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RESEARCH ARTICLE

CPAP combined with oral appliance therapy reduces CPAP requirements and pharyngeal pressure swings in obstructive sleep apnea

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Tong BK, Tran C, Ricciardiello A, Donegan M, Chiang AKI, Szollosi I, Amatoury J, Carberry JC, Eckert DJ. CPAP combined with oral appliance therapy reduces CPAP requirements and pharyngeal pressure swings in obstructive sleep apnea. *J Appl Physiol* 129: 1085–1091, 2020. First published September 10, 2020; doi:10.1152/japplphysiol.00393.2020.—Oral appliance (OA) therapy is the leading alternative to continuous positive airway pressure (CPAP) for obstructive sleep apnea (OSA). It is well tolerated compared with CPAP. However, ≥50% of patients using OA therapy have incomplete resolution of their OSA. Combination therapy with CPAP and oral appliance (CPAP + OA) is a potential alternative for incomplete responders to OA therapy. This study aimed to determine the extent to which combination therapy reduces therapeutic CPAP requirements using gold-standard physiological methodology in those who have an incomplete response to OA therapy alone. Sixteen incomplete responders [residual apnea/hypopnea index (AHI) > 10 events/h] to a novel OA with a built-in oral airway were recruited (3 women:13 men, aged 31–65 yr, body mass index: 22–38 kg/m^2, residual AHI range: 13–63 events/h). Participants were fitted with a nasal mask, pneumotachograph, epiglottic pressure catheter, and standard polysomnography equipment. CPAP titrations were performed during non-rapid eye movement (NREM) supine sleep in each participant during three conditions (order randomized): CPAP only, CPAP + OA (oral airway open), and CPAP + OA (oral airway closed). OSA was resolved at pressures of 4 ± 2 and 5 ± 2 cmH_2O during CPAP + OA (oral airway open) and CPAP + OA (oral airway closed) conditions versus 8 ± 2 cmH_2O during CPAP only ($P < 0.01$). Negative epiglottic pressure swings in oral airway open and closed conditions were normalized to CPAP only levels [−2.5(−3.7, −2.6) vs. −2.3(−3.2, −2.4) vs. −2.1(−2.7, −2.3) cmH_2O]. Combined CPAP and OA therapy reduces therapeutic CPAP requirements by 35%–45% and minimizes epiglottic pressure swings. This combination may be a therapeutic alternative for patients with incomplete responses to OA therapy alone and those who cannot tolerate high CPAP levels.

NEW & NOTEWORTHY Combined CPAP and oral appliance therapy has been suggested as an alternative for incomplete responders to oral appliance therapy. We used a novel oral appliance incorporating an oral airway together with CPAP to show that pharyngeal pressure swings were normalized at reduced CPAP levels. Our findings demonstrate that using CPAP and oral appliance together may be a beneficial alternative for incomplete responders to oral appliance therapy and intolerant CPAP users due to high-pressure requirements.

non-CPAP therapies; sleep-disordered breathing; upper airway

INTRODUCTION

Continuous positive airway pressure (CPAP) is the recommended first-line therapy for obstructive sleep apnea (OSA) (19). It is highly efficacious in reducing OSA severity in most people with OSA (29). Additional benefits of CPAP may include reductions in blood pressure (4), subjective daytime sleepiness (5), and improved cognitive function (13, 14). However, these health benefits are often limited by poor adherence to CPAP therapy. Approximately 30% of patients, who are prescribed CPAP, are not adherent to treatment after 1 mo of therapy (26). A further 15% abandon treatment within 10 mo (37). Common reasons for poor CPAP adherence include physical complaints (i.e., mouth dryness, nasal obstruction) (15, 25), mask-related discomfort (15, 25, 37), pressure intolerance (15), dislike of equipment (15, 37), and preference for other treatment options (37). Indeed, individuals who use their CPAP less than 4 h/night are effectively undertreated and have some degree of residual OSA as estimated by the Sleep Adjusted Residual AHI (SARAH index) (30). Given the substantial portion of patients who fail CPAP therapy, strategies to improve treatment effectiveness and development of alternative therapeutic approaches are required.

Oral appliance therapy is recommended for mild-to-moderate OSA and as second-line therapy for those who are intolerant to CPAP (27). Oral appliances are well tolerated with adherence rates of ∼80% at 3 mo (36) and after 1 yr of treatment (11). OSA severity reduces by ∼50% on average with oral appliance therapy (23). However, successful treatment outcome [apnea/hypopnea index (AHI) <5 events/h] varies between patients, ultimately influencing treatment effectiveness. Indeed, at least 50% have some degree of residual OSA on therapy (32). Prediction of treatment success with oral appliance therapy is difficult and current prediction methods are inadequate (31).

Alternative treatment options are urgently needed for patients with OSA, who are CPAP intolerant and incomplete responders to oral appliance therapy. Combination therapy with CPAP plus an oral appliance (CPAP + OA) has been suggested as a viable alternative for these patients (10, 22, 35). Recent studies have demonstrated that CPAP requirements needed to resolve OSA are lower with CPAP + OA therapy compared with CPAP alone (12, 21). Additionally, compliance and comfort with CPAP + OA therapy may also be superior compared with CPAP therapy alone (8).

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However, previous studies that have assessed CPAP + OA therapy on these outcomes have used standard polysomnographic measures. This includes surrogate measures of airflow via a pressure transducer, which is typically highly filtered and respiratory effort via abdominal and thoracic bands from commercially available diagnostic software. Standard CPAP titration methods to identify the therapeutic CPAP level rely on visual identification of respiratory events or autotitration from these signals. However, subjective assessments that rely on imprecise and often over-filtered signals can easily lead to under titration (i.e., missing mild-moderate airflow limitation) or over titration (i.e., difficult to precisely identify the point where airflow limitation first subsides). Thus, gold-standard physiological techniques such as pneumotachograph-derived airflow and respiratory effort from an airway catheter downstream from the site of pharyngeal narrowing/collapse combined with an objective quantification approach are required to accurately determine the mechanistic effect of CPAP + OA therapy on the upper airway and the precise reductions in CPAP requirements that combination therapy can yield.

A recent pilot study found that a novel oral appliance with a built-in oral airway (Fig. 1*A*) was able to reduce pharyngeal pressure swings during sleep and CPAP requirements when used in combination with CPAP (1). However, the patient population in this preliminary investigation was small (n = 4), and the efficacy of the oral appliance therapy alone in these participants was not known. Therefore, this study aimed to compare pharyngeal pressure swings and therapeutic CPAP requirements in CPAP + OA therapy versus CPAP only via objective physiologically derived measures in the clinically relevant group of incomplete responders to oral appliance therapy.

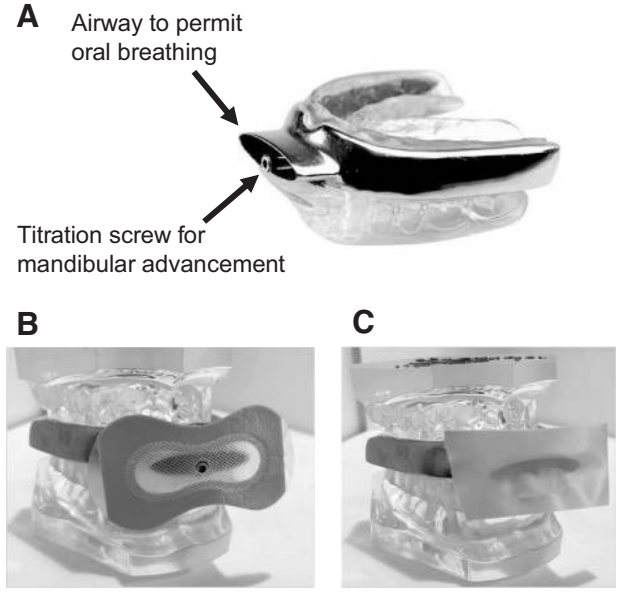

Fig. 1. *A*: picture of the two-piece titratable oral appliance (OA) that was used in the study. It incorporates a hollow enclosure, which enables air to flow directly from the mouth to the pharyngeal airway. *B*: picture of the one-way valve that was used to seal the oral airway to allow oral breathing but minimize continuous positive airway pressure (CPAP) leak via the oral airway during the CPAP + OA (open) condition. *C*: picture of the nonporous adhesive tape that was used to completely seal the oral airway for the CPAP + OA (closed) condition.

MATERIALS AND METHODS

Clinical Trials

The trial protocol "Targeted combination therapy with Mandibular Advancement Device (MAD) and Continuous Positive Airway Pressure (CPAP) : Physiological mechanistic studies to inform treatment for obstructive sleep apnoea (OSA)" was pre-registered on the Australian New Zealand Clinical Trials Registry and the Registration No. is ACTRN126 17000492358 (Part B) (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=372279).

Participants

Sixteen incomplete responders to oral appliance therapy alone (residual AHI >10 events/h) were recruited for this sub-study from a larger clinical study (Fig. 2) that investigated the efficacy of a novel oral appliance device (O_2Vent T, Oventus Medical, Indooroopilly, QLD, Australia, Fig. 1*A*) on OSA. Findings from the larger clinical study (Registration No. ACTRN12617000492358, Part A) were recently reported (33). The current protocol was preregistered on the Australian New Zealand Clinical Trials Registry (Registration No. ACTRN12617000492358, Part B). Some of the study participants also completed an oral appliance plus expiratory positive airway pressure valve combination therapy study on a separate occasion (Registration No. ACTRN12617000492358, Part C) (20).

Participants were otherwise healthy with documented OSA, were untreated or CPAP intolerant, and were recommended oral appliance therapy by their treating sleep physician. Exclusion criteria included contraindications for oral appliance therapy by the study dentist (e.g., periodontal disease, insufficient teeth for device retention, or a strong gag reflex), central sleep apnea (>5 events/h), intellectual or mental impairment, pregnant or nursing mothers, or medications known to affect sleep or breathing. Written informed consent was obtained from the participants before enrolment. The study was approved by the South Eastern Sydney Local Health District Human Research Ethics Committee (HREC No. 16/356).

Participant Setup and Equipment

Overnight polysomnography. The participants were fitted with electroencephalograms (F3, F4, C3, C4, O1, and O2 referenced to A1–A2), electrooculograms, surface submental electromyograms, and finger pulse oximetry for overnight polysomnography.

Physiological measurements. A modified non-vented nasal mask (ComfortGel, Philips Respironics, Murrysville, PA) was attached to a pneumotachograph (Series 3700A, Hans Rudolph, KS), and differential pressure transducers (DP45, Validyne, Northridge, CA) were used for measurement of airflow and mask pressure. A pressure transducer-tipped catheter (MPR-500, Millar, Houston, TX) was inserted via the most patent anesthetized nostril (Co-Phenylcaine Forte spray, ENT Technologies Pty. Ltd. Hawthorn, VIC, Australia) 1–2 cm below the base of the tongue for epiglottic pressure (Pepi) measurement.

Oral appliance. The participants were fitted with an O2Vent T oral appliance (Oventus Medical, Indooroopilly, QLD, Australia, Fig. 1*A*), followed by an 8- to 12-wk acclimatization period. The magnitude of mandibular advancement was kept consistent with at least 75% of maximum mandibular advancement similar to our previous study (33).

CPAP titrations. CPAP from a positive pressure device (Pcrit 3000, Philips Respironics, Murrysville, PA) was delivered through standard CPAP tubing to the modified non-vented nasal mask with a whisper swivel expiratory valve (Philips Respironics, Murrysville, PA) in series.

CPAP titrations during the CPAP + OA combination conditions were conducted with the oral appliance in place. In the CPAP + OA (open) condition, the oral airway in the device was sealed with a one-way valve (Theravent, Foundation Consumer Healthcare LLC, Pittsburgh, PA) in the CPAP + OA (open) condition, to facilitate oral inspiration, if required, and prevent CPAP leakage (Fig. 1*B*).

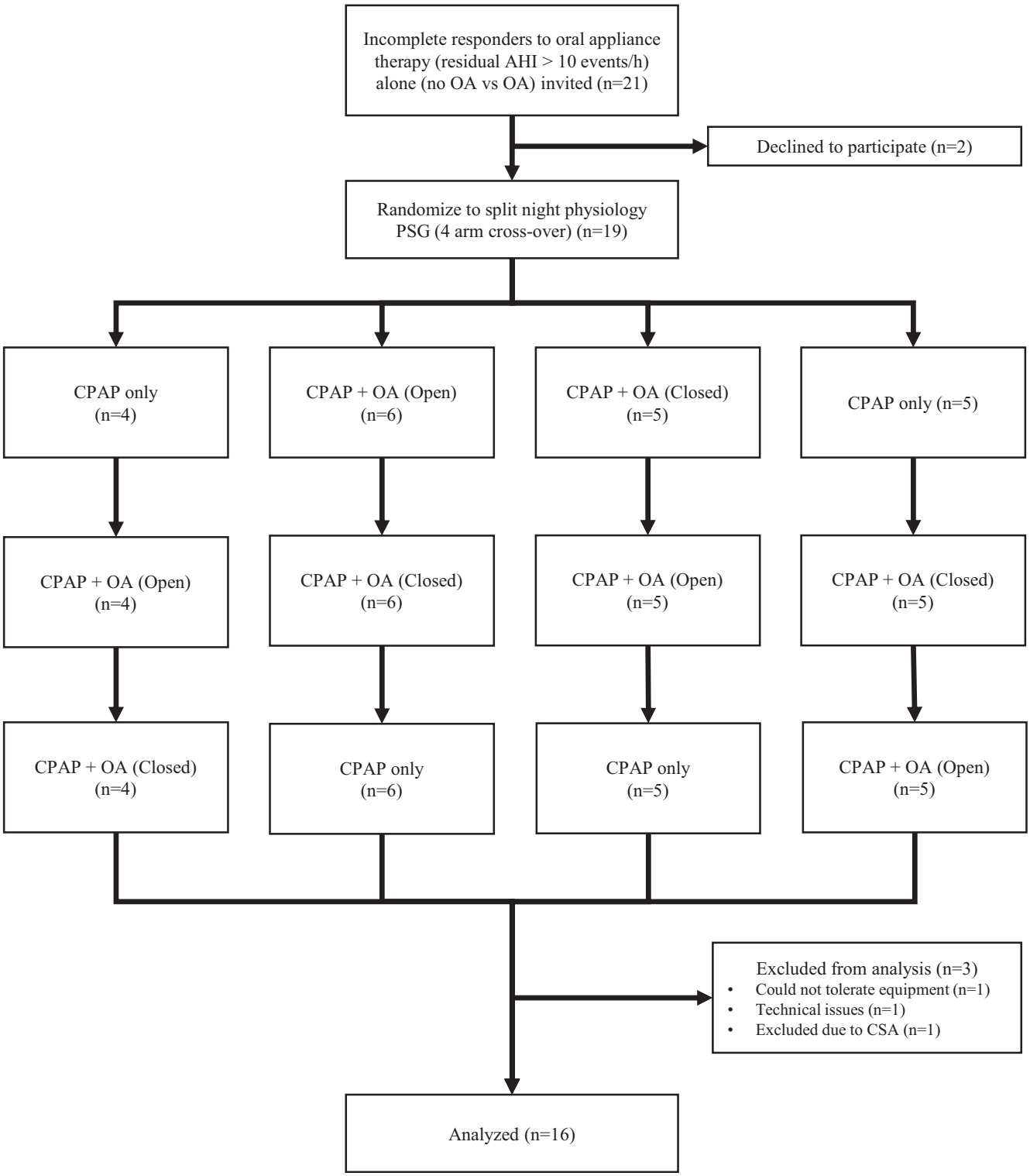

Fig. 2. CONSORT diagram detailing the participant recruitment and flow through the study. Incomplete responders (n = 21) to oral appliance therapy were invited to participate, and 2 participants declined to participate. A total of 19 participants were recruited and randomized to split night physiology PSG (4 arm crossover). Three participants were excluded from the final analysis due to technical issues, equipment discomfort and intolerance, and presence of central sleep apnea during the study. Thus, a total of 16 participants were included in the final analysis. AHI, apnea hypopnea index; CPAP, continuous positive airway pressure; CSA, central sleep apnea; OA, oral appliance; PSG, polysomnography.

Nonporous adhesive tape (Hy-Tape, Hy-Tape International, Patterson, NY) was applied over the oral airway of the device in the CPAP + OA (closed) condition, to promote nasal breathing only (Fig. 1*C*).

Protocol

Initially, at least 5 min of quiet nasal breathing data were collected while awake in the supine position without OA or CPAP. Pepi swings and CPAP requirements were then measured throughout an overnight sleep study during the following three study conditions in all the participants in random order: CPAP only, CPAP plus oral appliance with the oral airway open [CPAP + OA (open), Figs. 1*B*], and CPAP plus oral appliance with the oral airway closed [CPAP + OA (closed), Fig. 1*C*]. Randomization order of the study conditions was conducted by an external study clinical trials monitor. The setup of each study condition was conducted by a research assistant to blind the investigator to the intervention assignment during data collection. A summary of the patient flow through the study protocol is detailed in Fig. 2.

During the split-night polysomnography, the participants were instructed to sleep in a supine position. CPAP titrations were conducted throughout the night during NREM sleep (N2 and N3) in each condition. CPAP was initiated at 1 cmH_2O and incrementally increased at 0.5–1 cmH_2O increments as required. Each pressure level was assessed for at least 2 min before the next CPAP increase. Increments in CPAP were delivered until at least 3 cmH_2O above the level in which sleep-disordered breathing/snoring/airflow limitation was abolished, based on the airflow/Pepi relationship where airflow limitation equals no increase in inspiratory flow despite $\geq$1 cmH_2O increase in Pepi (Fig. 3). Sleep and breathing data at the established therapeutic CPAP level were then recorded for at least 15 min before changing over to the next condition.

Data Acquisition and Analysis

Data were collected using a 16-bit analog-to-digital converter (Power 1401, Cambridge Electronic Design Limited, Cambridge, UK) and data acquisition software (Spike2, version 7.20, Cambridge Electronic Design Limited, Cambridge, UK).

Data analysis was performed on a breath-by-breath basis using validated, custom-designed, and semi-automated software (24). Minimal therapeutic CPAP requirements for each participant were objectively quantified based on a plot of the mean Pepi swings versus CPAP level within each condition (at least 20 stable breaths were analyzed per condition). Specifically, minimal therapeutic CPAP requirements were defined as the CPAP level at which Pepi first stabilized (Fig. 3) and where the Pepi swings were within one standard deviation or less than the average wakefulness levels. Data analysis was performed blinded to the intervention conditions.

Statistical Analysis

Data normality was assessed using a Shapiro–Wilk test. Therapeutic CPAP requirements, Pepi swings, and proportion of N2 and N3 sleep between conditions were compared using a one-way repeated-measures ANOVA (Sigma Plot, version 11). Pairwise comparisons were conducted using the Student–Newman–Keuls method. Friedman repeated-measures ANOVA on ranks was conducted for non-normally distributed data. Data are reported as means ± SD or median with interquartile ranges for non-normally distributed data.

RESULTS

Participant Characteristics

In total, 21 incomplete responders to oral appliance therapy alone were invited to participate in the current combination therapy study. Of the 21 participants, 19 consented and were randomized, and three were excluded from the analysis [1 could not tolerate the equipment setup, and 1 had central sleep apnea (>5 events/h), and 1 due to technical issues in data collection]. Thus, data were analyzed in 16 participants across all conditions (Fig. 2). The characteristics of these participants are detailed in Table 1.

Effect of Combination Therapy (CPAP + OA) on Therapeutic CPAP Requirements

The effect of combination therapy (CPAP + OA) on minimal therapeutic CPAP requirements is summarized in Fig. 4. Therapeutic CPAP levels were reduced with CPAP + OA compared with CPAP only. CPAP requirements were reduced by 43 ± 27% in the CPAP + OA (open) condition ($P < 0.001$), and 33 ± 31% in the CPAP + OA (closed) condition ($P < 0.001$). There was no difference in the CPAP requirements between the CPAP + OA (open) and CPAP + OA (closed) conditions ($P = 0.386$).

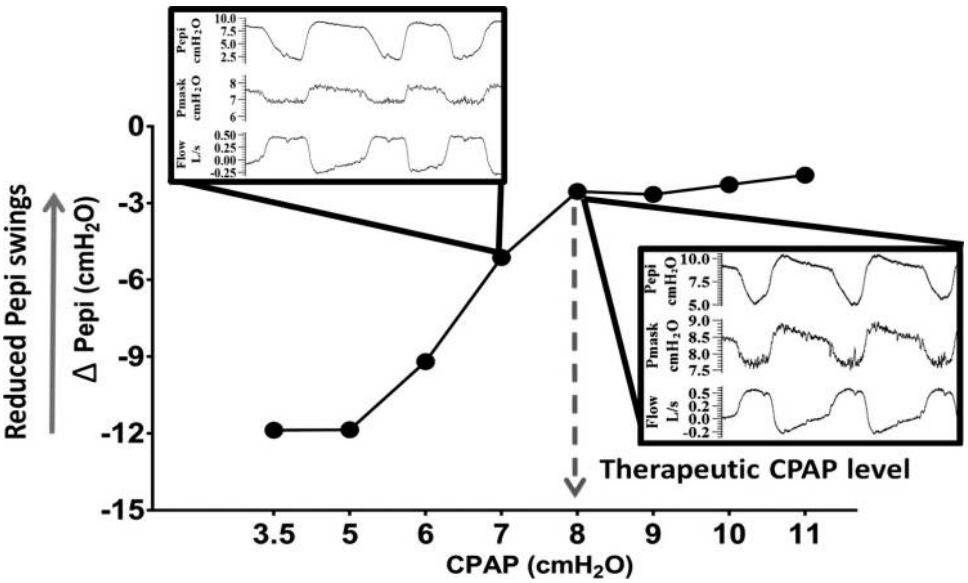

Fig. 3. Therapeutic CPAP requirements were determined by plotting pharyngeal pressure swings versus CPAP as shown in this individual example. The therapeutic CPAP level was defined as the first point where pharyngeal pressure swings stabilized. In this example, flow limitation and large pharyngeal pressure swings are present at 7 cmH_2O. At 8cmH_2O, airflow is restored, and pharyngeal pressure swings are minimized. Hence, this point is defined as the therapeutic CPAP level. Black circles represent mean delta (Δ) epiglottic pressure (difference between end expiration and nadir during inspiration) at each CPAP level. CPAP, continuous positive airway pressure; Pepi, epiglottic pressure; Pmask, mask pressure.

Table 1. *Participant characteristics*

Characteristic	Value
Sex	3W/13M
Age, yr	48 ± 11
Body mass index, kg/m^2	29 ± 5
No. of participants who were CPAP intolerant	3
Maximum mandibular advancement, %	83 ± 14
Epworth sleepiness scale	7 ± 4
Residual AHI on OA therapy alone, events/h	26 ± 13

Data are means ± SD unless otherwise stated. N = 16. AHI, apnea/hypopnea index; CPAP, continuous positive airway pressure; OA, oral appliance; M, men; W, women.

The average total sleep time for data collection in each condition [CPAP only, CPAP + OA (open), and CPAP + OA (closed)] was 102 ± 75 versus 70 ± 30 versus 67 ± 20 min, respectively. CPAP requirements were measured during supine NREM sleep, predominantly in N2 sleep. There was no difference in the proportion of N2 sleep [53 ± 17 vs. 60 ± 19 vs. 59 ± 18% total sleep time (TST), P = 0.445] and N3 sleep (26 ± 25 vs. 25 ± 24 vs. 17 ± 16%TST, P = 0.508) between the three study conditions [CPAP only, CPAP + OA (open), and CPAP+OA (closed)].

Pharyngeal Pressure Swings with Combination Therapy (CPAP + OA)

Figure 5 summarizes the Pepi swings at therapeutic CPAP requirement levels during combination therapy conditions compared with CPAP only. Pepi swings were successfully normalized to CPAP levels and were not different between conditions (P = 0.144).

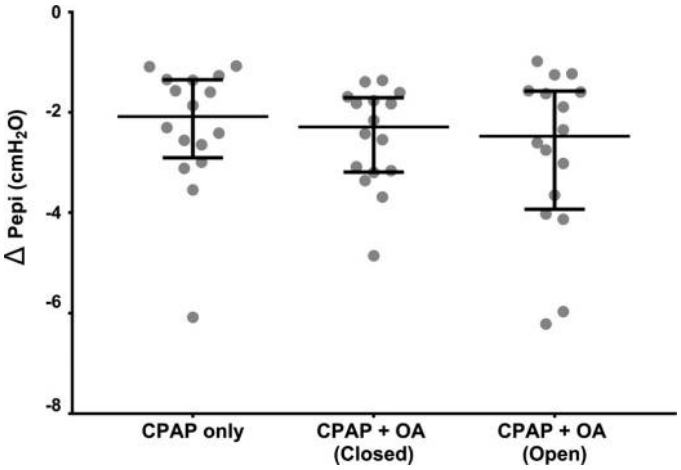

Fig. 5. Pharyngeal pressure swings at therapeutic CPAP requirements for each of the three conditions: CPAP only, CPAP + OA (closed), and CPAP + OA (open). Gray circles represent individual data. Black lines and error bars represent the median and interquartile range. CPAP, continuous positive airway pressure; OA, oral appliance; Δ Pepi: difference in epiglottic pressure swings between end expiration and nadir during inspiration.

DISCUSSION

The main findings of this study are that combination therapy with CPAP and a novel oral appliance can normalize pharyngeal pressure swings and lower CPAP requirements by ~40% compared with CPAP alone. These findings conducted in the clinically relevant group of incomplete responders to oral appliance therapy alone and derived using gold-standard physiological assessments to objectively quantify CPAP requirements provide novel insight into the role of combination therapy on upper airway physiology and breathing during sleep. This information is important to inform combination therapy strategies for OSA.

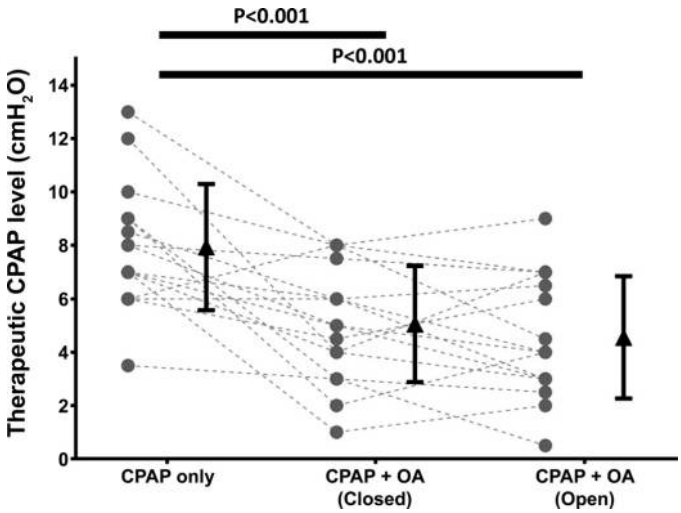

Fig. 4. Therapeutic CPAP requirements for each of the three conditions: CPAP only, CPAP + OA (closed), and CPAP + OA (open). Gray circles represent individual data. Black triangles with error bars represent the group means ± SD. CPAP, continuous positive airway pressure; OA, oral appliance.

The magnitude of the reduction in CPAP requirements with combination therapy in the current study is comparable with previous studies that used standard polysomnography approaches in which therapeutic CPAP requirements were reduced by 29%–48% (8, 12, 21). Thus, despite the use of different oral appliances, methodology, and patient characteristics, combination therapy appears to reduce CPAP requirements by 30%–50%.

The reduction of 3–4 cmH_2O in CPAP requirements in the current study is also comparable with that reported in previous physiology studies that have investigated the mechanisms of oral appliance therapy. For example, Bamagoos et al. (2, 3) demonstrated a dose-dependent 3–6 cmH_2O reduction in the critical closing pressure of the upper airway (Pcrit) with oral appliance therapy and a 4 cmH_2O reduction in therapeutic CPAP requirements with combination therapy. A similar reduction in the closing pressure of the upper airway (Pclose) of 5.5 cmH_2O was observed in patients under anesthesia with 6 mm of mandibular advancement (18), whereby anterior movement of the mandible widens the retropalatal airway and tongue base in the passive pharynx (17). Our findings therefore suggest that the reduction in therapeutic CPAP requirements with combination therapy is related to reduced upper airway collapsibility from oral appliance therapy.

Two participants did not have a reduction in therapeutic CPAP requirement with combination therapy. Both were obese and had high nasal resistance while supine (>3 cm$H_2O \cdot L^{-1}s^{-1}$) (33). One had upper airway crowding based on the Mallampati score of 3. Previous studies have indicated that obesity, upper airway crowding (16, 34), and increased nasal resistance (38) are predictors of unsuccessful oral appliance therapy outcome. Thus, this combination of factors likely yielded minimal

anatomical benefit with oral appliance therapy in these individuals and therefore, no change in therapeutic CPAP requirements.

Lower CPAP levels have been assumed to help improve CPAP compliance. Patient preference between the different conditions in the current acute physiology studies was not assessed. Nonetheless, previous studies have demonstrated high compliance with combination therapy with an average usage time of 6 h/night (8, 12, 21). Indeed, in one study, long-term compliance with combination therapy was reported to be ~75% with an average nightly usage of 6 h/night over 3 yr (21). De Vries et al. (8) also reported that patients, who require high therapeutic CPAP levels, prefer combination therapy (CPAP + OA). The current findings indicate that the addition of an oral appliance can reduce CPAP requirements by ~40% while normalizing pharyngeal pressure swings. Thus, this approach may be a viable alternative for people with high CPAP requirements who have difficulty tolerating the high pressures and for people who have an incomplete response to oral appliance therapy alone. However, the role of combination therapy on adherence and compliance was not assessed in the current physiological study. This remains an important clinical question to pursue in the clinically relevant patient groups including those who have incomplete responses to oral appliance therapy alone and those who are unable to tolerate CPAP alone due to high-pressure requirements.

In the current study, epiglottic pressure swings and CPAP requirements were comparable when the oral airway within the novel oral appliance device was open versus closed. This finding suggests that CPAP can be delivered effectively while providing an oral breathing option, which may offer an alternative to oronasal masks in those who have difficulty breathing exclusively through their nose. Borel et al. (6) also demonstrated that velopharyngeal resistance is reduced when CPAP and an oral appliance are used together compared with other mask interfaces.

Methodological Considerations

Although the current study has several methodological strengths including the rigorous objective assessment of CPAP requirements across the conditions using epiglottic pressures, pneumotach-derived airflow, and a clinically relevant patient population, there are certain limitations that need to be acknowledged. For example, this study was designed as a single night study in which three different conditions were assessed throughout the night. This limits the amount of sleep time available for each condition. However, on an average, over 1 h of sleep data were obtained in each condition, which was sufficient to address the study aims. Sleep architecture also changes across the night with a greater proportion of rapid eye movement (REM) sleep later in the night (9). Additionally, upper airway collapsibility and pharyngeal muscle activity are sleep-stage dependent (7). This likely results in different therapeutic CPAP requirements between sleep stages, especially during REM and NREM sleep. Therefore, the current study focused on the effects on supine NREM sleep comprising comparable amounts of N2 and N3 between conditions. Thus, while this design was appropriate to address our primary study aims, we cannot be certain that the magnitude of the reductions detected is comparable in REM sleep and in different body positions. However, study conditions were randomized to prevent potential time of night biases on the study outcomes. In addition, we did not measure airflow through the oral airway of the oral appliance during the airway open condition. Thus, we may have underestimated airflow and therefore overtitrated CPAP during this condition. However, this is unlikely, as we were able to take advantage of the epiglottic pressure sensor to assess upper airway function accurately and objectively across the study conditions. Finally, an EPAP valve was used in the current study to prevent CPAP leakage, which as recently demonstrated (20) may have itself led to some improvement in airway stability.

Summary

In conclusion, combination therapy using CPAP and oral appliance therapy can normalize pharyngeal pressure swings and lower CPAP requirements by 35%–45% compared with CPAP alone. Combination therapy may be a therapeutic option for patients with OSA who are incomplete responders to oral appliance therapy alone and those who struggle with CPAP due to high-pressure requirements. This requires further investigation.

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DISCLOSURES

Outside the submitted work, D. J. Eckert has received grants and serves as a consult for Bayer and Apnimed. The other authors do not have any conflicts of interest to disclose. Nonfinancial disclosure: Oventus Medical provided the O2Vent T MAS devices for the study but was not involved in the data collection, analysis, or interpretation of the study findings.

AUTHOR CONTRIBUTIONS

B.K.T., I.S., J.A., and D.J.E. conceived and designed research; B.K.T., C.T., A.R., M.D., J.A., and D.J.E. performed experiments; B.K.T., A.K.I.C., and D.J.E. analyzed data; B.K.T. and D.J.E. interpreted results of experiments; B.K.T. and D.J.E. prepared figures; B.K.T. and D.J.E. drafted manuscript; B.K.T., A.K.I.C., I.S., J.A., J.C.C., and D.J.E. edited and revised manuscript; B.K.T., A.K.I.C., I.S., J.A., J.C.C., and D.J.E. approved final version of manuscript.

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