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TITLE: PHENOTYPING THE PATHOPHYSIOLOGY OF OBSTRUCTIVE SLEEP APNEA USING POLYGRAPHY / POLYSOMNOGRAPHY: A REVIEW OF THE LITERATURE

INTRODUCTION

Continuous Positive Airways Pressure (CPAP) is the first-line treatment for the majority of patients affecting by Obstructive Sleep Apnea syndrome (OSA) and represents the paradigm of "one-size-fits-all" therapeutic strategy (**1**). However, long-term compliance with CPAP therapy is limited and alternatives to CPAP therapy are therefore required to address the increasing need to provide tailored therapeutic options (**2-4**). In this context, it is important to focus on the patients' pathophysiologic traits (PT).

In OSA, PT can be phenotyped in sleep laboratories by applying positive airway pressure device, with the patient in supine position, during non-rapid eye movement sleep (NREM) stage 2. At the same time ventilation is recorded while changing upper airway (UA) pressure. Four different PT have been identified: upper airway anatomical collapsibility (UA anatomical trait), Loop Gain (LG trait), Arousal Threshold (AT trait), Upper Airway Gain (UAG trait) (**5-7**).

Although the presence of predisposition to UA anatomical collapsibility is important in the concept of apneic events, it may not be the leading factor for the development of OSA as apneas and hypopneas may be caused as a result of the non-anatomical PT (LG, AT, UAG) (**7**). In some patients with OSA, UA anatomical collapsibility can be critical to produce the apneic events, independent of any other PT ("*inevitable OSA"*); other patients without sufficient UA anatomical collapsibility do not develop OSA, even in the presence of significant features of other PT. Finally, there are different grades of anatomical collapsibility ("*UA vulnerable anatomy"*) and patients only develop apneic events depending on the presence of any of the other three pathophysiological traits, LG, AT and UAG (**7**).

A recent study proposed a possible classification of OSA patients in three subgroups, based on the impairment of UA anatomy and the non-anatomical phenotypes (LG, AT and UAG), the **PALM** scale (**Pc**ritical, **A**rousal threshold, **L**oop Gain, **M**uscle responsiveness) (**8**). This kind of phenotyping allows for different possible therapeutic strategies which, however, have only been developed on small clinical groups and with theoretical models (**3**, **7-8**):

- **PALM scale 1:** A subgroup of patients (23%) who are characterized by a critical occlusion pressure (Pcrit) above +2cmH_2O with high passive anatomical collapsibility develop apnoeic events, due to anatomical factors, independent of other non-anatomical pathophysiological traits, this is called *"inevitable OSA"*. In these patients, treatment options focus on the anatomical basis [e.g. CPAP, Mandibular Advancement Device (MAD), UA surgery, Positional Therapy, weight loss].

- **PALM scale 3:** A subgroup of patients (19%) that is characterized by a Pcrit lower than -2cmH_2O with a low passive collapsibility develop apneic events due to non-anatomical pathophysiological factors (LG, AT, UAG). In these patients, the treatment does not focused on the anatomical modification of the UA, but its stabilization by means of single or combined treatment with oxygen therapy and/or pharmacological treatment on LG and AT.

- **PALM scale 2:** A subgroup of patients (58%) who are characterized by a Pcrit between +2 and -2 cmH_2O with relative high passive collapsibility who are subdivided into **subgroup 2a**, which relates to anatomical pathophysiological factors (*"inevitable OSA"*), and **subgroup 2b**, which relates to anatomical and non-anatomical pathophysiological factors prevalent. The Authors thought that the predominant therapeutic approach for **subgroup 2a** is the anatomical basis (CPAP, mandibular advance splint, upper air way surgery, positioning therapy, weight loss), while **subgroup 2b** may be treated using anatomical and non-anatomical treatment options.

Understanding the PT lies at the heart of the customized OSA treatment. This is important as that non-CPAP tailored treatments focusing on LG, AT and UA anatomy may obtain the stabilization in 19-38% of OSA patients, one single tailored treatment may obtain the stabilization in 48% of OSA patients, and combined tailored treatment strategies may achieves respiratory control in 48-81% of OSA patients (**7**).

Nowadays, the sleep research laboratories capable to phenotype OSA patients are available only in few centers of excellence and the procedures are time-intense, costly and require expertise, albeit some new novel and non-invasive methods for characterizing and quantifying some of the pathophysiological phenotypes have been recently introduced (**9-10**). Nevertheless, the question remains whether the use of routine clinical polysomnography or /nocturnal portable multi-channel monitoring (PSG/PM) can provide similar information, useful at least to define qualitative definition properties of the different PTs of OSA.

The aim of present review is to deduce the information obtainable from the clinical PSG/PM analysis, independently of the scope and context of the original studies, useful to define qualitatively the PT of the single OSA patient.

THE UPPER AIRWAY ANATOMICAL COLLAPSIBILITY

UA anatomical collapsibility has been defined by means of the passive Pcrit that describes the endolaryngeal pressure threshold (**11-12**). The Pcrit maneuvers are difficult to establish in clinical routine, because of the required technological equipment, time and expertise needed, the complexity in obtaining and interpreting the pressure/volume curves and the difficulties in obtaining defined sleep stages during the maneuver. Although this does not negate physiological usefulness of the concept, it substantially limits clinical availability of this method which is expressed by the high percentage of physiological studies in OSA that fail to gather these data. Moreover, there is little standardization of the diagnostic protocol which limits comparability between available studies using this method (**13**).

The current literature review has focused on the link between the PSG/PM data and the UA anatomical collapsibility, taking into account that data have to be linked to the different sensors and scoring standards applied by different studies.

-Predominant Obstructive Apneic Pattern represents a PSG/PM marker useful to identify patients with high collapsibility of the upper airway. Gleadhill et al (**14**) reported that OSA characterized by a predominant obstructive apneic pattern [where obstructive apneas represent at least 90% of the total apnea-hypopnea index (AHI; **Figure 1**)] were likely to have a Pcrit value >2 cmH_20. The patients' studied had predominantly severe OSA (AHI 70±24/hour and were studied using nasal and oral thermistor and defining obstructive apnea as the absence of airflow and hypopnea as the airflow reduction of 50%, associated with a ≥ 3% desaturation or with an arousal. This information is helpful in understanding that predominant obstructive apneic PSG/PM patterns are linked to a high UA anatomical collapsibility, which is described as PALM scale 1.

-Upper Airway Resistance Syndrome (UARS) Pattern is coherent with low UA anatomical collapsibility. Gold et al (**15**) reported that patients affected by UARS showed a PSG/PM pattern characterized by respiratory effort related arousals (RERAs; **Figure 2**), which is linked to a Pcrit lower than - 2 cmH_20. Thus, UARS patients match the PALM scale 3 which is characterized by a low upper airway anatomical collapsibility and a significant role of non-anatomical PT. The PSG scoring standards applied by the authors for the RERA and UARS are not strictly coherent to the current and more accepted definitions (**16-17**).

-AHI severity pattern. It is possible to gather information concerning the UA anatomy promoting

pharyngeal collapsibility by analysis of the Apnea Hypopnea Index (AHI) severity. The data by Eckert et al (**8**) indicated that it is possible to analyze the relation between the Pcrit value and AHI severity and they showed that only 10.3% (3/29) of the OSA patients with an AHI>40/hour had a Pcrit lower than -2 cmH_2O (**PALM scale 3**), whereas only the 3.7% (1/27) of the patients with AHI<40/hour had a Pcrit higher than +2 cmH_2O (**PALM scale 1**). In summary, OSA patients with AHI >40/h have a low risk to be included in PALM 3 scale classification as well as OSA patients with AHI<40/h have a low risk to be included in the **PALM 1 scale**. These information cannot be generally applied to PSG/PM without taking into account the sensors and scoring standards used by the authors in the study (**18**), which are not those currently recommended by the AASM (**19**).

-**Therapeutic CPAP Value**. Landry et al (**20**) found that patients with a mildly collapsible UA (Pcrit ≤ -2cmH_2O) required lower therapeutic CPAP and found that a therapeutic CPAP level ≤ 8.0cmH_2O (overall therapeutic control of apneas, hypopneas, inspiratory flow limitation and snoring during NREM sleep stage) was sensitive (89%) and specific (84%) for detecting a mildly collapsible UA. When applied to the independent validation dataset (n=74), this threshold maintained a high specificity (91%) but resulted in reduced sensitivity (75%). Therefore the level of therapeutic CPAP may be used to accurately differentiate OSA patients with mild airway collapsibility (**PALM scale 3**) from those with moderate-to-severe collapsibility (**PALM scale 2 and 1**).

-Positional OSA. Body posture can have a significant impact on UA anatomy and UAG. Joosten et al. (**21**) demonstrated in 20 OSA patients that the lateral position results in a significant improvement of UA collapsibility and UAG, with no consequences in LG and AT. The Pcrit decreased by a mean of 4 cmH_2O, changing from the supine to lateral position, with a stabilization of the UA lumen in 7/20 OSA patients studied. The Authors believed that the administration of an AT pharmacological stabilizer, but not a drug active on LG, could stabilize the patients with residual high AHI in lateral position.

LOOP GAIN (LG) AND VENTILATORY CONTROL

The ventilatory control helps to maintain the homeostasis of the blood gas and it is state and sleep stage dependent, with supra-pontine effects during wakefulness and during REM sleep and predominantly metabolic control during NREM sleep stages. The metabolic complexity of ventilatory control during NREM sleep has been simplified and summarized by the engineering model of Loop Gain (LG), which consists of one control component (chemoreceptor: controller gain), one exchange component (lung: plant gain) and one connection component (circulation: circulatory delay). The responsiveness of LG is measured in no-dimensional unit: a LG >1 is related to a very efficient and hyper-reactive system, which determines a quick and excessive ventilatory response (periodic breathing) response to destabilizing respiratory events during sleep, whereas a LG <1 is related to a low ventilatory response to a destabilizing event during sleep with a rapid new balance of the system (**22**).

Periodic breathing with Cheyne-Stokes Respiration (CSR) is characterized by a “waxing and waning” respiratory effort and represents the most know sleep disturbance caused by ventilatory metabolic control instability (high LG). Sands et al reported a rapid method for calculating the LG on patients affected by heart disease with CSR by means of graphic elements from clinical PSG trace (**23**).

The high LG represents an important PT also in a significant percentage of OSA patients. The LG can be measured by means of a bi-level positive pressure device, UA continuous pressure devices (**3-24-25**) or sophisticated mathematical analysis of clinical PSG/PM (**26**). Nowadays, these techniques of LG measurement are not available in clinical routine, but it is possible to obtain information related to high

ventilatory control instability during sleep from clinical PSG/PM recordings:

-**Mixed OSA-CSR pattern.** This is a relatively common pattern, consisting of alternation and mixing periods characterized by UA obstructive events and CSR periods (**27**). The presence of CSR has to be considered a PSG/PM pattern related to instability of ventilatory metabolic control and a hyper-responsive LG.

-**Predominant obstructive pattern with some central/mixed events.** This pattern is identified using PSG/PM and characterized by a predominant obstructive pattern with some percentage of central/mixed events (**Figures 3 and 4**). This is another pattern related to instability of ventilatory metabolic control and a hyper-responsive LG. The ventilatory instability control is due to two main factors: the LG control system and the CO_2 reserve. The CO_2 reserve is defined as the difference between the $PaCO_2$ value during eupneic ventilation asleep and the $PaCO_2$ value at which the apneic event occurs (**28**). A high LG determines periodic breathing, whereas a low CO_2 reserve can produce central respiratory events, which occur during the decreasing phase of ventilation during periodic breathing (**29**). Xie et al. (**30**) studied 21 OSA patients, identifying two subgroups: the first subgroup consisted of 9 patients with obstructive PSG pattern and a second subgroup consisted of 12 patients with a PSG pattern that was characterized by predominant obstructive events and a percentage of central/mixed events (28.2±6.3%), which were related to a high CO_2 chemoresponsiveness with low CO_2 reserve and consequent central/mixed events. The authors did not report a different Pcrit between the two subgroups, which would be related to anatomical UA collapsibility.

-**Predominant NREM OSA Pattern**. OSA can be classified in relation to the predominant sleep stages (NREM vs REM). Joosten et al. (**31**) studied 1,064 patients with OSA reporting predominantly REM-related OSA in 45.3% of patients (AHI-REM: AHI-NREM >2), isolated REM-related OSA in 13.6% of patients (AHI-REM : AHI-NREM >2 with AHI NREM <5/hour) and OSA during predominantly NREM sleep in 18.9% of patients (AHI-REM : AHI-NREM <0.5). In NREM sleep stage, ventilator control is exclusively metabolic, whereas in REM sleep stage is mixed: metabolic and behavioural. Obstructive respiratory events in predominantly REM-related OSA are characterized by significant muscular hypotonia/atonia and lower chemoresponsiveness (**32-33**), whereas predominantly NREM-related OSA may be characterized by an unstable ventilatory metabolic control during NREM sleep stage, which is related to a high LG. In patients with predominantly NREM-related OSA the supra-pontine control is active during REM sleep and determines the improvement of apneic events when transitioning from NREM (a state of instability of the ventilatory metabolic control characterized by a high LG) to REM sleep (a state of increased stability of the ventilatory control, which now isn't exclusively metabolic but mixed metabolic/behavioural). Terril et al. (**26**) suggested a method of LG measurement in 28 patients with moderate-severe OSA based on the clinical PSG analysis. The authors reported a significant correlation between high LG and predominantly NREM-related OSA ($r= -0.46$, $p=0.02$) and suggested that a difference between the REM-AHI and NREM-AHI that is higher than 25 events is related to a LG>1. Moreover, the authors reported a significant correlation between LG and post-apneic events hyperventilation ($r= -0.60$, $p <0.001$) and inter-event pause ($r= -0.56$, $p=0.001$): the regression analysis of the patients with post-apneic event hyperventilation duration $\leq$ 12 seconds and with an inter-event pause $\leq$30 seconds are characterized by a LG $\geq$1. Summarizing, predominantly NREM related OSA has a PSG pattern that is characterized by a high LG.

THE AROUSAL THRESHOLD (AT)

AT is defined as the level of inspiratory effort, as measured by the esophageal pressures, at which obstructive events terminate, usually with an arousal from sleep (**34-35**). For a long time, arousals from sleep have been considered as unavoidable and necessary for ending an obstructive event. However, in more than 25% of obstructive events arousals may not be observed at the end of the obstructive event (**36-38**). During an obstructive event, "non-muscular" (increasing of inspiratory flow, duty cycle and respiratory frequency) and "muscular" mechanisms are recruited via chemical and mechanical triggers. When these mechanisms achieve a balance to obtain sufficient ventilation (Sustainable VE) then an arousal may not be required to achieve ongoing ventilation. The threshold of the UA reopening, sufficient to achieve a sustainable VE, is

defined as Threshold of Effective Recruitment (Ter). Essentially, the relation between the AT and Ter determines whether there is an arousal at the end of an obstructive event: the arousal occurs when the AT is lower than Ter or when there is hyperventilation following UA reopening that stimulates the arousal center (**39-40**). AT and Ter are related to sleep stage and to other factors, such as age, drugs, alcohol consumption, sleep fragmentation and sleep deficiency (31). Finally, the arousal intensity could represent an independent pathophysiologically trait: high arousal intensity is related to increased ventilation and unstable ventilatory control (**41**).

Low AT Pattern

A low AT can be characterized by three PM/PSG parameters. Edwards et al. (**9**) studied 147 patients by means of PSG and epiglottic catheter and found independent predictors of AT. They developed a PSG score based on three parameters, an AHI<30/h, associated with oxygen desaturating of a nadir SpO_2 >82% and with a hypopnea/apnea ratio>58.3%, which was useful to identify a low AT; 2 / 3 of these scores predict a low AT in 84.1% of patients with a sensitivity of 80.4% and specificity of 88%. Consequently, UARS (**Figure 5**) characterized by a low collapsibility, normal AHI range and RERAs is an extreme version of this low AT pattern (**11**).

High AT Pattern

A PSG characterized by prolonged and severe desaturations is consistent with a high AT, especially in patients with severe AHI (**figures 6-7**). The desaturation nadir of an UA obstructive event is mainly dependent on two factors: the first factor is represented by the AT which is sleep stage dependant (NREM 1 equals the one at REM and it is higher in NREM 2 and NREM 3), it increases with the sleep fragmentation, chronic sleep deficiency and AHI severity (**9**). The second factor is represented by the slope of ventilatory response to the hypoxemic and hypercapnic stimuli which are also sleep stage dependant (**30**). These two factors allow the interpretation of the different severity of desaturation nadir, which are, for example, observed during NREM 1 and REM sleep stages, characterized by the same AT but different chemo-responsiveness slope. Summarizing, these observations suggest that prolonged and severe desaturations on PSG/PM are related to a reduced ventilatory response to a chemical stimulus and a high AT.

UPPER AIRWAY GAIN (UAG)

The UAG defines the UA neuromuscular recovery in response to an obstructive event. The UA collapse during obstructive events can be recorded with three different flow limited patterns during PSG/PM, all of which are characterized by negative effort dependence (NED): the appearance of a plateau or airflow reduction, even with increased inspiratory effort (**42-43**):

1. **Starling Resistor Model (NED-pattern 1)**: during an obstructive event it is possible to observe a first phase during a single inspiration during which flow increases in a linear way with increasing effort, and the second phase during which flow remains stable and independent of any effort. In this model, the inspiratory flow limitation persists for all inspiratory efforts during an obstructive event.
2. **Intra-Event Negative Effort Dependence Pattern (NED-pattern 2)** (**Figure 5**): following the first phase in which the flow increases in a linear way, flow gradually decreases during the second part of the inspiration. The level of inspiratory flow limitation is repeated stereotypically for all parts of the same obstructive event.
3. **Inter- and Intra-Event Negative Effort Dependence Pattern (NED-pattern 3)** (**Figure 8**): after a first phase during which flow increases in a linear way, flow gradually decreases during the second part of the inspiration. This inspiratory flow limitation gets progressively worse during every part of the obstructive event.

The collapse pattern of the airflow is related to different capacities of the UA to defend patency against the negative effort dependence, and can also be used to identify the site of collapse. The Starling resistor pattern (a small plateaued flow limitation pattern) seems to be related to the site of collapse at the base of the tongue (a small amount of NED), whereas the two other patterns of negative effort dependence seem to be related to

weaker structures such as the soft palate, lateral pharyngeal walls (large NED) and the epiglottis (severe NED) (**44**).

DISCUSSION

About 50% of patients with sleep-disordered breathing, who use CPAP therapy, are either partially (less than 4 hours per night) or entirely non-compliant with CPAP application (**45**). Current non-CPAP therapies (weight loss, MAD, UA stimulation and UA surgery) provide variable results that are often poorly predictable. So far therapeutic strategies for OSA do not systematically consider different pathophysiological phenotype as an essential aspect of a decision-making algorithm.

Only recently, the therapeutic approach of "one-size-fits-all" has been overcome and new non-CPAP therapies have been introduced, based on pathophysiological characteristics of an individual patient. The PALM scale allows identification of three clusters of OSA patients (**8**). Owens et al. have simulated in their patient population the effect of various trait manipulations using non-CPAP treatments predicting the proportion of patients treated by each intervention: a single intervention on one PT could treat OSA in approximately ¼ of all patients, while combination therapy using two interventions was predicted to potentially treat OSA in greater than 50% of patients (**7**).

Phenotyping of pathophysiological SDB/OSA traits is currently not available to most sleep centers or in clinical routine, potentially useful non-CPAP therapies (mainly drugs and oxygen) aiming to treat these three PT (LG, AT and UAG) are not available for most patients because of a lack of appropriate clinical validation studies. However, following the analysis of data reported in review, it is possible to consider that PSG/PM recordings can be used to qualitatively characterize some of these clinical traits. We believe that this pragmatic approach is important to facilitate the delivery of evidence based polycentric studies in the clinical setting to improve access to large scale validation studies for many patients with OSA.

Although this approach requires a multi-disciplinary collaboration between respiratory physicians, somnologists and neurologists, the otorhinolaryngologist is in an optimal position to deliver such validation studies, to understand the relationship between different clinical phenotypes of OSA using PM/PSG recordings and compare specific surgical therapies, due the setup of clinical services: operating services have databases available for retrospective studies and therapeutical instrumentation is easily coded and identified for prospective studies**.**

The understanding of the underlying PT is crucial to the selection of surgical treatment options in OSA; a good example is, to our knowledge, the only study that reported on a decreasing Pcrit following UA surgical therapy (**Uvulo-Pharyngo-Palato-Plasty, UPPP**) in 13 OSA patients: a subgroup analysis of responders and non-responders demonstrated that significant differences in Pcrit were confined to the responders. Specifically, responders demonstrated a significant fall in Pcrit from -0.8 +/- 3.0 to -7.3 +/- 4.9 cmH_2O ($p = 0.01$), whereas no significant change in Pcrit was detected in the non-responders (1.1 +/- 1.6 versus 0.6 +/- 2.0 cmH_2O; p=NS) (**46**).

Nevertheless, although validation studies for the phenotyping of OSA patients using clinical PM/PSG have not been carried out so far, interventional treatment for OSA should start to request qualitative PM/PSG phenotyping in sleep laboratories**.** If the grade of UA collapsibility (Pcrit), AT and LG are known, the outcomes of surgical therapy will be more suitable: for the same reduction of Pcrit obtained different grades of successful outcomes might be available in relation to the impact of other identified PT. Recently, electrical neurostimulation has become clinically available in OSA and the polygraphic pattern of the muscular response should be taken into account, if this approach is considered (**47-48**). Finally, retrospective analysis of existing databases and prospective clinical validation studies with standardized patient populations are

required to establish this approach in clinical practice.

Conclusion

Up to now, the different aspects of the pathophysiology of OSA have not been systematically considered when selecting therapeutic options which are usually proposed without taking into account the patient's phenotyping using PT. The PALM scale has helped to overcome a "one-size-fit-all" approach and introduces the concept of customized therapy for OSA patients, adding value to the role of non-CPAP therapy, in single or combined modality. The sleep research laboratory phenotyping of PT will not be available in the clinical routine in the near future and, amongst other non-CPAP therapy, pharmacological options to modify LG/AT/UAG lacks validation studies. This identifies the need to establish available diagnostic pathways for the identification of different phenotypes using PT. In the current review, the authors report the data independent of the scope and context of the original studies which is useful to qualitatively define the PT of the patient with OSA using standard PSG/PM recordings. The otorhinolaryngologist takes an important role in the mulit-disciplinary team treating patients with OSA by performing validation studies analyzing the relation between the clinical PSG of OSA phenotypes and different surgical procedures. The delivery of this approach will allow the patient to benefit within their clinical services from the phenotyping of their OSA and facilitate taylored therapeutical options.

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