophysiological perspective

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SUMMARY

The phenotyping of the pathophysiology of obstructive sleep apnoea (OSA) lies at the core of tailored treatments and it is one of the most debated topics in sleep medicine research. Recent sophisticated techniques have broadened the horizon for gaining insight into the variability of the endotypic traits in patients with OSA which account for the heterogeneity in the clinical presentation of the disease and consequently, in the outcome of treatment. However, the implementation of these concepts into clinical practice is still a major challenge for both researchers and clinicians in order to develop tailored therapies targeted to specific endotypic traits that contribute to OSA in each individual patient.

This review summarizes available scientific evidence in order to point out the links between endotypic traits (pharyngeal airway collapsibility, upper airway neuromuscular compensation, loop gain and arousal threshold) and the most common non-continuous positive airway pressure (CPAP) treatment options for OSA (mandibular advancement device, upper airway surgery, medication therapy, positional therapy) and to clarify to what extent endotypic traits could help to better predict the success of these therapies. A narrative guide is provided; current design limitations and future avenues of research are discussed, with clinical and research perspectives.

Introduction

Obstructive sleep apnoea (OSA) syndrome is the most common type of sleep-disordered breathing whose prevalence in the general population is 32.7–71.9%, considering apnoea–hypopnoea index (AHI) $\geq$ 5 and 11.3%–36.1% with AHI > 15 [1,2]. However, many cases of OSA still remain under diagnosed and untreated at present [3].

Patients with OSA experience excessive sleepiness and fatigue [4], neurocognitive deficiency [5], with a low quality of life as a consequence [6]. Road traffic and work accidents [7], as well as increased cardiovascular morbidity and mortality are the most severe complications reported [8]. For these reasons, OSA causes significant increases to health care and social costs [9].

To date, the pathophysiology of OSA has been related to isolated or associated alterations of four known endotypic traits: pharyngeal airway collapsibility, upper airway (UA) neuromuscular compensation, ventilatory control system or loop gain (LG) and the arousal threshold (AT). The relative contribution of each trait varies substantially among patients, and this could characterize the different clinical presentations of OSA [10]. Indeed many factors, hereditary or acquired [11], through different mechanisms, were found to modulate one or more endotypic traits, conditioning the final pathophysiological configuration of the patient [12].

Currently, continuous positive airway pressure (CPAP) constitutes the first-line therapy for OSA. It is highly effective, but can be poorly tolerated [13]. UA surgery, mandibular advancement device (MAD), and positional therapy are well-recognized non-CPAP treatment options for OSA [14], the efficacy of which depends on

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Abbreviations

AHI	apnoea hypopnoea index
AT	arousal threshold
CPAP	continuous positive airway pressure
GG	genioglossus
H-UP3	horizontal-uvulopalatopharyngoplasty
LG	loop gain
MAD	mandibular advancement device
NREM	non-rapid eye movement
OSA	obstructive sleep apnoea
P_{crit}	pharyngeal critical pressure
POSA	positional obstructive sleep apnoea
PSG	polysomnography
REM	rapid eye movement
UA	upper airway
UP3	uvulopalatopharyngoplasty

proper patient selection due to OSA endotypic variability. More recently, albeit on a limited number of healthy participants or patients with OSA, the effect of medications on the endotypic traits of OSA has also been described [15].

A reliable quantification of endotypic traits would help to better predict treatment response and to guide tailored therapies targeting specific endotypic traits that contribute to OSA in each individual patient [10,16]. However, the analysis of the four endotypic traits, using detailed physiology-based techniques, is not widely accessible in clinical practice and requires specialized equipment, or technically challenging methodologies. For these reasons, much effort is currently being made to find simple and cost-effective methods for the characterization of key endotypic traits in individual patients with OSA [11,17–21].

This narrative review summarizes currently available evidence on this important topic in order to clarify 1) the links between endotypic traits and the most common non-CPAP treatment options for OSA (MAD, UA surgery, medication therapy, positional therapy) and 2) how the characterization of endotypic traits could predict the success of these therapies.

Methods

A comprehensive search of the PubMed database was carried out from 1st January 2010 to 30th September 2020. We opted for a temporal window spanning the last 10 y because most of the literature on endotypic traits and OSA was produced in this period [22–57]. We used numerous search strings about endotypic traits and non-CPAP treatment (the search strategy is illustrated in Table S1). Only full text papers involving human adults, clinical trials, published in the English language and relevant to the purpose were considered eligible. All abstracts found were read and, if someway linked to the topic, the original study was read too. No search string led to the retrieval of useful studies other than the 36 already known to the authors (six of which were previous to the search time window).

Endotypic traits in OSA

The measurement of endotypic traits in patients with OSA is a rapidly growing field of research, moving from procedures limited to the research setting, to the current phase of validation of simplified procedures accessible to daily clinical practice.

The gold standard of anatomic pharyngeal collapsibility measurement is passive pharyngeal critical pressure (P_{crit}), the value of pharyngeal pressure at which complete pharyngeal collapse occurs during fast and short CPAP reductions, from therapeutic value in non-rapid eye movement (NREM) sleep and supine position [58]. More recently other parameters have also been introduced, $\dot{V}0$—passive for example, which describes the flow expressed as an absolute value, or as a percentage of eupnoeic ventilation developed when the CPAP value is reduced from therapeutic to 0 cmH_2O [59].

The ability for neuromuscular compensation of an obstructive event has active P_{crit} as the gold standard measure, i.e., the pharyngeal pressure value at which complete pharyngeal collapse occurs during slow CPAP reductions from therapeutic value, during NREM sleep and supine position [58]. Instead $\dot{V}0$—active describes the flow, expressed as an absolute value or as a percentage of eupnoeic ventilation, developed when CPAP is reduced from minimum tolerable value avoiding arousal to 0 cmH_2O. In the $\dot{V}0$—passive procedure, pharyngeal muscles are hypotonic or relatively passive, while in the $\dot{V}0$—active procedure the pharyngeal muscles may become active, stiffening the airway [59]. Another parameter for neuromuscular compensation is electromyographic pharyngeal muscle responsiveness to negative pharyngeal or oesophageal pressure [40,42].

Ventilatory control contributes to the homoeostasis of blood gases. It depends upon stage and state of sleep; it is characterized by supra-pontine and metabolic control during rapid eye movement (REM) sleep and predominantly by metabolic control during NREM sleep stages. An engineering model of LG has been adopted to simplify the complexity of metabolic ventilatory control during NREM sleep. It consists of a control component (chemoreceptors and ventilator centres: controller gain), an exchange component (lung: plant gain), and a connection component (circulation and tissue diffusion: circulatory time). A high LG can lead to excessive ventilatory responses and destabilization of ventilation during sleep, resulting in periodic breathing and facilitating subobstructive and obstructive UA events. Initially, LG was measured by means of mechanical ventilators or continuous pressure devices: LG is the ratio of ventilatory overshoot (response) above V-eupnoea when returning to optimal CPAP pressure from a period of suboptimal CPAP with reduced ventilation (disturbance) [59]. More recently, LG has been measured by software analyzing clinical polysomnographies (PSGs) [60].

Arousals from sleep have been traditionally considered unavoidable and necessary in order to end an obstructive event. However, in more than 25% of obstructive events, arousals may not be observed [61,62]. Currently it has been demonstrated that even a low AT can promote the recurrence of obstructive events, causing sleep fragmentation and excessive daytime sleepiness [12,61]. The AT is defined as the level of inspiratory effort, measured by oesophageal or epiglottic pressure, at which obstructive events terminate with an arousal from sleep [61,63]. Today, even AT is easier to calculate, with software analyzing clinical PSGs [18].

Endotypic traits and MAD

MAD is increasingly prescribed as a non-invasive treatment in patients with low to moderate OSA.

Understanding the effects on pharyngeal collapsibility and muscle function may provide better information on the mechanisms of action of MAD, and thereby help in patient selection. The main findings of included studies are summarized in Table S2 and their analysis led to the concepts reported below.

Mode of action of MAD

Three studies clearly indicate that the main mechanism of action of MAD is anatomical, by means of passive pharyngeal anatomy improvement, as measured by the passive closure critical pressure (passive P_{crit}) [22–24].

Ng et al. [22] demonstrated that MAD reduced UA collapsibility during sleep: in 10 OSA patients, they found significant improvements in the AHI (25.0 ± 3.1 versus 13.2 ± 4.5 events/h, $P < 0.03$) and passive UA closing pressure in Stage 2 sleep (1.6 ± 0.4 versus −3.9 ± 0.6 cmH_2O, $P < 0.01$), using a custom-made MAD compared with no therapy.

In 11 patients treated by MAD for severe OSA, Bamagoos et al. [23] quantified passive P_{crit}, pharyngeal muscle responsiveness to negative pharyngeal pressure, effectiveness in restoring airflow and minute ventilation (Vi) after 1-min transient CPAP reductions inducing airflow-limitation. Different mandibular advancement positions were adopted: 0% (habitual bite), 50% and 100% of maximum comfortable mandibular protrusion. Passive P_{crit} decreased with mandibular advancement in a dose-dependent manner (1.8 ± 3.9 versus −0.9 ± 2.9 versus −4.0 ± 3.6 cmH_2O; $P < 0.001$), but no systematic change in muscle responsiveness or effectiveness in the restoration of peak airflow or Vi was detected along with mandibular advancement.

A further study by Bamagoos et al. [24], in 17 patients presenting moderate to severe OSA, used a remotely controlled mandibular positioner to determine dose-dependent effects on CPAP requirements, varying mandibular advancement as follows: 0% or habitual bite, 25%, 50%, 75% and 100% of maximum mandibular protrusion. Optimal CPAP setting proved to be reduced by mandibular advancement in a dose-dependent manner (8.9 ± 2.4 versus 7.9 ± 2.8, 6.4 ± 1.8, 5.7 ± 1.9 and 4.9 ± 1.8 cmH_2O; respectively, $P < 0.0001$).

All these studies highlighted that MAD is an anatomical therapy; increased mandibular advancement determines a dose-dependent decrease in P_{crit} value.

The role of endotypic traits as predictors of MAD success and the effect of MAD on endotypic traits

Therapeutic CPAP value is in general an indirect measure of pharyngeal collapsibility and a cut-off value of ≤8 cm H_2O has been related to low anatomical collapsibility [17]. Since available evidence indicates that MAD is effective in patients with low to moderate pharyngeal collapsibility, it is conceivable that this CPAP value has a high probability to detect responders to MAD.

Tsuiki et al. [25] evaluated CPAP pressure requirement to detect MAD responders (AHI ≤ 5/h or 50% reduction of baseline AHI) in 35 Japanese patients with OSA. Patients with a CPAP therapeutic value > 10.5 cmH_2O, consistent with moderate-severe collapsibility, were unlikely to respond to MAD therapy.

In a study conducted on Australian patients, Sutherland et al. [26] reported that a therapeutic CPAP value of ≥13 cmH_2O identified MAD non-responders (AHI >10 events/h and <50% reduction in AHI from baseline).

Neither study aimed to assess the relationship between CPAP and the severity of pharyngeal collapse, rather both focused solely on predicting therapeutic success with MAD. The difference between the two cut-off values described above [25,26] could be due to ethnicity or population-specific characteristics, such as obesity and craniofacial phenotypes, difference in gender, difference in patient selection (Tsuiki and colleagues included males only with a BMI 26 (24–29) kg/m^2 and with long-term CPAP adherence).

Two studies evaluated MAD impacts on all the endotypic traits [27,28].

In a randomized crossover study conducted on 14 patients with OSA, Edwards et al. [27] analyzed how the four endotypic traits changed with MAD and how this predicted the therapeutic outcome. UA collapsibility under passive and active conditions was improved, muscle function showed a trend towards improvement, while no changes were noted in LG and AT. Subgroup analyses of responders versus non-responders demonstrated that a low baseline passive UA collapsibility and a low LG were independent predictors of AHI reduction.

In 93 patients with moderate OSA (AHI > 20 events/h), Bamagoos et al. [28] showed that greater MAD efficacy was associated with a lower baseline LG, higher AT, lower ventilatory response to arousal, moderate collapsibility and weaker dilator muscle compensation.

Globally, these studies suggest that the MAD treatment success rate is higher in patients with mild collapsibility and a low LG. However, in pre-therapeutic evaluation, the assessment of endotypic traits should be just one of the useful elements for better patient selection for MAD treatment.

Collapse site and the relationship with MAD effect

The collapse site is an essential component of the decision-making process for MAD therapy patient selection.

In 25 patients with OSA treated with MAD, Marques et al. [29] performed an UA endoscopy during natural sleep to evaluate tongue obstruction (through the identification of three patterns: 1, vallecula entirely visible; 2, vallecula obscured; 3, vallecula and glottis obscured) and obstruction in other pharyngeal sites (i.e., palate, lateral walls and epiglottis). Overall, MAD reduced P_{crit} by 3.9 ± 2.4 cmH_2O and AHI by 69 ± 19%. Type 1 pattern lowered the P_{crit} only 2.6 (±1.3) cmH_2O while type 2 and type 3 lowered P_{crit} respectively by, 4.5 (±2.7) and 4.1 (±2.5) cmH_2O. Responders (defined as a 70% average AHI reduction) were found only among patients with both types 2 and 3 tongue obstruction associated with less severe collapsibility ($P_{crit} < 1$ cmH_2O). This study suggested that the tongue as the site of collapse, associated with low to moderate collapsibility, determines the endotype that benefits maximally from MAD therapy.

In 81 patients with OSA, Vena et al. [30] developed a model to predict MAD treatment response (>50% AHI reduction from baseline plus a treatment AHI < 10). Both the average drop in airflow during respiratory events (event depth) and flow shape features, which has been demonstrated to indicate the site of collapse (palate, tongue, epiglottis) [64], were examined. The model developed with airflow features calculated from routine PSG and combined with age and body mass index, enabled a MAD treatment response prediction with a 74% accuracy rate: non-responders had more pharyngeal collapsibility (event depth) and more palatal collapse.

The data from these two studies suggest that the site of collapse, endoscopically or polygraphically defined, together with mild to moderate collapsibility, seem to represent a useful criterion for patient selection. Interestingly, it has been confirmed that the P_{crit} recovery of MAD can reach about 6 cm H_2O.

Key points:

- MAD therapy acts mainly on passive collapsibility;
- MAD recovery in P_{crit} does not exceed 6 cmH_2O; consequently, this therapy is effective in a low to moderate collapsibility range;
- A low LG and the site of collapse at tongue level are important predictors of success with MAD.

Endotypic traits and UA surgery

Like MAD, UA surgery is often recommended for treating patients with OSA who refuse or cannot tolerate CPAP. The main results achievable with UA surgery are the expansion and the stabilization of UA, and/or the demolition of UA pharyngeal obstructions [65], namely the reduction of anatomical collapsibility. Moreover the clinical identification of unfavourable non-anatomical endotypic traits may also predict response to surgery (Table S3).

UA surgery for OSA modifies anatomical pharyngeal collapsibility

Four main articles are currently available on the relationship between UA surgery and pharyngeal collapsibility, which demonstrate that the major impact of UA surgery is on the modification of passive collapsibility.

Schwartz et al. [31] reported a significant decrease in passive P_{crit} (from 0.2 ± 2.4 to −3.1 ± 5.4 cmH_2O, P = 0.016) after uvulopalatopharyngoplasty (UP3). Subgroup analysis of responders (NREM reduction AHI ≥ 50%) versus non-responders demonstrated a significant fall in P_{crit} in responders only (from −0.8 ± 3.0 to −7.3 ± −4.9 cmH_2O), whereas no significant change was detected in non-responders (from 1.1 ± 1.6 to 0.6 ± 2.0 cmH_2O, P = 0.01).

Woodson [32–34] compared transpalatal advancement pharyngoplasty with UP3, reporting increased maximal retropalatal airway size and a decreased passive P_{crit} (up to over than 9 cmH_2O).

Overall, these studies confirm that the primary mechanism of action of UA surgery for OSA is the modification of anatomical pharyngeal collapse and the level of recovery on P_{crit} and this provides insight as to the significant success rate of UA surgery for OSA, even in well selected patients with severe pharyngeal anatomical collapsibility.

Clinical endotypic traits analysis could predict UA surgical outcomes

Analyzing UA surgical outcomes, it has been frequently speculated that variability in the response to surgery can also be ascribed to the fact that it does not improve non-anatomical factors (LG and AT), which are often unfavourable in non-responders. To date, some studies have verified whether surgical procedures are capable of modifying extrapharyngeal endotypic traits as well [35,36], and their role as possible predictors of surgical success [36–38].

Li et al. [35] compared 15 control subjects with 30 OSA patients who underwent UA surgery, including horizontal-UP3 (H-UP3) alone (a conservative UP3 modified technique) for 13 patients, H-UP3 with concomitant transpalatal advancement pharyngoplasty for 15 patients, velopharyngeal and retroglossal surgery (H-UP3 and concomitant genioglossus (GG) advancement or hyoid suspension) for 2 patients. UA surgery improved AHI (from 60.8/h to 18.4/h): 15/30 (50%) of patients with OSA were responders (≥50% reduction in AHI and post-surgery AHI < 20 events/h), 8/30 (26.7%) were cured (post-surgery AHI < 10 events/h without residual symptoms), LG decreased by 24.2% from 0.70 (0.58–0.80) pre-operatively to 0.53 (0.46–0.63) post-operatively (P < 0.001), while no statistically significant change in LG occurred in a control group. A positive association was also observed between LG decrease and AHI improvement (P = 0.025). The authors concluded that LG was reduced by UA surgical treatment and this reduction suggests that high LG may be, at least partially, either acquired or mutable. Therefore, the reduction of the severity of OSA and prevention of exposure to intermittent hypoxaemia may improve maladaptive chemoreflex control abnormalities, consequently lowering LG.

Joosten et al. [36] analyzed the effect of UA surgery on extrapharyngeal endotypic traits and tried to test the value of LG and AT in predicting surgical success rate. Forty-six patients with OSA underwent UA surgery. 39/46 patients underwent multilevel UA surgery (20/46 with tongue surgery, 4/46 tonsillectomy only, 3/46 nasal surgery only). Overall, 26% of the patients were responders (AHI 50% reduction and a post-operative AHI < 10 event/h). Surgery decreased AHI (39.1 ± 4.2/h versus 26.5 ± 3.6/events/h; P < 0.005) but did not modify LG in the entire group or in the two subgroups of responders and non-responders. AT decreased both in the entire group and in the subgroup of responders, suggesting that the AT is at least partially an acquired endotypic trait and the improvement of OSA improves AT. Increased AT is linked to the severity of OSA and the main acquired factors are: sleep fragmentation, repetitive hypoxaemia, damage of UA mechanoreceptors by noise and vibrations, brain habituation to increased levels of inspiratory effort [66,67]. Surgical responders had a lower baseline LG and logistic regression showed that a lower LG was a significant predictor of surgical success.

Li et al. [37] tested whether the integration of both pharyngeal and extrapharyngeal endotypic traits in a physiology-based predictive model would improve the ability to predict outcomes of UA surgery for OSA. Their physiological model, which included AHI REM (collapsibility parameter), the fraction of events that were hypopnoea (arousal parameter), the ratio of AHI REM and AHI NREM (muscle responsiveness parameter), and LG plus central/mixed apnoea index (control of breathing parameters), explained 61% of the variance in post-operative AHI. A similar result was obtained with a further simplified physiological model without the LG measure.

The definition of hypopnoea can be of pivotal importance in the calculation of LG and in predicting the surgical success rate. Landry et al. [38] performed a retrospective analysis of 46 polysomnograms before and after UA surgery, and found that LG measured noninvasively by clinical PSG can be influenced by hypopnoea scoring criteria.

Key points:

- UA surgical treatment for OSA mainly, but not exclusively, modifies pharyngeal collapsibility;
- UA surgical treatment for OSA could achieve a P_{crit} improvement up to 9 cmH_2O in well selected patients;
- the correct clinical identification of non-anatomical endotypic traits could represent a positive predictive factor for surgical outcome but could be limited by different endotypic traits measurements methods.

Endotypic traits and pharmacological treatment

All four endotypic traits can be pharmacological targets [15]. Available literature includes several randomized-controlled trials or observational studies which mostly aim to test the effects of medications on OSA severity [15]. However to date, there is still no approved pharmacotherapy for OSA.

In this review 16 studies have been analyzed according to the prevalent pharmacological effects on the endotypic traits (Table S4).

Primary target: pharyngeal collapsibility and neuromuscular compensation

Pharyngeal muscles control pharyngeal patency and can limit or completely offset the negative effects caused by anatomical passive factors. UA muscles are an interesting target for the pharmacological treatment of OSA. The effect of neuromuscular compensation

can be measured using multiple parameters, but the gold standard is active critical occlusion pressure (active P_{crit}), measured during sleep by the slow manipulation of airway pressure [58].

Taranto-Montemurro et al. [39] showed that in healthy subjects, desipramine decreased the reduction of tonic genioglossus (GG) muscle activity from wakefulness to non-REM sleep less than on the placebo night (4.2% vs. 25.4%) but no significant difference in the reduction of phasic electromyographic GG activity has been reported. A significant small passive collapsibility reduction was observed with desipramine compared to the placebo, while active P_{crit} remained unchanged.

In OSA patients desipramine did not modify passive P_{crit}, but did reduce active P_{crit} by 3.1 cmH_2O and improve neuromuscular compensation [40]. Responders to the administration of desipramine (AHI reduction > 20 events/h) showed a low neuromuscular compensation during PSG with a placebo night.

Noradrenergic and antimuscarinic processes are crucial for the modulation of sleep-related reductions in pharyngeal muscle activity. Lim et al. [41] evaluated the effect of a combined noradrenergic and antimuscarinic intervention (reboxetine and hyoscine butylbromide) on pharyngeal muscle activity in 10 sleeping healthy adults compared to wakefulness. The activity of GG in NREM increased with the placebo and decreased with the combination; the activity of the tensor palatini decreased more with the placebo than with the combination.

Taranto-Montemurro et al. [42] evaluated the one night combination of a norepinephrine reuptake inhibitor (atomoxetine) and an antimuscarinic (oxybutynin) in 20 OSA patients. The primary outcome was AHI modification and the secondary outcome was GG responsiveness to negative oesophageal pressure swings. The ato-oxy combination lowered AHI from 28.5 (10.9–51.6) events/h to 7.5 (2.4–18.6) events/h ($P < 0.001$). All the other respiratory and oximetric parameters improved without any modification of the macro and microstructure of sleep. GG responsiveness increased approximately threefold from placebo to ato-oxy combination. AHI was not reduced when ato-oxy were administered separately.

Finally, Taranto-Montemurro et al. [43] evaluated the effect of the combination of atomoxetina and oxybutin on endotypic traits. The pharmacological combination of both medications improved AHI (primary outcome) by 65%. Both medications also improved passive pharyngeal collapsibility by approximately 73%, muscle compensation (+29% of basal value), reduced LG (−11% of basal value), and AT responsiveness (−9% of basal value). According to multiple regression analysis, only AHI < 40 events/h and hypo/apnoeas ratio >65% were independent success rate variables.

Primary target: AT and ventilatory control

AT and ventilatory control are key pathophysiological factors for about 20% of patients with OSA with mild collapsibility [16] and are an interesting target for oxygen and hypnotic molecules [15].

Eckert et al. [45] studied 7 patients with OSA and a low AT (arousal with epiglottic pressure swings $\leq$ 15 cmH_2O) underwent overnight PSGs following the administration of trazodone (100 mg) immediately prior to sleep. Respiratory AT increased by 32 ± 6% (−11.5 ± 1.4 versus −15.3 ± 2.2 cmH_2O, $P < 0.01$) but no change was observed in AHI (39 ± 12 versus 39 ± 11 events/h, $P = 0.94$) or in dilator muscle activity and P_{crit}. The authors' conclusion was that while 100 mg of trazodone did not improve the severity of OSA in patients with low AT, it did not worsen it either. Likewise, in 12 patients with predominantly severe OSA, one week of zopiclone didn't change OSA severity but did increase AT without reducing GG muscle activity or responsiveness to negative pharyngeal pressure [46].

Carberry et al. [47] tried to determine the effects of temazepam (10 mg), zolpidem (10 mg), zopiclone (7.5 mg) or placebo in 21 participants (10/21 OSA) during sleep. AT increased with zolpidem and zopiclone compared to placebo, but not with temazepam. GG activity during stable non-REM sleep and responsiveness during airway narrowing was similar with temazepam and zopiclone compared to the placebo but paradoxically, zolpidem led to a threefold increase in muscle responsiveness during airway narrowing. P_{crit} did not change with any of the hypnotics. Globally, the results of these studies challenged the concept that all hypnotics reduce central drive to pharyngeal muscles during sleep.

Eckert et al. [48] determined the effects of a single night non-benzodiazepine sedative, eszopiclone, on AT and AHI in 17 OSA patients without marked overnight hypoxaemia: eszopiclone increased AT and lowered AHI severity by 23.9%; the greatest reductions in AHI occurred in those with a low AT. This study suggested that certain sedatives may be of therapeutic benefit for a definable subgroup of patients.

Edwards et al. [49] administered acetazolamide (500 mg twice daily for 7 d) to 13 patients with OSA. Acetazolamide slightly reduced NREM AHI and LG, but did not significantly alter pharyngeal collapsibility, UA gain or AT.

Wellman et al. [50] compared the effect of oxygen (3–5 L/min) on AHI in 12 patients with OSA, six of which with a high LG (LG > 0.45) and six with a low LG (LG < 0.30). Contrary to the group with high LG, in the low LG group oxygen did not show any effect on LG and very little effect on AHI. These data suggested that supplemental oxygen can reduce LG and can improve AHI in patients with OSA and an unstable ventilatory control system. On the other hand, patients with a stable system are relatively unaffected by oxygen.

Sands et al. [51] investigated the effect of high flow supplemental oxygen on OSA severity. Overall, oxygen lowered AHI by 30%; responders ($n = 9/36$) exhibited a 70% reduction in AHI and 6/9 responders had an AHI of <15 events/h on oxygen (complete responders). Oxygen lowered LG and AT but not passive collapsibility or neuromuscular compensation. In the multivariable logistic regression, a higher LG increased the probability of being a responder in patients with better compensation, whereas poor neuromuscular compensation and poor collapsibility reduced the probability. In summary, these data showed that measuring the pathophysiological variables causing OSA can predict which patients are most suitable for supplemental oxygen therapy.

Li et al. [52] evaluated the use of donepezil, an acetylcholinesterase inhibitor, in 41 OSA patients and reported that a single dose of donepezil did not seem to affect the overall severity of OSA, AT and LG.

Edwards et al. [53] analyzed 20 patients with OSA receiving combination therapy (eszopiclone and 40% oxygen) versus placebo/room air. Nine participants were responders (AHI < 15 events/h and an overall improvement >50%), six were considered cured (AHI < 10 events/h). Combination therapy significantly reduced LG and increased AT but not UA collapsibility and neuromuscular compensation. At baseline PSG, the responders showed less passive UA collapsibility (P_{crit} and $\dot{V}$passive) and greater active UA collapsibility ($\dot{V}$active) whereas all non-responders had a high LG. In summary, the combination therapy of lowering LG and raising AT is mostly effective in patients whose anatomy is not severely compromised.

Landry et al. [54] compared UA collapsibility defined by the therapeutic CPAP level (a surrogate measure of UA collapsibility) versus the gold-standard pharyngeal collapsibility measurements (P_{crit} and $\dot{V}$passive), to predict the response to oxygen and eszopiclone. Therapeutic CPAP $\leq$8 cmH_2O provided a high predictive

accuracy in the detection of responders (AHI reduction $\geq$ 50% and AHI post-treatment < 15 events/h) compared to non-responders (AUC = 0.86 ± 0.9, 95% CI: 0.68−1.00, P = 0.007). However, both P_{crit} and $\dot{V}$passive performed equally well: the cut-off value of CPAP $\leq$8 cmH_2O was effective as the cut-off value of P_{crit} (2 cmH_2O) and the cut-off value of $\dot{V}$passive (<30% Eupnoea), in predicting the response to the oxygen and eszopiclone combination, with a positive predictive value of 78% and a negative predictive value of 82%. In summary, these data suggest that a lower therapeutic CPAP requirement, as a surrogate measure of milder collapsibility, can predict a stronger response to oxygen plus eszopliclone.

Taranto-Montemurro et al. [44] evaluated the anticonvulsant Tiagabine in 14 OSA patients and concluded that there was no significant effect on OSA severity and AT.

Key points:

- Except for donepezil and tiagabine, all assessed pharmacological treatments showed an action on the endotypic traits, almost always reporting an improvement in the severity of OSA;
- endotypic traits (AT, LG, neuromuscular impairment) treatable with medication therapy are overall more numerous compared to MAD and surgical therapy;
- the application of medication therapy on the endotypic traits of OSA is limited to the research field and is currently not clinically applied.

Endotypic traits and positional therapy

More than 50% of patients with OSA worsen in the supine position and this is referred as positional OSA (POSA). The Amsterdam positional OSA criteria, currently one of the most common classification systems for POSA, accurately identify candidates who will benefit from positional therapy [68,69]. To date, a limited number of studies have analyzed the relationship between POSA and endotypic traits (Table S5).

Joosten et al. [55] assessed the effect of lateral positioning on endotypic traits in 20 patients with severe OSA (AHI > 30 events/h). The Authors identified two subgroups of patients: seven patients with a supine AHI to non-supine AHI ratio of >4:1 on their diagnostic PSG (POSA subgroup) and 13 patients with a supine AHI to non-supine AHI ratio of <4:1 (position-independent OSA subgroup). Researchers used the CPAP dial-down method to measure endotypic traits: 1) $\dot{V}$ eupnoea, ventilation at optimal CPAP with no evidence of snoring or flow limited breathing; 2) passive $\dot{V}0$, ventilation at CPAP = 0 cmH_2O with completely relaxed pharyngeal muscles; 3) $\dot{V}$ arousal, ventilation just prior to a respiratory-induced arousal; 4) active $\dot{V}0$, ventilation at CPAP = 0 cmH_2O with maximally activated pharyngeal muscles; 5) LG, the ratio of ventilatory overshoot (response) above $\dot{V}$ – eupnoea when returning to optimal CPAP pressure from a period of sub-optimal CPAP with reduced ventilation (disturbance). In the whole group, lateral positioning significantly increased passive $\dot{V}0$ (0.33 ± 0.76 L/min versus 3.56 ± 2.94 L/min, P < 0.001), active $\dot{V}0$ (1.10 ± 1.97 L/min versus 4.71 ± 3.08 L/min, P < 0.001), and significantly decreased P_{crit} (2.02 ± 2.55 cmH_2O versus −1.92 ± 3.87 cmH_2O, P < 0.001). UA gain, a measure of neuromuscular recovery, showed a trend towards improvement. LG and AT were not significantly modified. The researchers then compared endotypic trait values in the lateral position between patients with POSA and position-independent OSA: the UA gain was significantly higher and the P_{crit} significantly lower in the POSA group, resulting in less instability.

A further study by Joosten et al. [56] examined 1) whether the measured dynamic LG, affected by a number of physiological factors, including lung volume change, increases with a change from lateral to supine sleeping position and 2) whether the change in measured dynamic LG is consistent with the magnitude of lung volume change. In 20 patients with OSA they retrospectively analyzed lung volume and dynamic LG: lung volume in the lateral position increased by 9.5% compared to a supine lung volume and dynamic LG decrease of 8.4%. The major finding was that the respiratory control system was slightly more stable when patients move from the supine to the lateral sleeping position, however the magnitude of dynamic LG change was very small and the contribution of ventilatory control instability to the change in the severity of OSA with body position was likely to be much less important than in previously reported studies on anatomical traits [51].

Ong et al. [57] analyzed 20 patients with OSA in order to quantify the within-participant overnight variability in passive P_{crit} together with the effects of sleep stage and body posture on P_{crit} variability. Coefficients of repeatability were selected as the measure of within-participants variability and were calculated on the whole sample, as well as on different body postures and sleep stages in different body postures. Since a substantial variability was found in overnight measures of passive P_{crit}, a single unqualified value of P_{crit} could not be used to characterize an individual's overall collapsibility during sleep. This variability was ascribed to changes in factors such as body position, neck posture, mouth opening and lung volume. The Authors concluded that multiple measures of P_{crit} should be carried out during sleep and that a single measure of P_{crit} could not be confidently regarded as different from other measures unless that difference exceeds 4.1 cmH_2O, which is the coefficient of repeatability of the measurement.

Key points:

Positional therapy is an anatomical treatment option mostly for patients with mild to moderate OSA, with no significant modification of LG.

Conclusions

OSA is a disease with a complex multifactorial pathophysiology that explains the current limited percentage of therapeutic failures. There is increasing evidence that a customized treatment approach improves both objective and clinical outcomes.

For surgery, MAD, or, if meeting criteria, positional therapy, two endotypic traits must be taken into consideration: anatomical collapsibility and LG. In general, if one patient has mild-moderate passive collapsibility and does not have a high LG, any of these therapies will probably work. Regarding pharmacological therapies, all endotypic traits are treatable and the choice of medication must be guided by its specific mechanism of action on one or more endotypic traits. In particular, patients with poor neuromuscular compensation at baseline experienced greater benefit from medications that stimulated UA muscles; patients with a high LG respond well to supplemental oxygen. However, in our opinion and for all therapies, in the next future the analysis of the four main endotypic traits will constitute just one of the keys to a successful targeted treatment for OSA.

It should also be acknowledged that data from the available literature are based on a limited number of studies, which have been carried out on a small number of patients through complex techniques currently limited to the research field. Furthermore, differences in study design, applied procedures, adopted measurements and patient selection make it difficult to obtain fully comparable results. All these concerns need to be clarified and explored further in the future.

From a clinical point of view, to date the production of simple and reliable tools for the semi-quantitative evaluation of individual traits from clinical PSGs is currently under way [17–21].

Practice points

1. Upper airway (UA) surgery and mandibular advancement device (MAD) mainly act on anatomical endotypic traits. Surgery can improve pharyngeal critical pressure up to over 9 cmH_2O, with significant success rates in patients with high pharyngeal collapsibility. MAD recovery in pharyngeal critical pressure does not exceed 6 cmH_2O, justifying this therapy in patients with low to moderate UA collapsibility. The best predictors of success are low collapsibility, low loop gain and collapse site location at lingual level.
2. Medications act on both anatomical and non-anatomical endotypic traits, with a wider range of action on the main endotypic traits compared to MAD and UA surgery. However, this approach is currently limited to the research field and not widely applied in daily clinical practice.
3. Positional therapy is an anatomical treatment option in patients with mild to moderate obstructive sleep apnoea, with no significant loop gain alteration.

Research agenda

1. A major challenge is the development of easy and accurate tools and scores for an accessible and widespread definition of the endotypic traits in the clinical setting. A technological implementation in diagnostic and therapeutic instrumentation is urgent.
2. Randomized multi-centre studies on adequate sample sizes are required to confirm the role of endotypic traits in pre-therapeutic medical and the surgical selection of patients with obstructive sleep apnoea.
3. Studies on the relationship between endotypic traits-targeted therapy and polysomnographic and short/long term clinical outcomes are needed.

Conflicts of interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2021.101521.

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