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Continuous positive airway pressure and adherence in patients with different endotypes of obstructive sleep apnea

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Abstract

Determining the endotypes of obstructive sleep apnea (OSA) has potential implications for precision interventions. Here we assessed whether continuous positive airway pressure (CPAP) treatment outcomes differ across endotypic subgroups. We conducted a retrospective analysis of data obtained from 225 patients with moderate-to-severe OSA from a single sleep center. Polysomnographic and CPAP titration study data were collected between May 2020 and January 2022. One-month CPAP treatment adherence was followed. OSA endotypes, namely arousal threshold, collapsibility, loop gain, and upper airway gain were estimated from polysomnography and dichotomized as high versus low. We examined associations between endotypic subgroups and 1) optimal CPAP titration pressure, 2) CPAP-related improvements in sleep architecture (proportions of slow-wave and rapid eye movement sleep), and 3) CPAP adherence. We observed that patients with high collapsibility required a higher CPAP pressure than those with low collapsibility (Δ = 0.4 cmH_2O, 95% confidence interval [CI]= 0.3–1.7]). Larger increase in slow-wave sleep and rapid eye movement sleep proportions after CPAP treatment were observed in patients with high arousal threshold, high collapsibility, high loop gain, or high upper airway

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gain than in those with low levels of endotypes. High loop gain and high collapsibility were independently associated with longer CPAP use hours per night (Δ = 0.6 h, 95% CI = 0.2–1.5 and Δ= 0.3 h, 95% CI = 0.03–1.5, respectively). In conclusion, different endotypic subgroups of OSA exhibit difference in outcomes of CPAP treatment. Knowledge of endotypes may help clinicians understand which patients are expected to benefit most from CPAP therapy prior to its administration.

Keywords

arousal threshold; collapsibility; loop gain; upper airway; sleep apnea

Introduction

Obstructive sleep apnea (OSA) has complex pathological etiologies (Carberry et al., 2018) including high upper airway collapsibility, poor muscle responsiveness, high loop gain, and low arousal threshold. Evidence is accumulating that different OSA endotypic subgroups may respond differently to treatments such as continuous positive airway pressure (CPAP), oral appliances, hypoglossal nerve simulation, or upper airway surgery. Endotype-based treatment can improve OSA symptoms and severity (Bosi et al., 2021; Edwards et al., 2016; Messineo et al., 2017). For example, oral appliances more effectively reduce OSA severity in patients with lower loop gain, higher arousal threshold, and lower muscle compensation (Bamagoos et al., 2019). However, OSA endotyping has not been available in regular clinical practice.

CPAP is a highly efficacious treatment for moderate-to-severe OSA but not all patients benefit from CPAP equally. In particular, poor tolerance is a major obstacle for its continuous use (Weaver & Grunstein, 2008). Some endotypes may be associated with poor CPAP tolerance. For example, CPAP reduces arousal threshold in patients with OSA (Haba-Rubio et al., 2005; Loewen et al., 2009), and patients with low arousal threshold exhibited poor CPAP compliance than did those with high arousal threshold (Gray et al., 2017; Zinchuk et al., 2018). CPAP directly opens the airway in the far majority of patients, virtually independent of the severity of collapsibility, and therefore has the greatest scope to benefit those with the most severe collapsibility. Therefore, patients with high collapsibility and high arousal threshold may tolerate CPAP better than those with milder collapsibility or lower arousal threshold. Furthermore, a rebound of slow-wave sleep (SWS) and rapid eye movement (REM) sleep during first CPAP use among patients with OSA is expected (Brillante et al., 2012), and the rebound is associated with subjective sleep quality improvements (Verma et al., 2001). However, it is unclear whether the treatment-related increases in SWS or REM differ across endotypic traits.

Several approaches have been proposed to identify OSA endotypes. Earlier studies employed specialized CPAP manipulation to examine ventilation under controlled ventilatory drive conditions, or quantified ventilation at different ventilatory drive levels via invasive measurements (e.g. diaphragm electromyography) in order to quantify endotypic traits (Eckert et al., 2013; Sands, Terrill, et al., 2018) (Wellman et al., 2013). However,

these methods have limited applicability beyond physiology laboratories. More recently, our collaborators developed a noninvasive technique (referred to here as Phenotyping Using Polysomnography, PUP) that uses clinically scored polysomnographic data to estimate OSA endotypes (Sands, Edwards, et al., 2018). Briefly, endotypic traits are quantified by estimating a ventilatory drive signal based on the notion that ventilatory drive is revealed when the airway reopens following events. This method theoretically enables endotype measurements to be incorporated into clinical practice in sleep centers and may help to identify subgroups of patients that share underlying pathophysiology that are most likely to benefit from CPAP therapy (i.e. precision medicine).

Here, we examined whether endotypic subgroups of patients with OSA exhibit different short-term outcomes of CPAP therapy. We examined CPAP treatment outcomes in terms of optimal pressure, CPAP treatment adherence, and sleep architecture improvements, in patients with moderate-to-severe OSA. In particular, we used the PUP method to examine (1) optimal CPAP treatment pressure during CPAP titration studies; (2) improvements in sleep architecture with CPAP titration; and (3) CPAP treatment adherence in patients with OSA with specific endotypes. We hypothesized that patients with high arousal threshold, high collapsibility, high loop gain, and low upper airway gain have better CPAP treatment outcomes.

Study Design and Methods

Participants and settings

This is a retrospective observational follow-up study. We retrieved diagnostic polysomnographic studies and subsequent CPAP titration studies performed between May 2020 and January 2022 at a single sleep center in Taiwan. Clinical patients were referred by physicians to the sleep center for laboratory polysomnographic studies. Participants were included if they were aged ≥20 years, had signed informed consent, and had an apnea–hypopnea index (AHI) of ≥15 /h and a central apnea index of <5 /h in the diagnostic polysomnographic study. The endotypes of 519 study participants were derived from polysomnographic signals (Figure 1). Subsequently, the patients underwent CPAP titration studies if both the physician and patient agreed that CPAP treatment at home was a suitable option. The differences in baseline characteristics between patients who had and had not undergone CPAP titration were shown in Supplementary Table S1. Our analysis included 225 participants who had undergone both polysomnography and CPAP titration studies, and they all provided signed informed consent. The average duration between the polysomnographic diagnostic and CPAP titration studies was 43 (standard deviation [SD] = 53) days. Demographic data were retrieved from the medical chart. The participants were followed up for CPAP treatment adherence one month after the CPAP titration study through telephonic interview. The participants were asked regarding the treatments they received, and whether they used CPAP at home. If the participant used CPAP, average daily use hours and use days per week were recorded through self-reporting. This study was approved by the Institutional Review Board of China Medical University Hospital (CMUH109-REC3-018).

PSG and CPAP study

The patients arrived at the sleep center before 23:00, and their blood pressure, pulse rate, neck and waist circumferences, body weight, and height were measured by technicians before polysomnographic studies. The patients were instructed to fill in a questionnaire, in which they check if they have allergic rhinitis, hypertension, cardiovascular disease, or diabetes mellitus. The questionnaire included items for whether the participants were current smokers, and whether they drank alcohol more than once per month.

The following parameters were measured in the polysomnographic study: six-channel electroencephalography, electrooculography, electrocardiography, nasal air pressure transducer, oronasal thermistor, chest and abdominal movements, electromyography with submental and chin leads, finger oxygen saturation, sound recordings, piezoelectric sensor for snore detection, and videotaping (Nox A1, Noxturnal, Nox Medical ehf, Reykjavik, Iceland). Sleep staging and respiratory event coding were manually performed by certified sleep technicians according to AASM recommended definition (Iber et al., 2007). We defined apnea as the cessation of airflow through the nose with paradoxical chest and abdominal movements and hypopnea as a ≥30% reduction in nasal pressure with paradoxical chest and abdominal movements resulting in an SpO2 desaturation of ≥4%. The AHI was calculated as the average number of apneas and hypopneas per hour. Sleep staging and respiratory events were manually scored by sleep technicians.

In CPAP titration studies, CPAP pressure was manually titrated by sleep technicians until the AHI was <5 during the REM stage and the patient was sleeping in a supine position (Kushida et al., 2008). The same sleep parameters were measured as in the polysomnographic study using the same measurement devices, except that nasal air pressure transducer was removed and replaced by CPAP flow sensor.

Estimation of endotypes

The PUP method, which was developed by Sands et al. (Sands, Edwards, et al., 2018; Terrill et al., 2015), was used to estimate four endotypes from the polysomnographic studies: arousal threshold, collapsibility, loop gain, and upper airway gain. The PUP method was implemented as a validated cloud-based Python implementation (PUPpy) (Finnsson et al., 2020). This method uses an uncalibrated estimate of ventilation during sleep, derived from the nasal pressure airflow signal in polysomnography. Scored respiratory events and arousals are also required. To estimate ventilatory drive, a simplified respiratory control system model inputs prior values of ventilation (e.g. apnea/hypopnea breaths) and outputs a ventilatory drive signal that best fits the ventilation signal during recovery breaths between respiratory events; the ventilatory response to arousal is also used as a covariate. Loop gain is estimated from this best-fit model (Sands, Edwards, et al., 2018); the value at one cycle per minute was used in this study. The arousal threshold is defined as the estimated ventilatory drive right before scored electroencephalography (EEG) arousals (Sands, Terrill, et al., 2018). Collapsibility was calculated as 1 − percentage of ventilation at the eupneic drive ($V_{passive}$). Upper airway gain (also known as dilator muscle effectiveness) was calculated as slope of the relationship between ventilation and ventilatory drive and was calculated using $y = \frac{V_{active} - V_{passive},}{Arousal \quad threshold - 100\% \quad eupnea}$, where V_{active} is the ventilation at the

arousal threshold. Upper airway gain is a commonly used indicator for upper airway muscle responsiveness to an increase in ventilatory drive, and it has been measured using the CPAP drop method (Wellman et al., 2013). Because physiological conditions are different between REM and non-REM sleep, only non-REM epochs were included for endotype estimation.

Statistical analysis

We dichotomized the four endotypes via median split and examined differences in demographic characteristics between the high-value and low-value groups. The association between each endotypic subgroup and CPAP optimal pressure in titration studies was determined using univariate linear regression models, which included a single endotype in each model. Age, sex, body mass index (BMI), neck circumference, AHI, and all endotypic subgroups were included in adjusted multivariate models. CPAP treatment adherence was compared between the high-value and low-value endotype groups using general linear regression models, adjusted for all other endotypic subgroups and sex, body mass index (BMI), neck circumference, and AHI.

Furthermore, we examined within-subject differences in respiratory events and sleep architecture, namely SWS and REM sleep proportions, between polysomnographic and CPAP titration studies by performing linear mixed regression analysis. Dichotomized endotypes were treated as between-subject variables. Age, sex, BMI, neck circumference, physical illnesses, drinking and smoking, AHI, and all endotypes were included in the adjusted models. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA), and the significance level was set at $p < 0.05$.

Results

Demographic characteristics

The average age of the 225 participants was 43.0 (Interquartile range (IQR) = 35–52) years (Table 1), and 85% of them were men. Fifty-two percent of the participants were obese (BMI ≥ 30 kg/m^2), and the average AHI of the patients was 43.9/h (IQR = 27.4–65.7). The patients with low arousal threshold were more likely to be women than those with high arousal threshold (Table 2). The patients with high collapsibility had a larger neck circumference and higher prevalence of diabetes mellitus than their low collapsibility counterparts. The patients with a high loop gain were older and more obese and had a higher prevalence of diabetes mellitus than did those with low loop gain. The patients with a high upper airway gain were more obese than the low upper airway gain counterpart.

Optimal CPAP titration pressures

Univariate linear regression models indicated that the patients with high arousal threshold (vs. low Δ=0.8 cmH_2O, 95% confidence interval [CI]= 0.2–1.5), high loop gain (vs. low Δ= 1.1 cmH_2O, 95% CI = 0.4–1.7), or high upper airway gain (vs. low Δ= 0.8 cmH_2O, 95% CI = 0.1–1.4) required a higher optimal CPAP pressure to achieve the treatment goal (Supplementary table S2). After adjustment for age, sex, BMI, neck circumference, AHI, and all the other endotypes, the high collapsibility endotype remained significantly

associated with a higher optimal CPAP pressure compared with the low collapsibility endotype (vs. low Δ=0.4 cmH_2O, 95% CI = 0.3–1.7, $P = 0.004$).

Sleep architecture improvements with CPAP

Figure 2 illustrates the absolute values of changes in SWS and REM sleep proportions between polysomnographic and CPAP titration studies, where positive values indicated improvements in CPAP studies compared with polysomnographic studies. Mixed-methods analysis results revealed a significant interaction effect between CPAP titration and arousal threshold (F[1,209] = 8.4, $P = 0.02$), and collapsibility (F[1,209] = 13.0, $P < 0.01$) on SWS. In other words, a larger increase in SWS sleep proportion was observed in the patients with high compared to low arousal threshold (+2.8% vs. +0.4%), and high compared to low collapsibility (+2.3% vs. +0.6%), after adjusted for all other endotypic trait subgroups, plus adjustments for age, sex, BMI, neck circumference, and AHI.

For REM sleep proportion, a significant interaction was observed between CPAP titration and collapsibility (F[1,209] = 17.9, $P < 0.01$), loop gain (F[1,209] = 9.6, $P < 0.01$), and upper airway gain (F[1,209] = 6.2, $P = 0.01$), after adjusted for all other endotypic trait subgroups, plus adjustments for age, sex, BMI, neck circumference, and AHI. Compared with low-level endotype counterparts, a larger increase in REM sleep proportion was observed in the patients with high collapsibility (+9.4% vs. +3.6%), high loop gain (+8.5% vs. +4.4%), and high upper airway gain (+7.9% vs. +5.0%).

CPAP treatment adherence

Among the 225 participants, 84 participants (37.3%) used Auto-CPAP (Sefam S.Box, French) at home, 62 (27.6%) received no treatment, 38 (16.9%) attempted to control body weight or underwent surgery, 13 (5.7%) underwent upper airway surgery, 8 patients (3.6%) received other treatments including medication or oral appliances, and 20 (8.9%) lost follow up (Figure 1). No significant differences in demographic, anthropometric, or polysomnographic study parameters were observed between those who used CPAP at home and those who did not (Supplementary table S3). The percentage using CPAP at home was not significantly different between high and low level endotypes (Table 2). Longer use hours were self-reported by the 84 CPAP-users with high loop gain than those with low loop gain (Δ= 0.6 h, 95% CI = 0.2–1.5, table 3), and the patients with high collapsibility than those with low collapsibility (Δ= 0.3 h, 95% CI = 0.03–1.5).

Discussion

This study examined CPAP treatment outcomes among the patients with OSA with different endotypes. We observed that a higher optimal CPAP titration pressure was required to treat the patients with high collapsibility than for those with low collapsibility. The patients with high collapsibility, high arousal threshold, high loop gain, or high upper airway gain exhibited larger improvements in sleep architecture as well as the AHI during CPAP titration studies than those with low levels of these endotypes. Furthermore, the patients with high collapsibility and patients with high loop gain demonstrated better CPAP treatment adherence compared with their counterparts.

Landry et al. reported that upper airway collapsibility, measured as pharyngeal critical closing pressure, was predictive of high therapeutic CPAP levels in patients with OSA(Landry et al., 2017). Our findings imply that collapsibility estimated using the PUP method was also predictive of optimal CPAP treatment pressure, regardless of demographic and anthropometric characteristics.

A higher optimal pressure may also be required to stabilize respiration in patients with high loop gain. In addition, patients with high loop gain may have concomitant high collapsibility and therefore require a higher CPAP treatment pressure. Although obstructive respiratory events were resolved by CPAP, central sleep apnea emerges in patients with high loop gain (Morgenthaler et al., 2006). High loop gain has been associated with poorer response to CPAP treatment for complex sleep apnea or Cheyne–Stokes respiration (Sands et al., 2011; Stanchina et al., 2015). Nevertheless, we observed a better adherence to CPAP treatment among patients with high loop gain. Notably, in this study, patients with central sleep apnea were excluded. Patients with complex sleep apnea may exhibit lower adherence to CPAP treatment. Therefore, we suggested that CPAP treatment may be recommended for OSA patients with high loop gain, while treatment-emergent central sleep apnea should be monitored.

Although high upper airway responsiveness has been considered to be protective against OSA severity(Loewen et al., 2011), we observed that high upper airway gain tended to be associated with a higher optimal titration pressure in the univariate regression model. We speculated that for patients with OSA with strong upper airway response to intrathoracic negative pressure, the CPAP titration process reduces the negative pressure stimulus to muscles. Therefore, the optimal CPAP pressure for these patients must first replace their endogenous muscle activity and then overcome upper airway obstruction.

CPAP titration improves sleep architecture and the AHI (Aldrich et al., 1989; Fietze et al., 1997) but to different extents in patients with different endotypes (Hang et al., 2021). In a Chinese sample of patients with OSA, CPAP titration resulted in an increase of 5.8% SWS sleep and 5.5% REM sleep compared to polysomnographic diagnostic studies (Cheng et al., 2021). In our study, patients with high collapsibility had a significant increase in SWS (2.3%) and REM sleep (9.4%) during CPAP titration studies compared to polysomnographic studies, which may have led to a better CPAP adherence. In contrast, patients with low arousal threshold exhibited less improvement in SWS proportion than did those with a high arousal threshold. A lack of SWS and REM sleep rebound after the first night of CPAP treatment was associated with insomnia and mood disorders (Cheng et al., 2021), which in turn, were associated with poorer CPAP compliance (Koo et al., 2012; Maschauer et al., 2017). Patients with low arousal threshold may experience small improvements in their sleep quality, which partially explains their lower compliance to CPAP treatment (Schmickl et al., 2020; Zinchuk et al., 2021). Nevertheless, we did not find a significant difference in CPAP adherence between patients with high and low arousal threshold. In a two-year follow-up study (Zinchuk et al., 2021), low arousal threshold was associated with worse CPAP adherence. A longer follow-up duration may yield more significant differences between high and low endotypes.

Specific endotypes have been observed to predict the response to non-CPAP treatments. For example, mandibular advancement devices have been found to be effective for patients exhibiting low loop gain and low-to-moderate collapsibility (Bamagoos et al., 2019; Edwards et al., 2016). A low loop gain predicts a better upper airway surgical outcome (Bosi et al., 2021). In the current study, high loop gain and high collapsibility endotypes were associated with better outcomes in regard to sleep architecture and CPAP adherence than low loop gain and low collapsibility endotypes. Therefore, surgical intervention may be preferred for patients with low loop gain and low collapsibility. Furthermore, medications improve OSA by increasing upper airway muscle responsiveness (Lim et al., 2019; Taranto-Montemurro et al., 2020; Taranto-Montemurro et al., 2016) and arousal threshold (Carberry et al., 2017; Carter et al., 2016; Eckert et al., 2014), and may therefore be used with CPAP treatment to enhance tolerability. Medications used to reduce loop gain, such as acetazolamide (Ni et al., 2021), may reduce optimal CPAP treatment pressure needed for patients with a high loop gain. With regards to sleep architecture, we recommend CPAP as the preferred choice in patients with OSA with high arousal threshold, high loop gain, or high upper airway gain. Long-term benefits of CPAP treatment in comorbidities and mortalities in patients with high collapsibility should be studied.

Our study is strengthened due to the retrieval of endotypes from polysomnographic studies by using the noninvasive and validated PUP method. We identified patients with specific endotypes who may tolerate and benefit from CPAP treatment the most. This method has potential to be incorporated into clinical practice and used to test treatment outcomes for patients with OSA with different endotypes. This study has some limitations. First, currently in Taiwan, treatment decision for OSA was based on patients' preference, financial capabilities, and physicians' recommendations. Unlike polysomnographic diagnostic studies, CPAP treatment is not covered by national health insurance. Therefore, only approximately half of the patients underwent a CPAP titration study following their polysomnographic studies, and less than half used CPAP at home thereafter. Sample attrition resulted in selection bias, as individuals who declined CPAP titration studies exhibited lower severity of OSA, arousal threshold, collapsibility, and loop gain compared to those who underwent CPAP titration studies (Supplementary Table S1). The generalizability of the study results to patients with milder OSA and lower levels of these endotypes may be limited. Second, objective records of CPAP use at home was not available. We examined CPAP adherence only one month after treatment started, and the long-term CPAP adherence among patients with different endotypes may change over time. Third, endotypes were derived from non-REM sleep using the PUP method, while they may change during REM sleep; e.g., loop gain is lower during REM sleep (Joosten et al., 2021). The optimal CPAP treatment pressure achieved during supine REM sleep may not be associated with non-REM endotypes. Fourth, it is noteworthy that 85% of the participants were men, and the pathology of OSA differ between men and women. Therefore, the findings of this study may not be generalizable to female patients with OSA. Additionally, the endotypes were dichotomized based on the median, which was determined by the distribution of the sample in this study. Hence, the results may not be directly applicable to other research or clinical settings.

In conclusion, OSA endotypes were associated with different CPAP treatment outcomes, including optimal treatment pressure, sleep architecture improvements, and treatment adherence. Although CPAP is often the first-line treatment for OSA, it is poorly tolerated by some patients (Patel et al., 2021). Determining OSA endotypes can assist in identifying patients who may not tolerate CPAP well and may benefit from combined surgical or medication treatments. Future studies should examine the long-term treatment outcomes for patients with OSA with different endotypes, as well as the interactions between endotypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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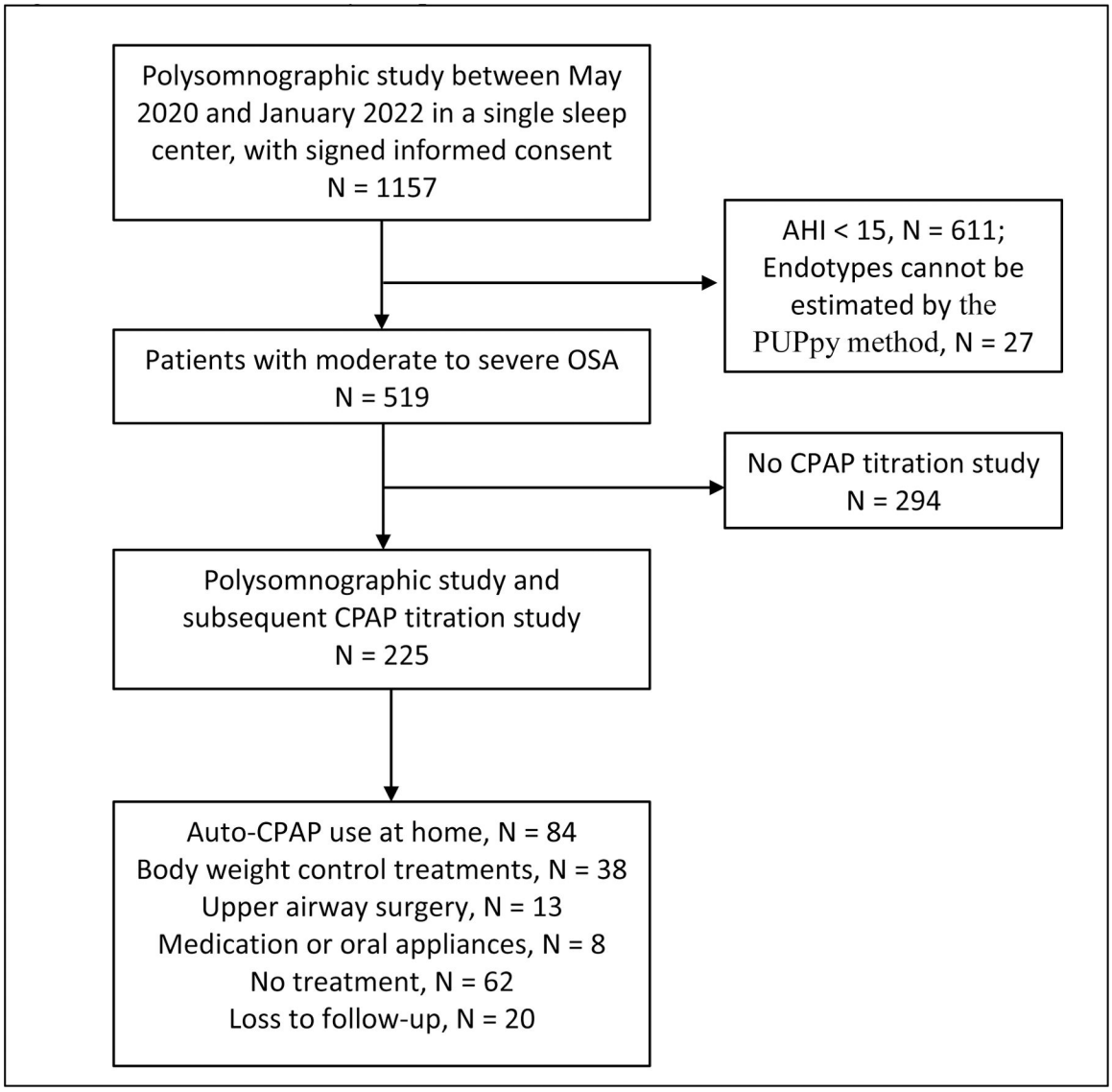

Figure 1.

Flow chart of study sample selection.

AHI = apnea-hypopnea Index; CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea; PUPpy = cloud-based Python implementation of Phenotyping Using Polysomnography

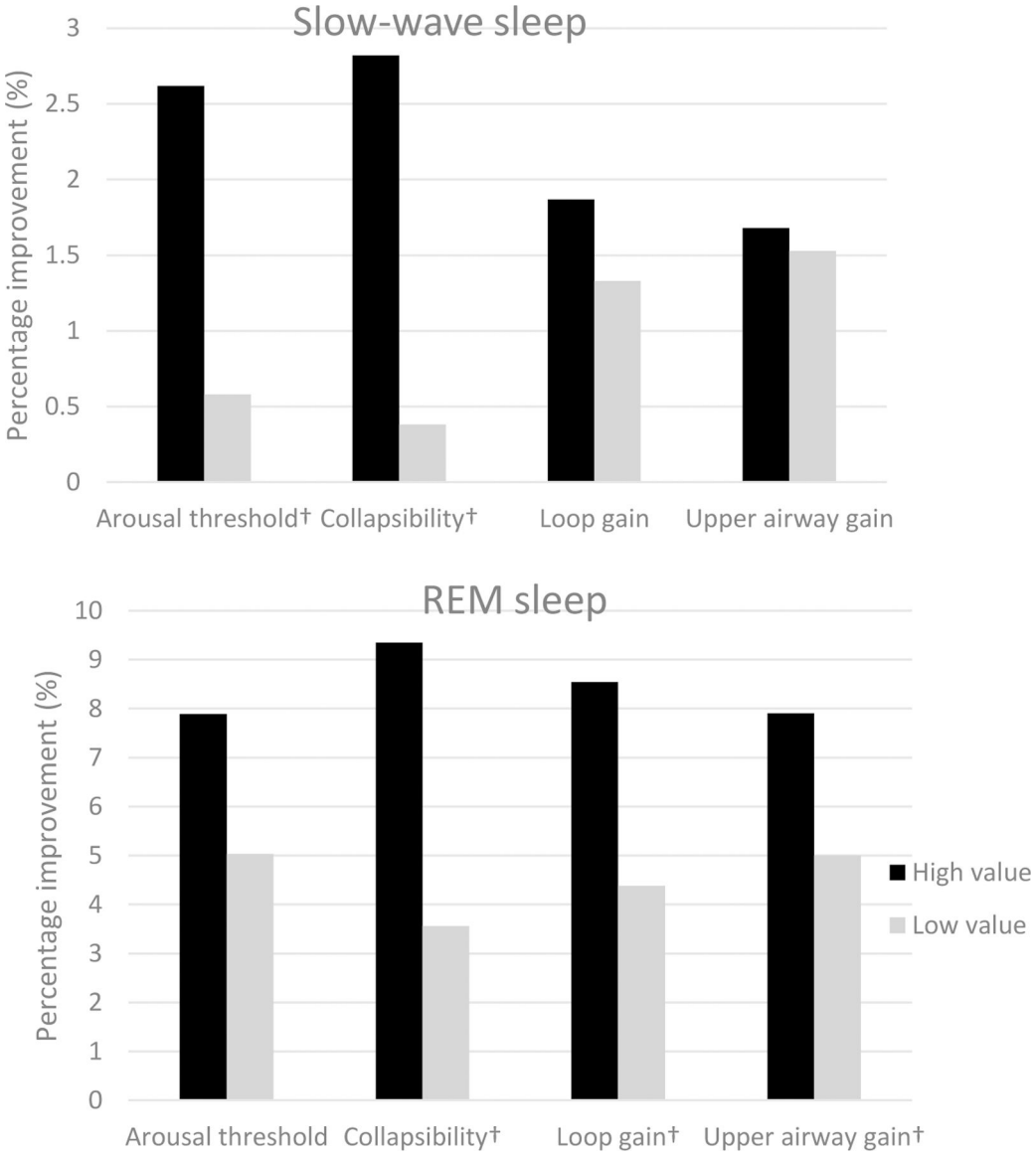

Figure 2.

Differences in sleep architecture with CPAP titration compared with polysomnographic studies (N = 225). Y axis is plotted to show the absolute mean difference between polysomnographic and CPAP titration studies.

CPAP = continuous positive airway pressure; REM = rapid eye movement.

† Interaction effect between CPAP titration and endotype in mixed method regression analysis adjusted for all other endotypic groups, age, sex, body-mass index, neck circumference, apnea-hypopnea index, alcohol drinking, smoking, and physical illnesses. $P < 0.05$.

Table 1.

Anthropometric characteristics and sleep parameters in polysomnography study (N = 225).

	Median	(IQR)
Anthropometric characteristics		
Age (years)	43.0	(35.0–52.0)
Waist circumference (cm)	99.0	(93.0–106.0)
Neck circumference (cm)	39.8	(37.5–41.8)
BMI (kg/m^2)	30.3	(27.6–33.2)
OSA severity and endotypes		
AHI (events/hour)	43.9	(27.4–65.7)
Arousal threshold (% eupnea)	143.6	(126.7–185.1)
Loop gain	0.59	(0.47–0.71)
Collapsibility (% eupnea)	16.6	(7.0–46.7)
Upper airway gain	−0.09	(−0.44–0.20)
Sleep architecture (%)		
Stage 1 sleep	39.8	(25.5–58.0)
Stage 2 sleep	39.7	(23.6–51.9)
Slow-wave sleep	0	(0–0.5)
REM sleep	18.3	(13.3–22.6)
Sleep efficiency	84.9	(77.5–91.2)

AHI = apnea–hypopnea index; OSA = obstructive sleep apnea; REM = rapid eye movement; IQR = interquartile range.

Table 2.

Personal characteristics and sleep architecture (mean values or proportion) of 225 patients with obstructive sleep apnea by different endotypes.

	Arousal threshold		Collapsibility		Loop gain		Upper airway gain	
	High (N = 113)	Low (N = 112)	High (N = 112)	Low (N = 113)	High (N = 113)	Low (N = 112)	High (N = 113)	Low (N = 112)
Demographic characteristics								
Age (years)	44.3	43.9	44.1	44.1	*46.4	*41.8	42.9	45.3
Gender (female, %)	*9.7	*19.6	10.6	18.8	15.9	13.4	11.5	17.9
Waist circumference (cm)	99.4	100.4	100.5	99.2	*102.0	*97.8	*101.4	*98.3
Neck circumference (cm)	40.4	39.4	*40.4	*39.4	*40.5	*39.2	*40.6	*39.2
Body mass index (kg/m^2)	30.2	31.2	30.7	30.8	*31.6	*29.9	*31.7	*29.8
CPAP use at home (%)	38.8	36.8	42.9	32.4	39.5	36.0	40.2	35.1
Personal history								
Cardiovascular disease (%)	12.8	7.3	11.8	8.3	10.9	9.3	8.4	11.7
Hypertension (%)	37.2	44.1	40.7	40.5	44.3	36.9	39.3	42.0
Diabetes Mellitus (%)	15.6	10.8	*18.2	*8.2	*19.8	*6.4	13.8	12.6
Allergic rhinitis (%)	39.5	38.5	42.7	35.2	40.4	37.6	37.0	40.9
Alcohol drinking (%)	26.4	27.6	28.0	25.9	22.5	31.8	27.8	26.2
Current smoker (%)	18.9	19.2	20.2	17.9	23.4	14.4	23.2	15.0
Sleep parameters polysomnographic studies								
Stage 1 sleep (%)	*49.5	*36.4	*53.8	*32.1	*49.3	*36.6	44.2	41.8
Stage 2 sleep (%)	*32.4	*43.7	*29.4	*46.7	*33.1	*43.0	37.2	38.9
Slow-wave sleep (%)	*0.8	*1.4	*0.9	*1.3	*0.7	*1.4	*0.8	*1.3
Rapid eye movement sleep (%)	17.3	18.5	*16.0	*19.9	16.9	18.9	17.9	18.0
Sleep efficiency (%)	82.1	82.4	*80.2	*84.6	*80.9	*83.9	83.3	81.4

*P <0.05 in chi-square tests for categorical variables and Mann–Whitney test for continuous variables between high and low-value endotypes.

Table 3.

Self-reported CPAP adherence (N = 84).

	Arousal threshold		Collapsibility		Loop gain		Upper airway gain	
	High (N = 49)	Low (N = 36)	High (N = 49)	Low (N = 36)	High (N = 49)	Low (N = 36)	High (N = 49)	Low (N = 36)
Self-report daily use hours	5.8	5.7	*5.9	*5.6	*6.1	*5.5	5.8	5.8
Self-report use days per week	6.2	6.3	6.3	6.2	6.4	6.1	6.3	6.2

CPAP = continuous positive airway pressure.

*$P < 0.05$ in multivariate linear regression models, adjusted for age, sex, body mass index, neck circumference, apnea–hypopnea index, and all the other endotypes.