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Phenotyping OSAH patients during wakefulness

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Abstract

Purpose Although currently there are simplified methods to measure the pathophysiological traits that stimulate the occurrence and maintenance of obstructive sleep apnea–hypopnea (OSAH), they remain difficult to implement in routine practice. This pilot study aimed to find a simpler daytime approach to obtain a meaningful, similar pathophysiological phenotypic profile in patients with OSAH.

Methods After obtaining diagnostic polygraphy from a group of consecutive patients with OSAH, we performed the dial-down CPAP technique during nocturnal polysomnography and used it as reference method. This allowed assessment of upper airway collapsibility, loop gain (LG), arousal threshold (AT), and upper airway muscle gain (UAG). We compared these results with a daytime protocol based on negative expiratory pressure (NEP) technique for evaluating upper airway collapsibility and UAG, on maximal voluntary apnea for LG, and on clinical predictors for AT.

Results Of 15 patients studied, 13 patients with OSAH accurately completed the two procedures. There were strong (all $r^2 > 0.75$) and significant (all $p < 0.001$) correlations for each phenotypic trait between the measurements obtained through the reference method and those achieved during wakefulness.

Conclusion It is possible to phenotype patients with OSAH from a pathophysiological point of view while they are awake. Using this approach, cutoff values corresponding to those usually adopted using the reference method can be identified to detect abnormal traits, achieving profiles similar to those obtained through the dial-down CPAP technique.

Keywords OSAH · CPAP · Polygraphy · Polysomnography · Airway collapsibility

Introduction

The obstructive sleep apnea–hypopnea (OSAH) syndrome has entered the precision medicine era [1]. Once the diagnosis is made, disease severity, biological activity, and the impact on the patient's life are all domains that may and should be evaluated in patients suffering from OSAH in order to choose the best therapeutic approach [1–4]. Recent studies have pointed out that OSAH is a heterogeneous disorder with different underlying pathophysiological mechanisms that are considered relevant in the development and maintenance of OSAH. The current ability to define and measure these pathophysiological traits (also named endotypes) [5–7] is now opening up the possibility of proposing different interventions [7], including pharmacological therapies, as an alternative to continuous positive airway pressure (CPAP) for many patients with OSAH who do not want or cannot use CPAP effectively [8–10].

Although the methods required to quantify the pharyngeal anatomy (passive collapsibility), the loop gain (LP), the arousal threshold (AT), and the upper airway muscle gain (UAG) have been recently simplified [6, 11], the measurements of these endotypes are still complicated. In fact, obtaining them still requires repeated manipulations of the CPAP level, usually overnight when the patients are asleep and are heavily instrumented to record EEG and respiratory signals [11].

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Therefore, obtaining pathophysiological traits remains a difficult task, limited to sleep research centers, Despite its paramount importance, this approach is still far from routine use in clinical practice.

This pilot study aimed to find a simpler method to phenotype patients with OSAH from a pathophysiological point of view during wakefulness after getting a diagnostic nocturnal cardio-respiratory polygraphy at home.

Methods

From April 2020, the present study considered patients referred to the Respiratory Unit of the Spedali Civili of Brescia for OSAH who showed moderate-to-severe OSAH (apnea–hypopnea index (AHI) ≥ 15) based upon the diagnostic cardio-thoracic polygraphy performed during sleep at home.

Consecutive patients who fulfilled the inclusion–exclusion criteria (BMI less than 45, absence of anatomic craniofacial or pharyngeal defects, neuromuscular diseases, overlap syndrome or endocrine diseases, and no prevalence of central sleep apnea, with central AHI less than 5/h) and gave their informed consent, were studied during one night in lab-polysomnography (PSG) in order to determine their pathophysiological OASH traits using the validated dial-down CPAP technique [11].

Overnight PSG recordings and scoring were performed in accordance with the American Academy of Sleep Medicine (AASM) guidelines [12]. All studies were scored by the same specialized sleep clinician, blinded to treatment assignment, according to AASM criteria [13]. AHI, ODI 4%, apnea and hypopnea type (obstructive or central), hypopnea ratio, and oxygen saturation were calculated from the PSG.

The study was performed in accordance with the Helsinki declaration, and the local University-Hospital Ethics Committee approved its protocol. All patients provided written informed consent upon enrolling.

Pathophysiological traits measurement: gold standard

In summary, we started by measuring ventilation obtained at optimal (no sleep-related respiratory disturbances) CPAP level (V,eupnea in L/m) during sleep. Ventilation was then measured after suddenly dropping CPAP to zero (V_0,passive in L/m). Then, after a progressive slow decrease of CPAP, previously brought back to optimal level, ventilation eliciting respiratory effort–related EEG arousals (V,arousal in L/m) was determined. Subsequently, after establishing the CPAP,min able to maintain ventilation without EEG arousals ($V_{,CPAPmin}$ in L/m), ventilation was measured again after suddenly dropping CPAP to zero (V_0,active in L/m). Finally, after resuming CPAP,min, CPAP was quickly restored to optimal level to measure ventilation obtained at dial-up (V,dial-up in L/m). This was necessary to achieve LG by calculating the ratio between the ventilatory response (V,dial-up-V,eupnea) and ventilatory disturbance (V,eupnea-$V_{,CPAPmin}$).

For a standard reference, upper airway collapsibility was estimated by the V_0,passive (judged low if < 1L/m); LG by the V,dial-up – V,eupnea/V,eupnea – $V_{,CAPmin}$ ratio (judged high if > 1); AT by difference from V,eupnea and V,Arousal in function of LG (judged low if < 10 L/m); UAG by the slope defined by the increase from V_0,passive to V_0,active in function of AT (judged low if < 0.4).

The next morning during wakefulness, the patients underwent the following tests, while breathing through a mouthpiece and wearing a nose-clip: (i) in supine position at the beginning of tidal expiration, they were suddenly exposed to a negative expiratory pressure of 5 cmH_2O, using a computer-driven Venturi system (NEP method), 200 ms after sensing an expiratory flow of 0.10 L/s (Negative Expiratory Pressure Direc/NEP Mod. 200B, Raytec Instruments, Bremgarten, CH). The volume exhaled in the first 500 ms was calculated by time integrating expiratory flow measured by a pneumotachograph ($V_{,NEP}$ 0.5). The volume exhaled in the next second of expiration was calculated similarly, always during NEP ($V_{,NEP}$ late). Both volumes were measured in the absence of intrathoracic expiratory flow limitation (Fig. 1); (ii) during regular tidal breathing, patients were asked to hold maximal voluntary apnea starting from FRC, and the volume of the second breath after resuming breathing at the end of apnea (Vt_{2nd}) was calculated and expressed as percent ratio of the average baseline tidal volume: Vt_{2nd} (%Vt). At least 2 acceptable trials were performed for each test, and the average values were retained for analysis. Finally,

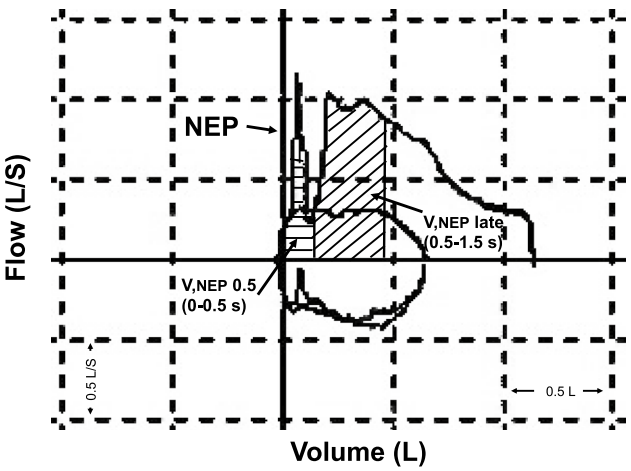

Fig. 1 This picture is an example of the NEP method to obtain the volume exhaled in the first 0.5 s ($V_{,NEP}$ 0.5) and in the subsequent sec. ($V_{,NEP}$ late) under NEP application during tidal expiration while the patients are awake in the supine position

AHI, percent fraction of hypopneas, and SpO2 nadir were obtained from diagnostic baseline cardio-thoracic polygraphy performed during sleep at home.

The volume exhaled under NEP has been shown to reflect the upper airway collapsibility [14, 15], and $V_{,NEP}$ 0.5 was chosen because it is not influenced by the reflex activity of the genioglossus [16]. Vt_{2nd} (%Vt) provided the estimate of the LG contribution to OSAH [17]. The combination of AHI < 30, more than 58% of hypopneas, and SpO2 nadir > 82.5% may accurately predict a low respiratory AT when 3 or at least 2 of these criteria are present (score ≥ 2) [18].

After computing the $V_{,NEP}$ late/$V_{,NEP}$ 0.5 ratio, we used the following formula, while keeping into account the AT level:

$$(V_{,NEP}\text{late}/V_{,NEP}0.5) \times \%_{hypo} \times (\text{SpO2nadir}/\text{AHI}).$$

This formula allowed us to assess UAG during wakefulness (UAGd) as an expression of upper airway muscle recruitment.

The protocol required no more than 30 min to be performed in each patient.

Statistics

The comparisons between the measurements relative to each pathogenetic trait obtained during wakefulness and during polysomnographic study were performed according to Pearson's correlations. The determination coefficients were determined. *P*-value < 0.05 was considered significant. Data were expressed as mean ± standard deviation.

Analyses were performed using SPSS 23.00 (IBM, Armonk, NY) and Graph Pad Prism 6.0 (Graph Pad Software, La Jolla, CA).

Results

Fifteen patients were recruited for the study, but 2 had to be excluded from the final analysis as it was not possible to collect all data for technical reasons.

The anthropometric and sleep characteristics of the 13 patients who completed the two protocols are shown in Tables 1 and 2, respectively.

Individual data for the four pathophysiological traits obtained with the reference method are displayed in Table 3.

As the data show, 11 out of 13 OSAH patients had an excessive collapsibility, 8 an elevated Loop Gain (LG), 9 a reduced arousal threshold (AT), and 8 a low upper airway muscle compensation (UAG), according to the gold standard method for phenotype measurements. None of them had just one abnormal trait, but 2 out 13 (15%) showed only non-anatomical abnormal phenotypic traits.

The corresponding individual data for the four pathophysiological traits obtained during the awake procedure are presented in Table 4.

Linear correlations between the respective measurements for each trait in all patients are shown in Figs. 2, 3 and 4.

Taking into account the predetermined abnormal values established for each trait according to the reference method, based on the lines fitting the data correlations, it was possible to establish the corresponding abnormal threshold values for the measurements obtained during

Table 1 Anthropometric data of the patients who completed the two protocols

Patient (*n*)	Age (yr)	Height (m)	Weight (kg)	BMI (kg/m^2)	Neck circumference (cm)	MALLAMPATI (score)
1	62	1.83	109	32.5	42	4
2	40	1.68	97	34.4	43	4
3	73	1.64	72	26.8	40	4
4	75	1.60	102	39.8	47	4
5	52	1.84	147	43.4	45	4
6	72	1.68	105	37.2	44	4
7	71	1.48	69	31.5	37	2
8	78	1.69	80	28.0	40	4
9	71	1.59	84	33.2	42	4
10	48	1.64	79	29.4	40	3
11	55	1.82	105	31.7	46	4
12	59	1.60	83	32.4	39	4
13	44	1.72	100	33.8	45	4
Mean ± SD	61.5 ± 12.8	1.68 ± 0.10	94.7 ± 20.7	33.4 ± 4.6	42.3 ± 3	3.8 ± 0.6

BMI Body Mass Index; *SD* standard deviation

Table 2 Sleep sudy characteristics of the patients who completed the two protocols

Patient (*n*)	AHI	AI	HI	% HYPO	OAHI	SpO2 mean (%)	Mean desaturation	CT90	ODI	SpO2 nadir
1	33	21	12	36.4	27	92	85	20.4	32	71
2	18	5	13	72.2	14	93	90	3.6	17	76
3	72	48	24	33.3	65	87	82	57.2	66	65
4	64	41	23	35.9	40	85	78	71.0	64	59
5	87	86	1	1.2	79	89	82	45.1	85	65
6	30	5	25	83.3	24	93	90	6.9	29	82
7	20	3	17	85.0	20	94	92	4.9	19	86
8	25	13	12	48.0	20	94	90	1.4	9	83
9	37	32	5	13.5	35	97	91	0.1	13	88
10	36	12	24	66.7	35	95	91	5.0	34	81
11	33	18	15	45.4	31	89	88	49.4	33	76
12	49	18	31	63.3	49	94	89	10.4	41	78
13	55	49	6	10.0	51	95	85	40.7	45	64
Mean ± SD	43 ± 21.1	27.8 ± 23. 5	15.2 ± 9.8	45.8 ± 27.4	37.7 ± 18.9	92.1 ± 3.5	87.1 ± 4.4	24.3 ± 24.8	41.3 ± 26.2	74.9 ± 9.3

AHI apnea–hypopnea index; *AI* apnea index; *HI* hypopnea index; *%HYPO* percent fraction of hypopnea; *OAHI* obstructive apnea–hypopnea index; *SpO2* oxygen saturation; *CT90* analysis time with SpO2 < 90%; *ODI* oxygen desaturation index

Table 3 Measurements of the pathophysiological traits according to the dial-down CPAP technique during nocturnal polysomnography for each patient. Bold characters identify predetermined abnormal values for each phenotypic trait

Patient (*n*)	Collapsibility *V,0p (L/min)*	LG *V,dial-up-V,e/V,e-V,CPAP min (ratio)*	AT *(L/min)*	UAG *V,0a-V,0p (L/min)/AT*
1	1.41	**2.8**	24.2	**0.12**
2	**0.47**	**2.5**	**6.4**	0.61
3	**0.57**	0.6	**5.8**	**0.33**
4	**0.66**	**1.7**	**7.8**	**0.03**
5	**0.54**	**2.3**	12.6	**0.23**
6	**0.39**	0.4	**5.5**	3.13
7	**0.52**	0.7	**3.6**	0.89
8	**0.67**	**1.6**	**4.6**	1.48
9	1.29	**2.5**	**8.3**	**0.05**
10	**0.76**	0.7	**7.8**	0.49
11	**0.78**	**1.9**	12.1	**0.19**
12	**0.88**	0.6	**9.7**	**0.12**
13	**0.89**	**2.6**	18.2	**0.11**

LG loop gain; *AT* arousal threshold; *UAG* upper airway muscle gain *V,0p* ventilation at 0 CPAP with upper airway muscles passive; *V,0a* ventilation at 0 CPAP with upper airway muscles active; *V,e* ventilation in eupneic condition

Table 4 Measurements of the pathophysiological traits according to the daytime protocol for the same patients

Patient (*n*)	Collapsibility V,NEP 0.5 (L)	LG Vt 2nd (%Vt)	AT score	UAG (V,NEP late/V,NEP 0.5) ×%HYPO ×SpO2 nadir/AHI
1	0.63	226.7	0	148.4
2	0.24	228.0	2	368.5
3	0.30	173.5	0	25.6
4	0.38	227.6	0	44.5
5	0.37	244.5	0	1.3
6	0.10	146.9	2	922.5
7	0.19	181.3	3	306.8
8	0.25	218.4	2	223.1
9	0.45	225.3	1	39.8
10	0.23	187.3	1	334.3
11	0.40	212.9	0	188.4
12	0.39	191.1	1	105.9
13	0.38	229.5	0	12.5

LG loop gain; *AT* arousal threshold; *UAG* upper airway muscle gain (UAGd)

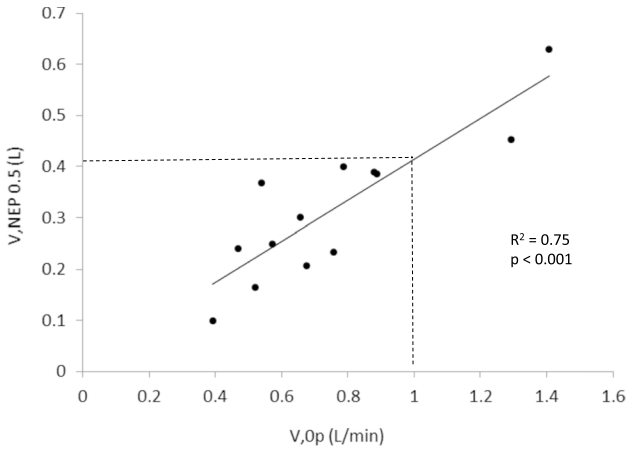

Fig. 2 Correlation between upper airway collapsibility measured through the ventilation value obtained after abrupt CPAP drop to zero during polysomnography (V_0,passive) and that evaluated at daytime using the volume exhaled under NEP in the first 0.5 s of tidal expiration ($V_{,NEP}$ 0.5). Note that all patients who showed low collapsibility evidenced by V_0,passive (V,0p) below 1 L/min had $V_{,NEP}$ 0.5 lower than 0.4 L

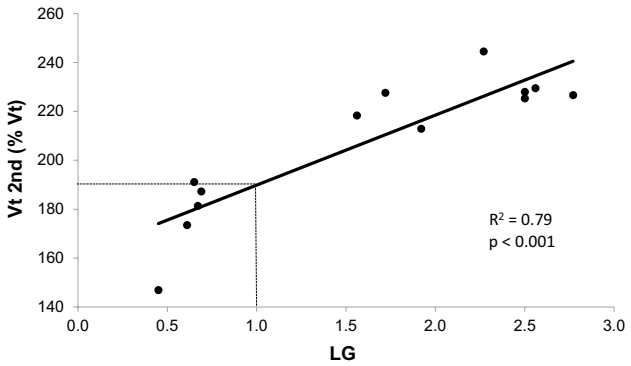

Fig. 3 Correlation between loop gain (LG) measured through the reference method and its daytime assessment using the % ratio of 2nd breath after maximal voluntary apnea from FRC, over average baseline tidal breathing (Vt_{2nd} (%Vt)). Note that all patients who showed an LG higher than 1 had a Vt_{2nd} (%Vt) value greater than 200

wakefulness in order to define the pathophysiological phenotypic profile for each patient with a new daytime procedure.

Hence, in our cohort, a $V_{,NEP}$ 0.5 value lower than 0.4 L was indicative of high pharyngeal collapsibility as shown by a V_0,passive lower than 1 L/m; a value of Vt_{2nd} (%Vt) greater than 200 after maximal voluntary apnea identified an LG higher than 1; a cutoff value of UAGd below 200 corresponded to a value for UAG lesser than 0.4, useful for recognizing a low UA muscle compensation. Finally, by comparing Tables 3 and 4, an AT score ≥ 2 derived from its clinical predictors have been obtained in the presence of AT lower than 10 L/m, indicating a low arousal threshold.

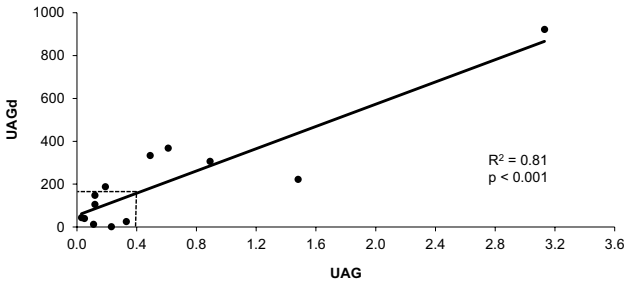

Fig. 4 Correlation between upper airway gain measured through the reference method (UAG) and that evaluated at daytime using the ratio between volume exhaled under NEP in the 0.5–1.5 s and in the first 0.5 s of tidal expiration (V'_{NEP} late/V'_{NEP} 0.5), times the AT clinical predictors (UAGd). Note that all patients with low UAG identified by a 0.4 value had a UAGd value lower than 200

Discussion

This is the first attempt to phenotype patients with OSAH while awake. The values of pathophysiological traits we obtained with daytime procedures optimally correlated with those found using the previously validated dial-down CPAP technique. This pilot study may also permit the establishment of the cutoff values during wakefulness that suggest the presence of an abnormal trait, corresponding to predefined critical values obtained with the polysomnographic technique.

Therefore, it is possible to draw a pathophysiological profile for each patient with OSAH during wakefulness as done using the polysomnographic technique. In our limited experience, such a procedure performed very well, allowing the recognition of similar abnormal pathophysiological traits in all patients with OSAH (Fig. 5).

Although today these four pathophysiological traits can also be measured thanks to offline validated algorithms by using PSG, which might be a promising alternative to the dial-down CPAP technique in the future, this method is not yet available for sleep specialists' daily practice [19–21]. Furthermore, such an approach requires an overnight sleep study with EEG and optimal flow signal, as the nasal pressure channel provides a surrogate uncalibrated ventilation signal from which the pathophysiological traits are extracted. Conversely, our daytime procedure may represent an easy, widely available and cheap tool to define the OSAH pathophysiological phenotypes, performed without the need for overnight PSG sleep studies.

We used a mouthpiece to apply NEP, which excludes the retropalatal region that may be a site of upper airway obstruction during sleep in patients with OSAH. This may limit the information about the upper airway collapsibility, leading to its underestimation in some cases [22]. However, in the supine position, there is no difference in using either the mouthpiece or the nasal mask with regard to the volume obtained during NEP application [23] .

This is a pilot study, and the sample of patients is small. However, these preliminary results are encouraging, and a larger validation cohort should be assessed.

Fig. 5 In the left panel, the grey squares indicate abnormal pathophysiological traits, according to predetermined values (shown in the header of the figure), detected for each patient with the standard procedure; in the right panel, they indicate abnormal pathophysiological traits detected for each corresponding patient during daytime procedure, using the cutoff values previously identified (shown in the header of the figure). Note the excellent comparison between the two procedures in drawing the pathophysiological phenotypic profile in all patients

	STANDARD PROCEDURE				DAYTIME PROCEDURE			
Patient (n)	Collapsibility V'_{0p} < 1 L/m	LG > 1	AT < 10 L/m	UAG < 0.4	Collapsibility V'_{NEP} 0.5 < 0.4 L	LG > 200	AT ≥ 2 score	UAG < 200
1		■		■		■		■
2	■	■	■		■	■	■	
3	■			■	■			■
4	■	■		■	■	■		■
5	■	■		■	■	■		■
6	■		■		■		■	
7	■		■		■		■	
8	■	■	■		■	■	■	
9		■		■		■		■
10	■				■			
11	■	■		■	■	■		■
12				■				■
13	■	■		■	■	■		■

Conclusion

In the era of precision medicine, this daytime approach, if validated, may make it much easier to phenotype patients with OSAH, allowing its routine integration in clinical practice. The technique may also pave the way for individualized treatment alternatives to CPAP.

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Author contribution Study design: CT and LP. Data collection: RM, GL, LZ. Data analysis: EP and LP. Interpretation of results: all authors. Initial draft: CT. Review of the manuscript for intellectual content: all authors.

Data availability Not Applicable

Code availability Not Applicable

Declarations

Ethics approval The study was performed in accordance with the Helsinki declaration and was approved by the University of Brescia's Department of Clinical and Experimental Science (DSCS) Ethic Committee.

Consent to participate All participants signed written informed consent upon enrolling.

Consent for publication All participants signed written consent for publication upon enrolling.

Competing interests The authors declare no competing interests.

References

1. Martinez-Garcia MA, Campos-Rodriguez F, Barbè F, Gozal D, Agusti A (2019) Precision medicine in obstructive sleep apnea. Lancet Respir Med 7:456–464
2. Uccelli S, Pini L, Bottone D, Ranieri P, Orzes N, Tantucci C (2020) Dyspnea during night-time and at early morning in patients with stable COPD is associated with supine tidal expiratory flow limitation. Int J Chron Obstruct Pulmon Dis 15:2549–2558
3. Taranto-Montemurro L, Messineo L, Perger E, Salameh M, Pini L, Corda L, Ferliga M, Tantucci C (2016) Cardiac sympathetic hyperactivity in patients with chronic obstructive pulmonary disease and obstructive sleep apnea. COPD 13(6):706–711
4. Quadri F, Boni E, Pini L, Bottone D, Venturoli N, Corda L, Tantucci C (2017) Exercise tolerance in obstructive sleep apnea-hypopnea (OSAH), before and after CPAP treatment: effects of autonomic dysfunction improvement. Respir Physiol Neurobiol 236:51–56
5. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. Am J Respir Crit Care Med 2013; 188:996–1004.
6. Malhotra A, Mesawi O, Pepin JL, Owens RL (2020) Endotypes and phenotypes in obstructive sleep apnea. Curr Opin Pulm Med 26:609–614
7. Messineo L, Magri R, Corda L, Pini L, Taranto-Montemurro L, Tantucci C (2017) Phenotyping-based treatment improves obstructive sleep apnea symptoms and severity: a pilot study. Sleep Breath 21(4):861–868
8. Deacon NL, Jen R, Li Y, Mallhotra A. Treatment of obstructive sleep apnea. Prospects for personalized combined modality therapy. Ann Am Thorac Soc 2016; 13:101–108.
9. Taranto-Montemurro L, Messineo L, Wellman A. Targeting endotypic traits with medications for the pharmacological treatment of obstructive sleep apnea. A review of the current literature. J Clin Med 2019; 8: 1846.
10. Lim R, Messineo L, Grunstein RR, Carberry JC, Eckert DJ (2021) The noradrenergic agent reboxetine plus the antimuscarinic hyoscine butylbromide reduces sleep apnoea severity: a double-blind, placebo-controlled, randomized crossover trial. J Physiol 599:4183–4195
11. Perger E, Taranto-Montemurro L, Rosa D et al. Reboxetine plus Oxybutinin for obstructed sleep apnea treatment. A 1-week randomized, placebo-controlled, double-blind, crossover trial. Chest 2021; in press.
12. Wellman A, Edwards BA, Sands SA et al (1985) A simplified method for determining phenotypic traits in patients with obstructive sleep apnea. J Appl Physiol 2013(114):911–922
13. Sateia MJ (2014) International classification of sleep disorders-third edition: highlights and modifications. Chest 146:1387–1394
14. Rosenberg RS, Hout SV (2014) The American Academy of Sleep Medicine Inter-scorer Reliability Program: respiratory events. J Clin Sleep Med 10:447–454
15. Taranto-Montemurro L, Bettinzoli M, Corda L, Braghini A, Tantucci C (2010) Relationship between critical pressure and volume exhaled during negative pressure in awake subjects with sleep-disordered breathing. Chest 137:1304–1309
16. Hirata RP, Schorr F, Kayamori F et al (2016) Upper airway collapsibility assessed by negative expiratory pressure while awake is associated with upper airway anatomy. J Clin Sleep Med 12:1339–1346
17. Tantucci C, Mehiri S, Duguet A et al (1985) Application of negative expiratory pressure during expiration and activity of genioglossus in humans. J App Physiol 1998(84):1076–1082
18. Messineo L, Taranto-Montemurro L, Azarbazin A et al (2018) Breath-holding as a means to estimate the loop gain contribution to obstructive sleep apnea. J Physiol 596:4043–4056
19. Edwards BA, Eckert DJ, McShurry DG et al (2015) Clinical predictors of the respiratory arousal threshold in patients with obstructive sleep apnea. Am J Respir Crit Care Med 190:1293–1300
20. Terrill PI, Edwards BA, Nemati S et al (2015) Quantifying the ventilatory control contribution to sleep apnoea using polysomnography. Eur Respir J 45:408–418
21. Sands SA, Terrill PI, Edwards BA et al (2018) Quantifying the arousal threshold using polysomnography in obstructive sleep apnea. Sleep 41:1–9
22. Sands SA, Edwards BA, Terrill PI et al (2018) Phenotyping pharyngeal pathophysiology using polysomnography in patients with obstructive sleep apnea. Am J Respir Crit Care Med 197:1187–1197
23. Hirata RP, Kayamori F, Schorr F et al (2017) Influence of interface and position on upper airway collapsibility assessed by negative expiratory pressure. Sleep Breath 21:631–638