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Patient Phenotyping in OSA

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Abstract

Purpose of Review OSA treatment paradigms are evolving from a "one treatment for all" philosophy to personalised therapeutic options based on anatomical and physiological phenotypes. Understanding these different phenotypes will become vital for clinicians as OSA testing and treatment become more targeted.

Recent Findings Phenotyping of the pharynx and upper airway is vital to inform anatomical treatment options such as surgery and mandibular advancement splints. Manipulated CPAP testing allows determination of traits such as arousal threshold, muscular responsiveness and ventilatory control. Targeted therapies of each of these physiological traits have shown promise in selected patients in the research context.

Summary Current treatment paradigms are based on anatomical therapies (CPAP, MAS, surgery); the limitations of which may be particularly evident in patients with physiological contributors to their OSA. Physiological phenotyping is an area of ongoing research into non-anatomical traits which contribute to airway obstruction.

Keywords Obstructive sleep apnoea · Phenotypes · CPAP · Surgery · Endoscopy · Upper airway · Polysomnography

Introduction

Adult obstructive sleep apnoea (OSA) is a heterogeneous disease both anatomically and physiologically. Physiological traits which contribute to the development of OSA are of research interest. Recent advancements may allow laboratory measurement of such traits, and the adoption of new techniques may lead to the delivery of targeted therapy to treat each individual's phenotypical traits [1••].

Upper airway anatomy and collapsibility is the most important contributing trait in the development of OSA. Tendency to airway collapsibility is quantified by the critical passive airway closing pressure (Pcrit). In those with low or intermediate collapsibility, non-anatomical traits appear to play a more important role in disease pathogenesis. These traits include inadequate upper airway muscular responsiveness, reduced arousal threshold to respiratory stimulus and high loop gain [2••, 3••]. Each of these "phenotypes" (Fig. 1) may be present in isolation or combination in a patient with OSA. The P4 medicine model (personalised, predictive, preventative and participatory) provides a basis for the future paradigm of OSA management [4•].

What Is Phenotyping?

Phenotyping might represent the next frontier in OSA therapy with the provision of personalised care [1••]. When discussed in this context, "phenotyping" refers to a combination of extended polysomnographic measures [5••] which allow identification of one or more treatable pathophysiological traits. Routine identification of these traits may lead to an era of personalised medicine, with targeted therapy based on previously identified pathophysiological causes ("phenotypes) in that particular patient.

Personalised endotyping and phenotyping are well established in the treatment of other upper and lower airway disorders such as COPD [6], asthma [7], chronic rhinosinusitis and allergic rhinitis [8]. In these domains, the terms

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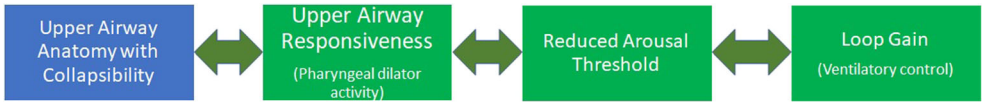

Fig. 1 4 primary phenotypic traits

"endotype" and "phenotype" are variably applied: 'An "endotype" is proposed to be a subtype of a condition defined by a distinct pathophysiological mechanism'.([7], p 356) vs "…a phenotype: 'a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression or death)". ([9], p 599).

Based on the traditional terminology, the application of laboratory techniques to identify pathophysiological causes of OSA should be labelled "endotyping" and the identification of visible resulting airway properties should be labelled "Phenotyping".

Issues with Current Paradigms of OSA Care

Current polysomnographic measures of OSA are constrained by the apnoea-hypopnea index (AHI). The AHI combines the number of apnoeas (cessations in airflow) with hypopneas (reductions in airflow) per hour. Whilst somewhat variable between laboratories, the currently accepted AHI cut-offs are defined as 0–5(no disease), 5–15 (mild), 15–30 (moderate) and > 30 (severe) [10]. This single measure is clinically used to define the presence and severity of disease; however, it has multiple major shortcomings.

Hypopneas are the more controversial component of this measure as they are variably and subjectively defined. Problems with the use of hypopnea as a measure include variable methods of detecting and quantifying flow limitation (30% vs 50%), variable definition regarding the amplitude of desaturation (3% vs 4%) and whether cortical arousals are included in the definition of an event [11]. Variations can lead to dramatic differences in reported AHI between labs, and significant variation in AHI from night to night [12]. Cardiovascular and neurocognitive complications of OSA are more closely linked to duration than frequency of hypoxemia [13] and disturbance of normal sleep architecture [14], respectively; however, AHI is used as a surrogate measure of risk of both outcomes for research and clinical purposes [15]. Clearly these concerns, amongst many others, highlight the limitations of overdependence on AHI as the main measure of OSA generated by a polysomnogram. Other data besides AHI must be incorporated to the decision-making process—oxygen desaturation index (ODI), lowest O_2 saturations (O_2 nadir), positional data and duration of respiratory events, amongst others.

Detailed upper airway examination has not previously been considered an important part of the OSA workup by most sleep physicians. Given that upper airway obstruction is the common, final pathophysiological pathway amongst all OSA endotypes, it is surprising more attention has not been paid to upper airway examination. In outdated paradigms of OSA, the sole focus is on one main treatment modality which is not anatomically selective (CPAP); therefore, comprehensive upper airway assessment has not been incorporated previously. These "one size fits all" or "trial and error" models of care were the antithesis of the P4 medicine focus on individualised therapy.

Patient Phenotyping in OSA

Irrespective of the nomenclature, the purpose of "phenotyping" and "endotyping" is the identification of pathophysiological and treatable traits which may lead to the application of a specific effective therapeutic modality based on that trait [1••].

A contemporary approach to OSA must include a detailed patient history which will inform the treating clinician about the patient's goals, expectations and potential treatment pathways. Detailed examination of the upper airway should form a routine component of contemporary OSA assessment, as this allows the identification of anatomical phenotypes which may favour or disfavour potential treatment modalities. For example, overweight and obese patients have less favourable outcomes with surgery and MAS, but those with significant intraluminal lymphoid hypertrophy and corresponding dynamically generated planes of collapse may obtain more favourable outcomes with soft tissue surgical options. Transoral and endoscopic examination of the airway form the mainstay of anatomical assessment. Cephalometric and radiological markers may also contribute to defining the anatomical phenotype, particularly in the context of craniofacial deficiencies.

Routine polysomnography does not include detailed physiological endotyping [2••, 15] as will be discussed below.

Anatomical Phenotyping

Since the advent of surgical approaches to sleep apnoea, anatomical phenotyping has played a role in advising surgical options and outcomes. Surgical outcomes have historically been less predictable than device treatment outcomes, so upper airway reconstruction is traditionally reserved as salvage

therapy. Surgical selection tools have been increasingly refined to optimise treatment outcomes, and the process of anatomical phenotyping has been gradually implemented into practice [16]. Accurate patient phenotyping may allow reconsideration of surgery as first line therapy over device use if the appropriate patient who will more likely benefit can be selected [17].

Outcomes from sleep surgery appear to be independent of markers of disease severity [18], but closely related to anatomical markers such as tonsil size and tongue grade [19]. Initial approaches to describing patients' anatomical sites of collapse in OSA were to classify them as dominantly retropalatal, retrolingual or both [20]. Early reports of UPPP in unselected patients demonstrated unreliable outcomes if the procedure was applied indiscriminately to patients with OSA [21]. As experience in surgical approaches progressed, Friedman described a transoral method of phenotyping pharyngeal and oral anatomy with the purpose of predicting success in uvulopalatopharyngoplasty (UPPP) [19]. In this original work incorporating modified Mallampati score, tonsil size and body mass index (BMI), the combined Friedman stage defined "success" in 80.6% of stage 1, 37.9% in stage 2 and 8.1% of stage 3 patients with UPPP alone (success defined as a > 50% reduction in RDI) [19]. The Friedman scoring system has since been refined [22•] to reflect subtle variations in transoral findings.

The most recognisable patient phenotype associated with OSA is that of increased body mass index. Obesity plays a significant role in disease pathogenesis: as a predisposing factor, [23] an adverse prognosticator [24] and a predictor of severity [25]. Poorer surgical outcomes are expected with increased BMI, but not necessarily observed in the literature due to exclusion of obese and morbidly obese patients from trials [26••]. Similarly, poorer oral appliance (OA) outcomes are seen with increased BMI [27] but not continuous positive airway pressure (CPAP) [28, 29].

Awake and drug-induced sleep endoscopy (DISE) techniques form the basis of the surgical anatomical assessment, allowing direct visualisation of the nasal, pharyngeal, laryngeal and subglottic airways. This permits assessment of both static intraluminal dimensions (lingual tonsil, pharyngeal tongue and palatal dimensions) and dynamic intraluminal dimensions, levels, planes and generators of collapse. Mueller's manoeuvre is an awake endoscopy technique which simulates the negative airway pressure encountered during obstructed sleep and allows the identification of contributory levels and planes of collapse [21]. Woodson's hypotonic method [30] provides further detail about airway dimensions when airflow and muscle tone are minimal, simulating the obstructed state. Combining the above techniques in the erect and supine awake positions has been found to improve OSA predictability [31].

Drug-induced sleep endoscopy (DISE) is an alternative endoscopic technique employed to assess sites and planes of upper airway obstruction. Unfortunately, DISE-directed surgical treatment has not translated to improved surgical outcomes over the awake assessment alone [32, 33]. Regardless of these concerns, DISE is employed routinely in some centres and selectively in others for upper airway assessment and has become a critical tool during workup for hypoglossal nerve stimulation (HGNS). This treatment option will be more closely examined below; however, the phenotype of concentric collapse at the level of the soft palate on DISE is a current contraindication to HGNS [34, 35].

Anatomical phenotyping of the upper airway can inform the likelihood of success of a variety of therapies. Transoral and endoscopic awake or asleep examination findings all coalesce during the surgical assessment into a variety of airway phenotypes. Woodson [36••] described a method to summarise the airway phenotype with a combination of seven luminal landmarks and one soft tissue landmark to generate patterns of upper (retropalatal) and lower (retrolingual) pharyngeal shape. Upper airway phenotypes are described by oblique (a gently sloping proximal and distal soft palate with a minimally defined genu), intermediate (partially horizontal proximal palate and partially vertical distal palate) and vertical (vertical proximal and distal palate) subtypes. Lower airway phenotypes are based on Moore's classification [37]. A (primary narrowing at pharyngeal tongue), B (primary narrowing at both proximal and distal tongue sites) and C (primary narrowing at epiglottis/distal tongue). These models of airway shape may assist selection of appropriate surgical reconstructive procedures at each site based on the anatomical phenotype.

Other anatomical features which may be readily identified and are of importance to anatomical phenotype include lingual tonsil hypertrophy [38], low-lying hyoid position [26••] and other craniofacial characteristics such as a shorter maxilla and mandible [39]. Patients with retrusive bony anatomy are more likely to have multilevel collapse and require less weight gain to achieve similar OSA severity to equivalent patients without retrusive bony anatomy [39].

Anatomical therapeutic options are well understood and include medical, surgical and device use. CPAP is the best studied and evidenced intervention; however, treatment adherence continues to be an issue and many patients remain suboptimally managed ([29, 40, 41]). Mandibular advancement splints (MAS), positional therapy and soft tissue and bony surgeries remain the salvage treatment options to remodel and reduce the collapsibility of the airway [42–44].

Physiological Endotyping

Further development of polysomnographic techniques will allow routine clinical assessment physiological traits contributing to OSA. As discussed above, multiple anatomical drivers of disease can be identified via comprehensive physical examination. The extent of anatomical contribution to upper airway

collapsibility can be quantified by measuring the passive airway critical closing pressure (Pcrit) [45]. This is defined as the applied airway pressure at which the transition between an open and collapsed passive upper airway occurs and airflow ceases [46]. In individuals without OSA, the pharynx is resistant to collapse/obstruction. Significant negative pressure must be applied to induce complete airway closure. In comparing the three groups—snorers, hypopnoeics and apnoeics—average Pcrit increases steadily as the capacity for airflow obstruction worsens [45]. As expected, there is an association between Pcrit and therapeutic CPAP pressure achieved during titration [47]. Patients with an elevated Pcrit (> + 2cmH2O) are likely to have worse disease with a highly collapsible airway, whereas those with low Pcrit (< − 2cmH2O) are likely to not have OSA at all or mild disease [3••]. In the intermediate range (− 2 to + 2cmH2O), there is significant variability in disease presence and severity, and non-anatomical factors appear to play a significant role in disease pathogenesis [3••].

Non-anatomical traits such as impaired upper airway responsiveness, reduced arousal threshold and increased loop gain (Fig. 1) have been found to contribute variably, and methods to quantify and treat each component are under increasing attention [15]. Measurement of these traits has been performed via manipulated CPAP with changes in pressure and analysis of resultant arousals, ventilatory response and neuromuscular responsiveness [5••, 48]. In patients with OSA, the prevalence of each non-anatomical trait is around 36%, with 28% demonstrating multiple non-anatomical traits [3••].

Upper Airway Muscular Responsiveness

Upper airway patency during wake and sleep is dependent upon the activity of upper airway dilators to maintain pharyngeal lumen calibre [49•]. The genioglossus muscle is the most important of these muscular dilators and selectively activates in a phasic manner during inspiration [50]. In addition, upper airway mechanoreceptors normally detect negative intraluminal pressure during obstruction and drive genioglossal activation to correct the obstruction [51]. Both central and peripheral chemoreceptors respond to hypercapnia (and to a lesser degree hypoxia) and are potent drivers of dilator muscle activity [52]. Dilator muscle activity varies significantly between sleep states, and this may partially explain increased upper airway collapsibility during REM than NREM sleep [53].

When compared to those without OSA, most individuals with OSA have been found to have equivalent or greater muscle responsiveness to negative airway pressure. This response may be inadequate to overcome the increased upper airway collapsibility [54]. A subgroup (36%) of OSA patients have been conversely found to have impaired muscle responsiveness and lack appropriate dilator responses to negative airway pressure [3••]. In manipulated CPAP testing, a controlled drop in airway pressure results in an inappropriately small increase in maximal genioglossal activity [3••]. When combined with anatomical upper airway deficiencies, this endotype is a key contributor to, and perpetuator of obstructive events [3••]. In individuals with anatomical compromise but adequate muscular responsiveness to compensate during NREM sleep, obstructive events may still occur as a result of loss of muscle tone during REM sleep [2••].

Hypoglossal nerve stimulation has the potential to address inadequacies in neuromuscular responsiveness in this subgroup of patients. This technology allows targeted stimulation of airway dilator muscles. Five-year outcomes [55] have recently been reported with improvements in sleepiness, quality of life and AHI (surgical "success" in 75% of patients). Patients with certain pharyngeal phenotypes may be better or worse candidates for hypoglossal nerve stimulation [56], and initial studies reported that patients with concentric patterns of palatal obstruction on DISE were less likely to respond [35]. Other potential therapies under investigation are myofunctional therapy/oropharyngeal muscle training and horizonal pharmacological therapies to improve dilator muscle activity.

Arousal Threshold

Obstructive events can result in cortical arousal; however, this is not essential to reverse collapse and restore upper airway patency. Obstructed breathing and negative intrathoracic pressure stimulates arousal which brings with it the drive to breathe and airway tone associated with wakefulness [57]. Evidence that arousal threshold was impaired (raised) in individuals with sleep apnoea led to the conclusion that this results in loss of protective cortical mechanisms and perpetuated obstructive events [58]. Recent data suggests that in 37% of patients, the arousal threshold is significantly lowered, and the resulting cortical arousal interferes with stable respiratory patterns [57].

Multiple mechanisms are thought to contribute to this OSA endotype. Firstly, small swings in intrathoracic pressure stimulate premature arousal and may interfere with effective dilator muscle recruitment needed to establish stable sleep [59]. Additionally, arousal from sleep is associated with increased tidal volume and this may perpetuate ventilatory control instability and periodic breathing patterns if the arterial CO_2 drops below the apnoeic threshold (see loop gain below) [57, 60]. Finally, sleep fragmentation may also prevent the progression to slow wave sleep (SWS), which is associated with greater pharyngeal dilator muscle activity and higher arousal threshold than non-slow wave NREM sleep and may allow more stable cortical and respiratory patterns [53]. This endotype appears to be of particular importance in OSA pathogenesis of non-obese patients [61].

Pharmacological agents under investigation to manage the low arousal threshold endotype are sleep promoting and hypnotics such as eszopiclone [62], zopiclone [63] and trazadone [64]. These agents increase the arousal threshold, and in the appropriate patients, these have been shown to reduce AHI by 25–50% without altering genioglossus tone [62]. In the wrong patient with OSA and a low arousal threshold, hypnotics have the potential to worsen disease indices and hypoxemia [1••]. Use of hypnotic agents in high doses, obese patients and those with severe disease has the potential to worsen polysomnographic indices and hypoxemia [57].

Loop Gain

Loop gain is a concept derived from engineering which is used to describe the "stability of a system controlled by negative feedback control loops" ([65], p1226). In respiratory applications, loop gain is quantified by the ratio between the size of a corrective ventilatory response to the size of the offending ventilatory disturbance. A high loop gain is characterised by a large magnitude corrective response compared with initiating disturbance. In this situation, small disturbances in respiration and CO_2 can result in large compensatory responses in ventilation and self-sustaining periodic oscillations. In individuals with a low loop gain, the ventilatory response to disturbance is smaller and allows decaying oscillations and a faster return to stable ventilation. In those with excessively low loop gain, sustained hypoventilation may result with maladaptive responses to hypercarbia [65].

High loop gain can contribute to obstructive sleep apnoea in multiple ways. Large compensatory swings in ventilation result in excessive inspiratory efforts and rapid negative airway pressure which can contribute to airway collapse [2••]. In the opposing phase, periods of excessively low ventilatory drive and pharyngeal dilator muscle activity may follow as a result of arousal from obstruction and hypocapnia. Excessive loss of upper airway muscle tone may result in upper airway closure and further obstruction [2••]. Thirty-six per cent of patients with OSA have inappropriately high loop gain. This endotype appears to be more prevalent in those with less anatomical deficiency (Pcrit < − 2cmH2O) than those with high Pcrit values [3••].

In patients with OSA and the high loop gain endotype, supplemental oxygen therapy has been found effective by lowering the AHI by 53% and reducing loop gain by around 50%. By contrast, in those with low loop gain, oxygen did not have a significant effect on loop gain or AHI [66]. Carbonic anhydrase inhibitors (acetazolamide) also appear to reduce loop gain in OSA patients by around 40% and overall AHI by 47%; however, the mechanisms by which this occurs are unclear [67]. Upper airway reconstructive surgery appears to be more effective in patients with low as opposed to high loop gain [68].

Future Clinical Paradigms

Future paradigms of OSA care may incorporate findings from the patient history, examination, polysomnography and physiological endotype testing [1••]. More data can be obtained from an overnight sleep study than just an imperfect marker of disease severity (the AHI). The endotypic and phenotypic traits can then be integrated (Fig. 2) to form a personalised suite of treatment options which are best suited to the patient and most likely to be of benefit (as opposed to "one size fits all" or "trial and error") [2••]. Notably, these endotypes and phenotypes may have significant overlap in any one patient and multiple arms may need to be addressed for a complete treatment response. The current reality of OSA management is, however, that physiological trait testing and implementation of targeted therapy are still horizonal and rigorous large volume trial data are not yet available [69].

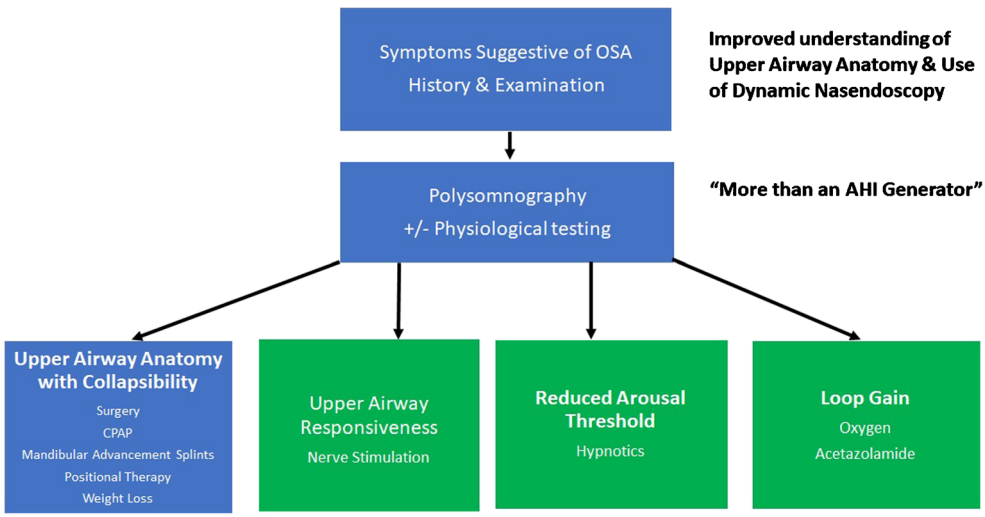

Fig. 2 Proposed future clinical paradigm

Anatomical and physiological traits can be summarised by the PALM scale (Pcrit, Arousal, Loop gain and Muscle responsiveness), proposed by Eckert et al. [3••] for the purpose of stratifying patients into treatment arms. PALM categories are generally arranged based on the anatomical contribution to OSA: PALM 1 patients have highly collapsible airway, with a Pcrit > + 2cmH2O; PALM 2 patients have a Pcrit between − 2 and + 2cmH2O; PALM 3 patients have minimally collapsible airway, with a Pcrit < − 2cmH2O. Category 2 is divided into 2a without identifiable physiological traits and 2b with identifiable physiological traits. Under this classification, PALM 1 and 2a patients would benefit from anatomical interventions such as CPAP or surgery; PALM 2b patients would likely need a combination [70] of anatomical and physiological interventions; and PALM 3 patients may benefit from one or more targeted physiological therapies depending on the traits they exhibit.

Conclusion

Investigated available anatomical treatments to date do not provide a panacea for all adults with OSA. Current clinical approaches to personalising OSA treatment are incomplete and dependent on AHI as a marker of disease severity. Anatomical and physiological phenotyping is of increasing interest and relevance to targeting disease subtypes. Clinical paradigms should include a detailed upper airway assessment. Horizonal physiological therapies such as oxygen, hypnotics and hypoglossal nerve stimulators promise to further broaden treatment options for appropriately selected patients.

Compliance with Ethical Standards

Conflict of Interest Dr. Kitipornchai and Dr. Jones declare that they have no conflict of interest. Dr. MacKay reports non-financial support from Genio-Nyxoah Hypoglossal nerve stimulator, grants from NH&MRC, grants from Garnett Passe conjoint grant, outside the submitted work.

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