Title

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Peer reviewed

ORIGINAL ARTICLE

Response to a combination of oxygen and a hypnotic as treatment for obstructive sleep apnoea is predicted by a patient's therapeutic CPAP requirement

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ABSTRACT

Background and objective: **Upper airway collapsibility predicts the response to several non-continuous positive airway pressure (CPAP) interventions for obstructive sleep apnoea (OSA). Measures of upper airway collapsibility cannot be easily performed in a clinical context; however, a patient's therapeutic CPAP requirement may serve as a surrogate measure of collapsibility. The present work aimed to compare the predictive use of CPAP level with detailed physiological measures of collapsibility.**
Methods: **Therapeutic CPAP levels and gold-standard pharyngeal collapsibility measures (passive pharyngeal critical closing pressure (P_{crit}) and ventilation at CPAP level of 0 cmH_2O ($V_{passive}$)) were retrospectively analysed from a randomized controlled trial ($n = 20$) comparing the combination of oxygen and eszopiclone (treatment) versus placebo/air control. Responders (9/20) to treatment were defined as those who exhibited a 50% reduction in apnoea/hypopnoea index (AHI) plus an AHI<15 events/h on-therapy.**
Results: **Responders to treatment had a lower therapeutic CPAP requirement compared with non-responders (6.6 (5.4–8.1) cmH_2O vs 8.9 (8.4–10.4) cmH_2O, $P = 0.007$), consistent with their reduced collapsibility (lower P_{crit}, $P = 0.017$, higher $V_{passive}$ $P = 0.025$). Therapeutic CPAP level provided the highest predictive accuracy for differentiating responders from non-responders (area under the curve (AUC) = 0.86 ± 0.9, 95% CI: 0.68–1.00, $P = 0.007$). However, both P_{crit} (AUC = 0.83 ± 0.11, 95% CI: 0.62–1.00, $P = 0.017$) and $V_{passive}$ (AUC = 0.77 ± 0.12, 95% CI: 0.53–1.00, P = 0.44)**

SUMMARY AT A GLANCE

This study compared the utility of different measures of upper airway collapsibility to predict therapeutic response to the combination of oxygen and a hypnotic for the treatment of obstructive sleep apnoea (OSA). Our findings suggest that a patient's continuous positive airway pressure (CPAP) requirement is equally predictive as other validated physiological measurements of upper airway collapsibility.

performed well, and the difference in AUC for these three metrics was not statistically different. A therapeutic CPAP level ≤8 cmH_2O provided 78% sensitivity and 82% specificity (positive predictive value = 78%, negative predictive value = 82%) for predicting a response to these therapies.
Conclusion: **Therapeutic CPAP requirement, as a surrogate measure of pharyngeal collapsibility, predicts the response to non-anatomical therapy (oxygen and eszopiclone) for OSA.**

INTRODUCTION

Patients with obstructive sleep apnoea (OSA) have an upper airway that is more collapsible compared with snorers and non-snoring controls.[1] However, even in patients with OSA the degree of upper airway collapsibility can vary markedly between afflicted individuals.[2,3] Importantly, patients with mild collapsibility are more likely to demonstrate a therapeutic response to non-continuous positive airway pressure (CPAP) interventions for OSA, such as weight loss,[4] oral appliance therapy,[5] as well as supplemental oxygen, hypnotics or a combination of both.[6] These findings suggest that physiological measurements of upper airway collapsibility may be useful tools for predicting therapeutic response. However, collapsibility measurements such as the passive pharyngeal critical closing pressure (P_{crit})[7] require specialised equipment which hampers its clinical utility. Simpler surrogate measures of collapsibility are required in order for this information to be accessible in clinical practice.

One such potentially feasible measure of upper airway collapsibility is a patient's therapeutic CPAP requirement, that is, the minimum CPAP level required to alleviate respiratory events and inspiratory flow limitation. Previously, Gold and Schwartz[8] have elaborated on the theoretical association between a patient's therapeutic CPAP requirement and their underlying P_{crit}. More recently, we have empirically confirmed the strong positive relationship between these variables, and in particular the accuracy of CPAP level to identify patients with mild upper airway collapsibility.[9] In addition, a lower therapeutic CPAP requirement is associated with a stronger response to oral appliance therapy.[10,11]

We sought to determine the utility of therapeutic CPAP requirement in predicting OSA responses to another alternative therapy for OSA. We retrospectively analysed data from our recent clinical trial that assessed the combined therapeutic effect of supplemental oxygen and eszopiclone on OSA severity.[6] We hypothesized: (i) a lower therapeutic CPAP level predicts response to this therapy and (ii) that this measure has similar utility for predicting responders to therapy compared with gold-standard laboratory assessment of upper airway collapsibility.

METHODS

Participants

We retrospectively analysed data from the 20 subjects who participated in our previously reported trial investigating the efficacy of combination therapy (3 mg of eszopiclone and 40% oxygen) for the treatment of OSA.[6] Participants represented an 'unselected' population of patients diagnosed with OSA (defined as an apnoea/hypopnoea index (AHI) >10 events/h) who were recruited from the Brigham and Women's Hospital's sleep clinics and from the general community. Exclusion criteria included any sleep disorder other than OSA (periodic leg movement and/or restless leg syndromes, narcolepsy, insomnia and central sleep apnoea/Cheyne–Stokes respiration) or any history of renal failure, neuromuscular disease, neurological disorders, thyroid disease, heart failure, uncontrolled hypertension, diabetes or any other instability in medical status. Written informed consent was obtained before participation in the study, which was approved by the Partners' Human Research Committee. The original study was registered with clinicaltrials.gov (NCT01633827).

Experimental design

Complete details of the experimental design and procedures have been reported previously.[6] Briefly, a single-blinded placebo-controlled cross-over design was employed to test the effect of the combination of eszopiclone (3 mg tablet taken orally prior to bedtime on the study night) and supplemental oxygen (delivered by Venturi mask at FIO_2 (fraction of inspired oxygen) = 0.4), versus placebo combined with room-air control. In a randomized order, participants were administered treatment (or placebo/sham) for two consecutive nights while they completed overnight polysomnographic studies (PSGs). One study was a routine clinical PSG to measure OSA severity, and the other was a physiological research study to assess the pathophysiology responsible for OSA (research PSG). The clinical and research PSGs were separated by at least 2 days. The order of treatment or placebo condition was randomized, and a 1-week washout period was mandated before participants crossed over to the opposing treatment/placebo condition.

Measurements

During the clinical PSG, a standard clinical montage was employed including electroencephalogram (EEG), electrooculogram (EOG), submentalis and anterior tibialis electromyogram (EMG), ECG, nasal pressure and thermistor, respiratory effort (piezoelectric bands placed around the chest and abdomen), body position and fingertip oximetry. End-tidal O_2 and CO_2 were recorded from a catheter placed inside the nostril. Sleep staging, cortical arousal and respiratory events were scored according to standard clinical criteria[12] by a single experienced sleep technician blinded to treatment condition.

During the research PSG, in addition to the standard clinical montage described above, patients were fitted with a sealed nasal mask attached to a pneumotachometer (model 3700A; Hans-Rudolph, Kansas City, MO, USA). Ports fitted to the mask allowed the measurement of mask pressure (Validyne, Northridge, CA, USA).

A continuous positive/negative pressure source (Pcrit 3000; Philips Respironics, Murrysville, PA, USA) was connected to the nasal mask while participants slept. During the research PSG, a CPAP titration was performed in order to determine each patient's therapeutic CPAP requirement (defined as the minimum CPAP level sufficient to abolish respiratory events and inspiratory flow limitation). From this CPAP level, a series of positive and negative mask pressure

manipulations were performed during stable supine NREM sleep (stages N2 and N3) in order to measure upper airway physiology. During this procedure, the passive collapsibility of the upper airway was measured by two previously published methods.

Ventilation at CPAP level of 0 cmH₂O ($V_{passive}$)

While the patient slept on their therapeutic CPAP, mask pressure was rapidly reduced to atmospheric pressure (0 cmH_2O) for five breaths. The ventilation on breaths 3–5 was measured and expressed as a percentage of the patient's eupnoeic (or resting) ventilation on therapeutic CPAP.

Passive pharyngeal critical closing pressure (P_{crit})

While the patient was sleeping on their therapeutic CPAP level, a series of stepwise reductions to subtherapeutic CPAP levels were performed (each for five breaths) until apnoea occurred. Peak flows from breaths 3–5 of each drop demonstrating flow limited morphology were plotted (y-axis) against mask pressures (x-axis). P_{crit} was determined as the x-intercept using linear regression (zero flow crossing).

Definition of responders to therapy

Responders to therapy were defined by 50% reduction in AHI and an AHI on-therapy below 15 events/h, as used in the original study.[5] Patients were otherwise considered non-responders.

Statistical analysis

Therapeutic CPAP requirement and collapsibility measures (P_{crit} and $V_{passive}$) collected during the placebo arm were used as 'baseline measurements' and were compared between responder and non-responder groups using unpaired Student's t-tests and Mann–Whitney U-tests wherever appropriate. Receiver operating characteristic (ROC) curve analyses were performed on each variable to determine the predictive value of therapeutic CPAP and measures of collapsibility (as measured by area under the curve (AUC)) and to determine useful threshold values defined by sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). AUCs from each of the three collapsibility measures were compared using U-statistics according to Delong's method.[13]

RESULTS

Of the 20 participants who completed the trial, 9 were determined to be responders. As previously reported,[6] there were no significant differences in age, sex or BMI between groups; however, responders had a significantly lower AHI at baseline (i.e. on placebo/sham; Table 1).

Table 2 shows the upper airway collapsibility characteristics of responders compared with non-responders. As reported in the original study, responders had lower/more negative P_{crit} (U = 15.0, P = 0.017, r = 0.55) and had a significantly higher $V_{passive}$ (t(9) = –2.71, P = 0.025, r = 0.54). Importantly, responders also had a lower therapeutic CPAP requirement compared with non-responders (U = 14.0, P = 0.007, r = 0.60; Fig. 1A).

ROC curves were generated for each of the collapsibility measures to predict responder status. P_{crit} demonstrated 'good' accuracy for predicting therapeutic response (AUC = 0.83 ± 0.11, 95% CI: 0.62–1.00, P = 0.017), whereas $V_{passive}$ was associated with 'fair' predictive accuracy (AUC = 0.77 ± 0.12, 95% CI: 0.53–1.00, P = 0.44). Therapeutic CPAP level demonstrated the highest predictive accuracy (AUC = 0.86 ± 0.9, 95% CI: 0.68–1.00, P = 0.007) with a therapeutic CPAP level of ≤8 cmH_2O being 78% sensitive and 82% specific for predicting the response to combination therapy (Fig. 1B). PPV was 78% indicating that CPAP levels ≤8 cmH_2O correctly predicted the response to combination therapy in 78% of individuals. NPV was 82% indicating that CPAP levels >8 cmH_2O correctly predicted the non-response to combination therapy in 82% of individuals. Multiple cut-off values and the corresponding sensitivity, specificity, PPV and NPV statistics for each are presented in Table 3.

When AUCs for each of the upper airway collapsibility measures were statistically compared, no significant differences were found between therapeutic CPAP level and P_{crit} (Z = 0.26, P = 0.80) or between CPAP and $V_{passive}$ (Z = 1.0, P = 0.32). Nor were there any difference between P_{crit} and $V_{passive}$ (Z = 1.47, P = 0.14), suggesting that each measure demonstrated similar predictive accuracy for determining therapeutic response. Of note, significant correlations were found between each of the collapsibility measures. Therapeutic CPAP level was positively associated with P_{crit} (r = 0.71, P < 0.001) and negatively associated with $V_{passive}$ (r = –0.60, P = 0.005). P_{crit} and $V_{passive}$ were negatively associated (r = 0.79, P < 0.001).

DISCUSSION

The present work represents a retrospective analysis of our recent randomized controlled trial (RCT) in which we discovered that the combination of oxygen and eszopiclone is particularly effective in OSA patients with mild collapsibility. Our current analysis found that a lower therapeutic CPAP requirement, as a surrogate of milder collapsibility, predicted a stronger response

Table 1 Demographic characteristics

Characteristics	Responders (*n* = 9)	Non-responders (*n* = 11)	*P*-value
Age (years)	52.6 ± 4.7	49.5 ± 3.1	0.583
BMI (kg/m²)	28.8 ± 1.8	33.9 ± 1.7	0.056
Sex (females)	2	6	0.142
AHI (events/h)	30.9 ± 3.6	64.5 ± 8.5	0.004

Data shown are mean ± SE of the mean (except for sex data). Group differences are assessed by independent samples t-test and Pearson's chi-square tests as appropriate.

AHI, apnoea/hypopnoea index; SE, standard error.

Table 2 Measures of collapsibility compared between responders and non-responders

Measure of upper airway collapsibility	Responders ($n = 9$)	Non-responders ($n = 11$)	P-value
Therapeutic CPAP (cmH$_2$O) (median)	6.6 (5.4 to 8.1)	8.9 (8.4 to 10.4)	0.007
P$_{crit}$ (cmH$_2$O) (median)	−1.9 (−3.9 to −0.1)	0.64 (−0.4 to −1.7)	0.017
V$_{passive}$ (%V$_{eupnoea}$)	37.4 ± 11.2	6.3 ± 2.2	0.025

Data shown are mean ± SE of the mean, or when non-normally distributed: median (lower–upper quartiles). Group differences are assessed by independent samples t-test and Mann–Whitney U-tests as appropriate.
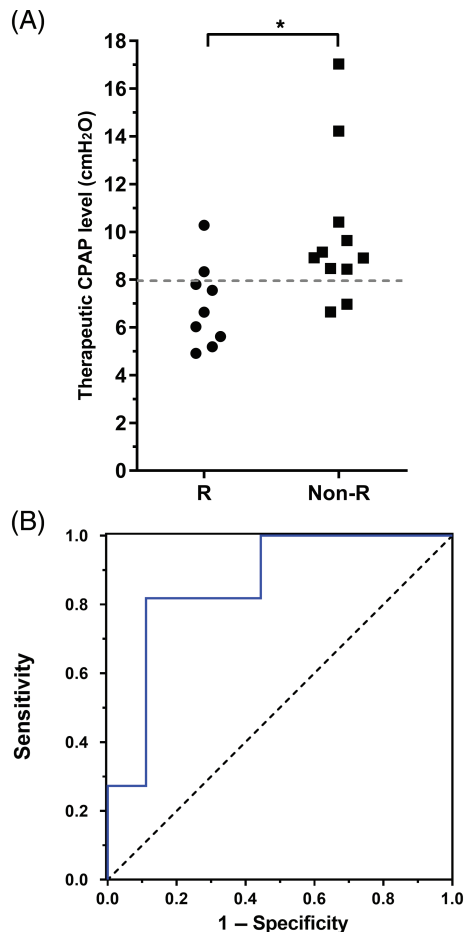
%V$_{eupnoea}$, percentage of the patients' eupnoeic ventilatory requirement; CPAP, continuous positive airway pressure; P$_{crit}$, passive pharyngeal critical closing pressure; SE, standard error; V$_{passive}$, ventilation at CPAP level of 0 cmH$_2$O.

to this therapeutic intervention. Importantly, an individual's therapeutic CPAP level was equally predictive of treatment response as the gold-standard physiological measurements of upper airway collapsibility, namely P$_{crit}$ and V$_{passive}$.[14] The key implication of this finding is

Figure 1 Therapeutic continuous positive airway pressure (CPAP) levels are lower and predict response to the combination of oxygen and a hypnotic. (A) Individual therapeutic CPAP values for both groups. Responders (R, circles) had significantly lower CPAP requirements compared with non-responders (Non-R, squares). (B) Receiver operating characteristic (ROC) curve indicates therapeutic CPAP level had 'good' predictive accuracy for determining responder status (AUC (area under the curve) = 0.86 ± 9, 95% confidence interval (CI): 0.68–1.00, $P = 0.007$). *$P < 0.01$.

that phenotypic information relevant to the likelihood of treatment response can be determined from routine clinical information, without requiring specialized laboratory assessments.

Our previous work has demonstrated that therapeutic CPAP levels and P$_{crit}$ share a strong positive association.[9] This finding is not unexpected given that these two measures are driven by and derived from the same upper airway pressure/flow dynamics.[8] The present data build on these findings by showing that therapeutic CPAP requirements also predict treatment responses in a similar fashion to other collapsibility measures. Taken together, these data further support the contention that a patient's therapeutic CPAP requirement is a useful measure of upper airway collapsibility.

CPAP levels have been shown to have utility in predicting the response to oral appliances in both Japanese[11] and Australian[10] populations. These studies found that responders typically had lower CPAP level requirements, and that patients with high CPAP requirements were unlikely to respond to oral appliance therapy. In the Japanese cohort, a CPAP level of 10.5 cmH$_2$O provided the most optimal cut-off value. By contrast, in the Australian study, while 10.5 cmH$_2$O provided strong PPV, its ability to predict correctly non-response based on therapeutic pressures higher than 10.5 cmH$_2$O (i.e. NPV) was relatively poor, with a higher threshold of 13 cmH$_2$O providing the most optimal cut-off value for in this predominantly Caucasian sample. In the present data, when predicting the response to a non-anatomically oriented combination therapy (oxygen and eszopiclone) lower pressures (between 6 and 10 cmH$_2$O) were found to be the most predictive, with CPAP levels ≤6 cmH$_2$O providing 100% likelihood of response (i.e. PPV = 100%) and 8 cmH$_2$O providing the best balance of PPV and NPV. We believe that this disparity in predictive CPAP ranges may represent a difference in OSA phenotypes most likely to respond to these interventions. Specifically, the lower therapeutic CPAP requirement in the current sample likely indicates that patients with mild collapsibility (CPAP levels of 8 cmH$_2$O of below, or particularly those with negative P$_{crit}$ levels) are the most effective target for interventions that address only non-anatomical causes of OSA. By contrast, oral appliances tend to have success across a wider span of collapsibility, including those with moderate collapsibility (up to pressures of 13 cmH$_2$O and overlapping into low/positive P$_{crit}$ values).

Table 3 Comparison of three measures of upper airway collapsibility for predicting combination therapy response

Cut-off:	Therapeutic CPAP (cmH$_2$O) Less than or equal to				P$_{crit}$ (cmH$_2$O) Less than or equal to			V$_{passive}$ (%V$_{eupnoea}$) Greater than		
	6.0	8.0	10.0	10.5	−2.0	−1.0	0.0	30%	10%	0%
Sensitivity	33	78	89	100	50	63	75	56	67	78
Specificity	100	82	27	18	100	91	55	100	73	36
PPV	100	78	50	50	100	83	55	100	67	50
NPV	65	82	75	100	73	77	75	73	76	67

CPAP level cut-off value of 10.5 cmH$_2$O was included to allow comparison to previous work using CPAP to predict oral appliance response.[10,11]

%V$_{eupnoea}$, percentage of the patients' eupnoeic ventilatory requirement; CPAP, continuous positive airway pressure; NPV, negative predictive value; P$_{crit}$, passive pharyngeal critical closing pressure; PPV, positive predictive value; V$_{passive}$, ventilation at CPAP level of 0 cmH$_2$O.

It should be noted that each of the collapsibility measures we investigated (therapeutic CPAP, P$_{crit}$ and V$_{passive}$) provided 'good' to 'fair' (AUC ~ 0.77–0.86) accuracy in predicting whether a patient will respond to this combination of interventions. Some of this variability may be driven by inter-individual differences in the physiological responses (i.e. the degree to which loop gain and arousal threshold are altered by these agents) that may not be predictable from baseline traits alone. In addition, these findings may suggest that although milder upper airway collapsibility is an important determinant of whether a patient responds to these therapies, collapsibility is not the only important factor. It is possible that novel approaches to assess other traits causing OSA using PSG (loop gain,[15] arousal threshold[16] and muscle responsiveness) may provide further predictive value. Indeed, in the future, data from a range of predictive indexes may be drawn together to provide an overall indication of a patient's OSA phenotype. Clinicians may then be able to use such classifications to determine the most appropriate therapeutic intervention.

A key limitation of this work is the relatively small sample size and the retrospective nature of our analysis. Despite this acknowledgement, our findings are consistent with two other studies that have investigated the accuracy of therapeutic CPAP levels to predict response to oral appliance therapy. In the present data, we found all three of the collapsibility measures (therapeutic CPAP, P$_{crit}$ and V$_{passive}$) were predictive of treatment response; however, we found no significant difference in AUC between these variables. It is possible given the sample size that this analysis may have been underpowered to detect small differences in AUCs for various collapsibility measures. In the future, large-scale prospective trials are needed specifically targeted at predicting which patients are likely to respond to non-anatomical treatment options for OSA. It is also important to note that our proof of concept RCT examined improvements in OSA severity (i.e. AHI) and pathophysiology following a single night administration of oxygen and eszopiclone. Further trials are needed in order to assess treatment efficacy, adherence and safety profile over a longer period of use, as well as to examine potential improvements in symptomatology, quality of life and cardiovascular outcomes.

Currently, CPAP is the gold-standard treatment for OSA, and given that it is highly efficacious at controlling upper airway collapse, reducing the hypoxic burden and improving sleep quality[17,18]; for the foreseeable future it is likely to remain the first-line treatment for OSA. However, our findings suggest that clinicians may be able to use information about a patient's therapeutic CPAP requirement, potentially determined from an initial trial of CPAP, to support future clinical decision-making about the likelihood of responses to alternative interventions for OSA such as supplemental oxygen and/or hypnotics.

Disclosure Statement

S.A.S. serves as a consultant for Cambridge Sound Management. As an Officer of the American Thoracic Society, A.M. has relinquished all outside personal income since 2012. ResMed, Inc. provided a philanthropic donation to the UC San Diego in support of a sleep centre. D.P.W. was the Chief Medical Officer for Philips Respironics until 31 December 2012 but is now a consultant. He is also the Chief Scientific Officer for Apnicure Inc. as of January 2013 and a consultant for Night Balance since 2014. G.S.H. and S.A.J. have received equipment to support research from ResMed, Philips Respironics and Air Liquide Healthcare.

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