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Kairos positive airway pressure (KPAP) equals continuous PAP in effectiveness, and offers superior comfort for obstructive sleep apnea treatment

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ABSTRACT

Study objectives: A recent study challenged the prevailing clinical view that maintaining inspiratory positive airway pressure (IPAP) is necessary for upper airway patency, demonstrating no differences in apnea hypopnea index (AHI) between continuous PAP (CPAP) with and without a resistor to reduce IPAP. In this study, we assessed the effect of Kairos PAP (KPAP), a new algorithm which features multiple drops in IPAP, only returning to therapeutic pressure near the end expiration, on sleep apnea severity and subjective comfort.

Methods: Two randomized clinical trials were conducted. In the *Efficacy* trial, the effect of KPAP vs. CPAP on AHI in PAP-treated OSA patients was examined using a split-night design, adjusting for period, sequence and fraction of supine sleep (mixed models). Unintentional leak differences between treatments were also examined. Exploratory analyses assessed the effect of KPAP vs. CPAP on key polysomnography outcomes. In the *Comfort* trial, we tested subjective preference for KPAP vs. CPAP at 9 and 13 cmH_2O in PAP-naïve OSA patients.

Results: In the *Efficacy* trial (N = 48), KPAP reduced AHI more than CPAP (mean difference [95%CI]: −0.5 [−0.8, −0.2] events/h, P = 0.007). Unintentional leak was also reduced by over 50 % (−2.5 [−3.2, −1.7] L/min, P < 0.001). No significant change was observed in the exploratory variables assessed. In the *Comfort* trial (N = 150), 69 [61, 77] % and 84 [77, 89] % of participants preferred KPAP over CPAP at 9 and 13 cmH_2O, respectively (P < 0.001).

Conclusions: KPAP is as effective as CPAP in reducing respiratory events, but is more comfortable and potentially better tolerated.

1. Introduction

Nearly four decades after its invention, continuous positive airway pressure (CPAP) remains the gold-standard of care for obstructive sleep apnea (OSA). However, despite its effectiveness and in the face of numerous technological advancements, CPAP still suffers from low adherence rates [1–3], as patients often struggle with many aspects of this therapy including mask discomfort, claustrophobia, leaks, and noise from the device [4,5]. Many of these issues have been effectively addressed over the years with smaller, quieter, and well-humidified devices and much improved masks. However, one of the biggest problems has always been the airway pressure itself which substantially alters normal inspiratory and expiratory flow patterns and the work of breathing across the respiratory cycle. Several attempts have been made to improve the discomfort produced by PAP, including bilevel positive pressure (BPAP), C-Flex, and expiratory pressure relief algorithms (EPRAs) with all such attempts having the same goal, reducing expiratory pressure. The logic always was that reducing pressure during expiration would reduce the expiratory work of breathing produced by the positive airway pressure. However, studies failed to demonstrate better adherence rates on BPAP vs. CPAP [6–8]. Similarly, EPRAs, including C-Flex [8,9], also yielded no improved adherence vs. CPAP

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[8]. It is also possible therefore that the pressure support created when expiratory PAP (EPAP) is reduced below inspiratory PAP (IPAP) could be deleterious in OSA for several reasons. First, IPAP > EPAP increases the risk of treatment emergent central sleep apnea (TECSA) in patients with ventilatory control close to instability (high loop gain) [10]. Second, several studies suggest that lowering EPAP below IPAP can decrease pharyngeal cross sectional area by both reducing the dilating force on the upper airway walls [11,12] and by lowering lung volume, which reduces tracheal traction, thereby yielding a more collapsible pharyngeal airway [13]. Thus, the literature does not support reducing expiratory pressure as a method to improve treatment adherence. However, reduced expiratory pressure (i.e., EPRAs) is still widely used to treat OSA.

Taking a different approach, we hypothesized that reducing IPAP below EPAP might be the key to improved CPAP tolerance [14]. This was initially accomplished by the addition of a non-compensated resistor (V-Com®) to the CPAP circuit which reduced IPAP by 1.5–2 cmH_2O (depending on the flow rate). This did lead to slightly longer CPAP usage vs. a standard auto-titrating PAP with no loss of efficacy and reduced leak [14]. Potential explanations for this include the possibility that breathing at lower IPAP more closely resembles natural breathing with more normal inspiratory flow rates and chest expansion.

To further improve PAP comfort, we designed a new algorithm with substantially reduced airway pressure during both inspiration and much of expiration, only returning pressure to the optimal treatment level towards the end of expiration. We called this Kairos PAP (KPAP) from the Greek term Kairos meaning “at the right time” (thus, pressure at the right time). As demonstrated in Fig. 1, this algorithm drops IPAP by 2 cmH_2O at the start of inspiration, and by an additional 3 cmH_2O at peak inspiratory flow, yielding a pressure 5 cmH_2O below the previously determined optimal pressure. This reduced pressure is maintained into expiration, only returning to the optimal level late in expiration. Of note, the algorithm does not allow airway pressure to fall below 5 cmH_2O. Thus, patients on less than 10 cm H_2O CPAP would experience lesser drops.

This paper will describe two studies. The first was designed to assess the efficacy of the KPAP algorithm versus standard CPAP, and the second to quantify subjective comfort of KPAP versus CPAP.

2. Methods

2.1. Participants

Participants aged 18–70 years, with a recent (within 1 year) diagnosis of OSA (per AHI≥10 events/h) and a BMI≥18 kg/m^2 were invited to participate to one of the following trials: the *Efficacy trial* tested the effect of KPAP vs. CPAP during a split-night, in-laboratory polysomnogram (PSG). For this study, participants were required to have at least 5 h of CPAP adherence during the 2-months prior to enrolment. The *Comfort trial* assessed in-office, subjective comfort during wake ventilation on KPAP vs. CPAP in CPAP-naïve participants (see below). Exclusion criteria for both trials included: any clinically significant or acute major organ disease, any sleep disorder other than OSA, schizophrenia, schizoaffective/bipolar disorder or attempted suicide in the year before the study, drug abuse history, nocturnal supplement oxygen usage, or hypoglossal nerve stimulation implantation.

Both trials were approved by the WIRB Copernicus Group ethics committee and prospectively registered on clinicaltrials.gov (*Efficacy trial*: NCT06238362; *Comfort trial*: NCT06264128). All participants provided written informed consent before enrolment. The research was conducted at the Sleep Centers of Middle Tennessee in adherence with the Declaration of Helsinki.

2.2. Protocol

Efficacy trial and description of KPAP. KPAP and CPAP were administered on the same night in random order (about 3.5 h for each treatment: split night design) after instrumenting the participant with standard PSG setup and their usual at-home CPAP mask. The sequence of randomization for each participant was assigned using a random number generator, however all participants started on CPAP until sleep onset to ensure blinding to treatment arm. Immediately after sleep onset, the randomized PAP (CPAP or KPAP) was initiated. CPAP and the baseline pressure for KPAP were set on the P90/P95 from the previous 2-months of home therapy (PAP able to treat disordered breathing for 90 % or 95 % of the time respectively) + 1 cmH_2O. KPAP was applied as follows (Fig. 1), ensuring that the baseline pressure never fell below 5 cmH_2O to ensure upper airway stability. Pressure decrements were selected based on preliminary observations from our local cohort, involving over 150 patients who underwent varying reductions in IPAP. Patients generally reported increased comfort with lower IPAP levels, with consistent improvements plateauing around a reduction of 5 cmH_2O, beyond which subjective comfort varied. Therefore, reductions in IPAP were set to never exceed 5 cmH_2O. Specifically, flow-dependent reductions in pressure begins at the start of inspiration with an initial drop that can be set at 1 or 2 cmH_2O, which adjusts to the patient’s inspiratory flow. Once peak inspiratory flow is reached, a second pressure drop begins, which can be set at 1, 2, or 3 cmH_2O. The transition into expiration happens

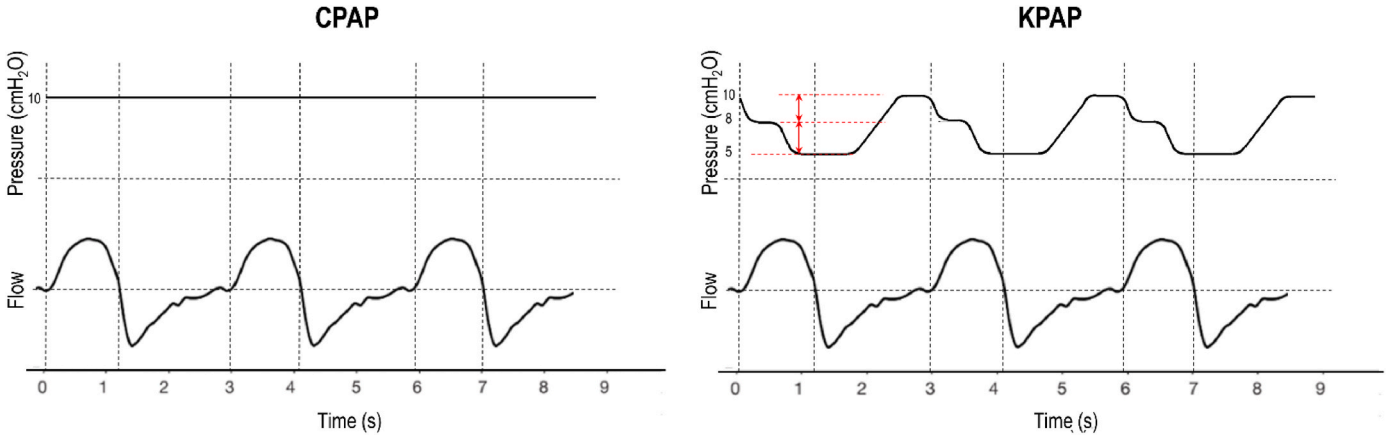

Fig. 1. Visual representation of the Kairos positive airway pressure (KPAP) algorithm. Pressure is dropped at the beginning of inspiration and again at peak inspiratory flow (arrows in red). Pressure starts to return to baseline levels about halfway through expiration. By contrast, continuous PAP (CPAP) has constant pressure throughout the entire respiratory cycle. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

when the pressure is already reduced by up to 5 cmH_2O. In a preliminary trial, we observed that a mid-expiratory return to therapy pressure (after peak expiratory flow) was efficacious in all patients and thus was instituted.

Thus, in this study, if the baseline pressure was above 10 cmH_2O, drops of 2 followed by 3 cmH_2O (total 5 cmH_2O) during inspiration were used. For a baseline pressure of 9 cmH_2O, drops were 2 + 2 cmH_2O: for a baseline pressure of 8 cmH_2O, drops were 2 + 1 cmH_2O: for a baseline pressure of 7 cmH_2O, drops were 1 + 1 cmH_2O: for a baseline pressure of 6 cmH_2O, drops were 1 + 0 cmH_2O. The reduced pressure continued into expiration, only returning to the therapeutic pressure toward the end of expiration (Fig. 1). Since the KPAP machine could also provide CPAP, the switch between CPAP and KPAP (or vice-versa) was operated through the interface screen on the device, using wireless communication between the control room and the bedroom. Mask pressure was measured with a manometer inserted in the PAP circuit. Vital signs were assessed before and after the overnight. Spontaneous adverse events, if any, were reported.

Comfort trial. During an in-office visit, participants were asked to breathe for approximately 1 min during each exposure during supine wakefulness while being administered, in random order, CPAP (at 9 or 13 cmH_2O) or KPAP at various pressure drops (Fig. 2). At baseline PAP of 9 cmH_2O, the initial drop was 2 + 2 cmH_2O and the participants were asked to choose their preference between CPAP and KPAP either by voice or raising their hand. Their choice, either KPAP or CPAP, was recorded and this result was the primary outcome of the comfort study at 9 cm H_2O pressure. If they chose CPAP, the next pressure drop administered was 1 + 2 cmH_2O and the question was repeated. Again, if KPAP was preferred, the choice was recorded, otherwise, a final drop of 1 + 1 cmH_2O was administered and their preference was noted. The protocol with the baseline PAP of 13 cmH_2O followed a similar pattern, with the comparison between CPAP and KPAP (2 + 3) being the primary outcome of the 13 cmH_2O trial. Subsequent pressure drops of 1 + 2, and 2 + 2 cmH_2O were then compared to CPAP. Of note, all pressure drops were assessed in one-to-one, paired comparisons with CPAP. The order of treatment administration was assigned with a random number generator. Baseline PAP of 9 cmH2O, rather than 13 cmH2O, was always used first to allow the naïve participants to acclimate to treatment at a lower pressure.

2.3. Data analysis

Respiratory events and arousals were scored in accordance with the American Academy of Sleep Medicine 2020 guidelines [15] by a registered PSG technician blinded to the study intervention. The patient flow signal was extracted from the flowmeter embedded in KPAP device, filtering off the leak flow from total flow (output). Subsequently, hypopneas were scored when there was a ≥30 % reduction in airflow from baseline, of a duration of at least 10 s, and associated with either an arousal from sleep or a decrease in oxyhemoglobin saturation of ≥3 %, yielding AHI_{3a}. AHI with hypopneas associated with 4 % desaturations (AHI_4) was also calculated. Sleep efficiency was calculated as total sleep time divided by time in bed (time in bed did not include time until sleep onset as all patients were started on CPAP for blinding purposes, thus not allowing for a CPAP/KPAP comparison on this variable).

Leak data were calculated from unintentional leak flow, which was obtained by subtracting patient flow and intentional leak flow from total flow. Patients used their own masks during the study, resulting in a large number of different masks with different intentional leak flow characteristics. In order to calculate intentional leak flow, a power-law formula was used to fit to the pressure/flow characteristics of each mask type during data periods within the total flow signal identified as having no unintentional leak flow.

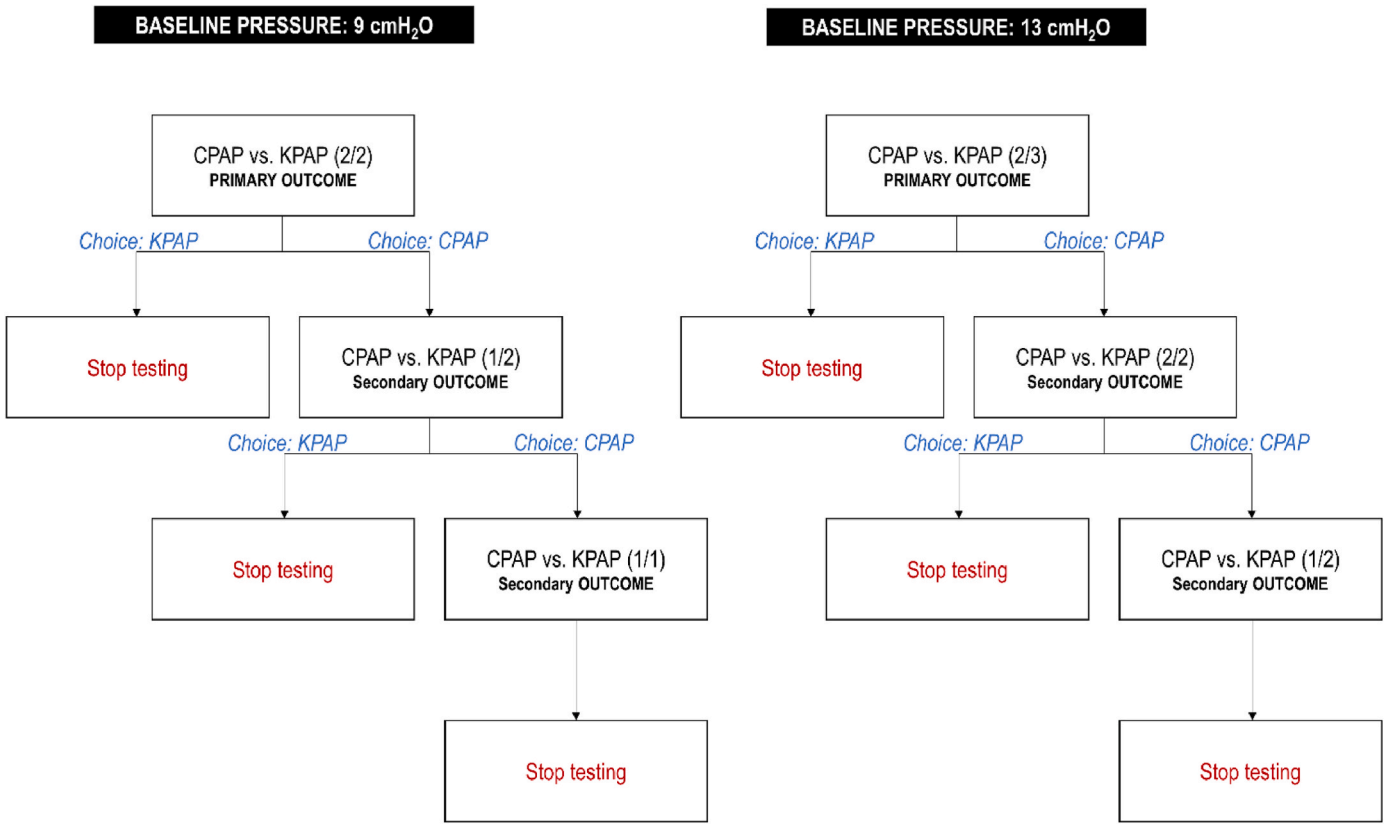

Fig. 2. *Comfort* trial flowchart. Kairos positive airway pressure (KPAP) (x/y) refers to sequential drops in inspiratory pressure of x + y cmH_2O. CPAP, continuous PAP.

2.4. Statistical analysis

Efficacy trial. The primary outcome was the overall effect of KPAP vs. CPAP on total AHI. Secondary outcomes were the effect of KPAP vs. CPAP on AHI during rapid eye movement (REM) and non REM (NREM) sleep, and on unintentional mask leak. Also assessed were total sleep time, arousal index, sleep architecture, sleep efficiency, oxyhemoglobin saturation (SpO_2) nadir, oxygen desaturation index of 3 % and 4 % (ODI_3 and ODI_4) and percent of sleep time spent under 90 % saturation (T90) under both conditions. Non-normally distributed data, including AHI and ODI data, were square-root transformed and back-transformed for presentation. All comparisons between treatment conditions were performed with linear mixed model analysis adjusting for supine sleep time (or NREM/REM supine sleep time where appropriate), CPAP setting, mask type (i.e., nasal pillows, nasal, full face) and period (i.e., first vs. second half of the study) and randomization sequence (i.e., CPAP or KPAP administered first in the split night), and with subject as a random effect. Sensitivity analyses were conducted using AHI_4, NREM AHI_4 and REM AHI_4. Given the preliminary nature of this study, we treated analysis of additional variables as exploratory and did not adjust for multiple comparisons.

To meet not-inferiority of KPAP vs. CPAP, 50 participants allowed 80 % power, estimating an expected standard deviation of AHI for CPAP and KPAP of 10 events/h, using a 1-sided 2.5 % significance level and accounting for a 5 % dropout rate.

Comfort trial. The primary outcome was to compare the number of patients selecting KPAP at 2 + 2 and 2 + 3 cmH2O pressure drops from 9 to 13 cmH_2O respectively to the number of patients selecting CPAP at the same baseline pressures (i.e., 9 and 13 cmH_2O). Secondarily, we assessed the effect of KPAP vs. CPAP on comfort at the other pressure drops.

A power sample calculation determined that 150 participants were needed to achieve 84 % power, based on a two-sided 5 % significance level and to detect a 12 % absolute difference in preference between treatments. Given that the study was brief and run in office, we did not account for potential dropouts.

3. Results

Of the 50 recruited participants for the *Efficacy* trial, 2 were excluded due to either insufficient sleep (N = 1) or inadequate signal quality (N = 1) on one treatment arm, while all 150 participants who were recruited for the *Comfort* trial completed the study. Baseline characteristics of these individuals are presented in Tables 1 and 2, respectively.

Table 1
Baseline characteristics and medications for the *Efficacy* study participants.

Characteristic	N = 48
Population Factors	
Age (years)	49.1 ± 12.1
Sex, N (M:F)	22:26
BMI (Kg/m^2)	37.8 ± 8.0
Race, N (White:Black:Asian:Pacific Islander)	41:5:1:1
Baseline AHI (events/h)	37.8 ± 21.3
Baseline CAI (events/h)	0
Baseline Epworth Sleepiness Scale	10.0 ± 4.9
Baseline P90/P95 (cmH_2O)	10.6 ± 2.5
Medications	
Antihypertensives, N	22
Asthma/Allergies, N	5
Anxiety/Depression, N	11
Antihyperglycemics, N	6
Sleep Aids, N	3

BMI, body mass index; AHI, apnea hypopnea index; CAI, central apnea index; P90/P95, pressure capable of addressing 90 % or 95 % of respiratory events (calculated from the previous 2-months of usage). Data are mean ± SD where appropriate.

Table 2
Baseline characteristics and medications for the *Comfort* study participants.

Characteristic	N = 150
Population factors	
Age (years)	43.1 ± 10.7
Sex, N (M:F)	85:65
BMI (Kg/m^2)	35.5 ± 7.7
Race, N (White:Black:Asian:American Indian or Alaskan Native: Unknown)	123:17:2:1:7
Baseline AHI (events/h)	27.8 ± 20.0
Mask of choice, N (Nasal Pillows:Nasal Cushions; Full Face Mask)	138:8:4
Starting therapy, N (CPAP:KPAP)	74:76
Medications	
Antihypertensives, N	64
Asthma/Allergies, N	11
Anxiety/Depression, N	46
Antihyperglycemics, N	25
Sleep Aids, N	8

BMI, body mass index; AHI, apnea hypopnea index; CPAP, continuous positive airway pressure; KPAP, Kairos PAP. Data are mean ± SD where appropriate.

3.1. Efficacy trial

Primary Outcomes. The efficacy of KPAP on OSA severity was comparable to that of CPAP, as summarized in Table 3. In brief, neither the overall AHI_{3a} nor the AHI_{3a} during NREM or REM sleep were worse when comparing KPAP to CPAP (Fig. 3). Rather, AHI_{3a} (for all sleep stages) and AHI_{3a} during REM sleep were lower on KPAP, though the difference was not clinically meaningful (Table 3). Sensitivity analyses using AHI_4 yielded similar results (Fig. 3). Unintentional mask leak data were available for 45 individuals: KPAP significantly reduced mask leak (Table 3).

Exploratory Outcomes. Total sleep time on KPAP vs. CPAP was longer by 9.9 [0.9, 19.0] min (Table 4), but so was time of KPAP administration (+8.8 [1.7, 16] min vs. CPAP). Sleep architecture was otherwise unchanged.

Similarly, nocturnal hypoxemia was reduced equally with CPAP and KPAP (Table 4).

Period (first vs. second half of the night) influenced REM duration (longer by ~9 % of total sleep time in the second half of the night) and consequently OSA severity (AHI_{3a} and AHI_4 increased by ~0.9 and

Table 3
Effect of KPAP vs. CPAP on key primary and secondary outcomes in the *Efficacy* study.

Characteristic	CPAP	KPAP	Mean difference [95% CI] P value
AHI_{3a} (events/h)	3.2 ± 3.9	2.9 ± 4.1	−0.6 [−10, −0.2] 0.005
NREM AHI_{3a} (events/h)	2.2 ± 3.7	2.3 ± 4.4	−0.1 [−0.4, 0.3] 0.724
REM AHI_{3a} (events/h)[a]	6.0 ± 6.8	4.3 ± 5.1	−1.5 [−2.5, −0.4] 0.014
AHI_4 (events/h)	1.0 ± 1.5	0.8 ± 1.0	−0.2 [−0.5, 0.1] 0.194
NREM AHI_4 (events/h)	0.4 ± 0.9	0.5 ± 1.0	0.1 [−0.1, 0.4] 0.501
REM AHI_4 (events/h)[a]	2.8 ± 4.3	1.9 ± 3.2	−1 [−2.7, −0.1] 0.028
Unintentional mask leak (L/min)‡	5.1 ± 4.3	2.8 ± 3.6	−2.0 [−2.5, −1.4] <0.001

[a] Paired values were not available in 16 individuals. ‡Data available in 45 individuals. Missing values were handled in the analysis by mixed models (see text for further details). All analyses are adjusted for percentage of sleep time spent supine, CPAP levels, mask type, period and randomization sequence. AHI_{3a}: apnea hypopnea index with hypopneas requiring 3 % desaturation or arousal; NREM, non-rapid eye movement sleep; REM; rapid eye movement sleep AHI_4, AHI with hypopneas requiring 4 % desaturations. Data are means ± SD where appropriate.

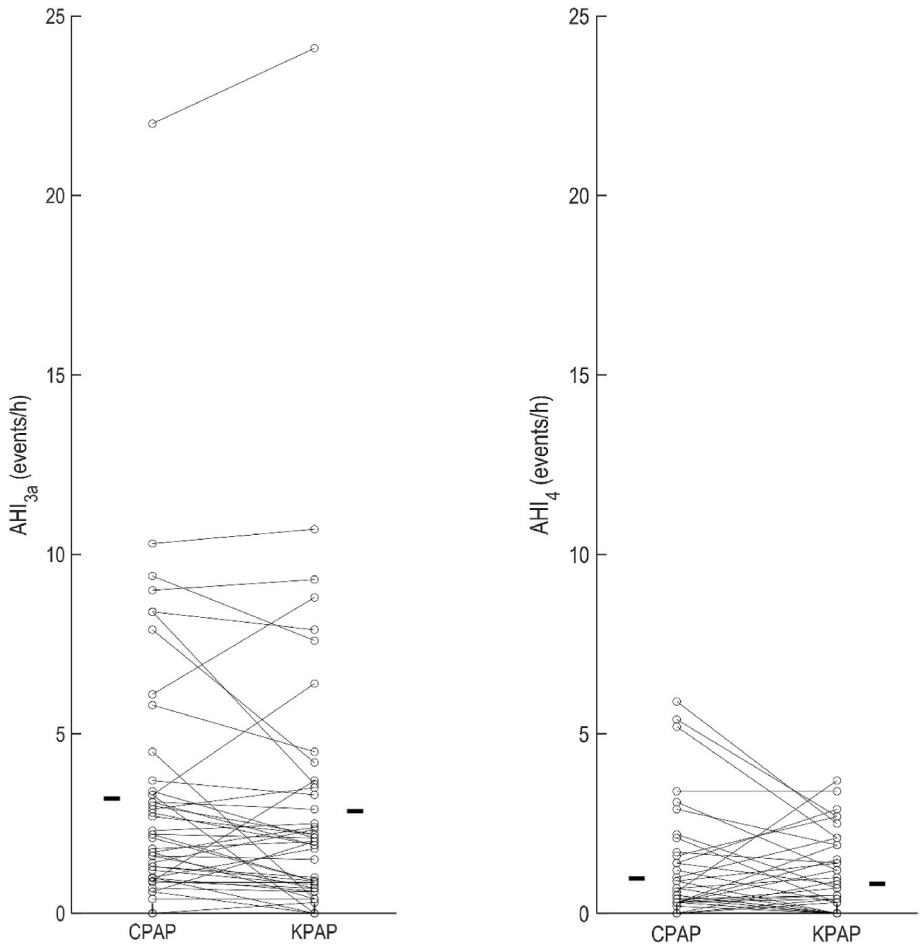

Fig. 3. OSA severity metrics on continuous positive airway pressure (CPAP) vs. Kairos PAP (KPAP), individual data. The apnea hypopnea index (AHI_{3a}) was the primary outcome of the *Efficacy* trial. AHI with 4 % desaturation (AHI_4), was assessed as part of sensitivity analyses. The bars in each panel are the mean values on the corresponding treatment arm.

~0.4 events/h, respectively, in the second vs. first half of the night). No other parameters assessed were influenced by the design of the study.

3.2. Comfort trial

At a baseline pressure of 9 cmH_2O, 69 [61, 77] % of participants preferred KPAP (IPAP drops: 2 + 2 cmH_2O; $P < 0.001$) rather than CPAP, while, at a baseline pressure of 13 cmH_2O, 84 [77, 89] % of participants preferred KPAP (IPAP drops: 2 + 3 cmH_2O; $P < 0.001$). These results are illustrated in Fig. 4. Additional comparisons between pressure preferences are shown in Fig. 5. Overall, 93 % and 95 % of individuals selected KPAP (any IPAP drop) vs. CPAP at 9 and 13 cmH_2O of baseline pressure, respectively.

Of note, at the baseline pressure of 9 cmH_2O, 85 % of participants randomized to CPAP first preferred KPAP, while only 46 % chose KPAP when CPAP was administered second. This suggests an indirect period effect in favor of the second treatment administered. Such a period effect was greatly reduced at a baseline pressure of 13 cmH_2O, where 92 % and 76 % of participants randomized to CPAP or KPAP first, respectively, chose KPAP.

4. Discussion

The main findings of this study are that KPAP is as efficacious as CPAP for the treatment of OSA despite pressure drops up to 5 cm H_2O, and it is subjectively more comfortable. If confirmed in longer trials, these results suggest that KPAP may be a reliable therapeutic alternative to CPAP. This could potentially represent an important advancement in the treatment of OSA.

4.1. Effect of KPAP on primary and secondary outcomes

With this study we demonstrate that the prevailing view that IPAP cannot be lowered while maintaining upper airway patency is incorrect. These results also confirm the findings of a previous study in which a resistor added to the circuit of CPAP (V-Com) to lower IPAP led to a reduced AHI vs. a standard CPAP [14], although the differences in AHI in both studies were quite small. Different from the resistor, which reduced IPAP by 1–2 cmH_2O depending on the patient's flow, KPAP provides larger (i.e., up to 5 cmH_2O), pre-determined drops in pressure that start in inspiration and continue halfway through the expiration, where upper airway obstruction may occur [11]. Thus, if sustained IPAP levels were necessary to preserve upper airway patency, one would have expected increased OSA severity on KPAP. However, our findings indicated that KPAP not only does not compromise therapy but may actually result in fewer respiratory events compared to CPAP, although the differences were small. In addition, unlike our previous study, where residual AHI was estimated via device algorithms, this crossover trial utilized PSGs with manual scoring, thereby confirming the previous study's results with a stronger methodology.

KPAP also halved mask leak compared to CPAP, resulting in a 2.5 L/min decrease (50.8 %; $P < 0.001$) in patients on chronic PAP therapy using their own masks. This reduction in leak, which was rigorously quantified, represents a significant improvement for patients

Table 4
Effect of KPAP vs. CPAP on exploratory variables in the *Efficacy* study.

Characteristic	CPAP	KPAP	Mean difference [95%CI] P value
Sleep efficiency (%)*	87.0 ± 11.7	88.2 ± 10.0	1.5 [−2.1, 5.1] 0.427
Total sleep time (min)	167.7 ± 33.2	177.7 ± 30.2	9.9 [0.9, 19.0] 0.032
Wake after sleep onset (min)	24.2 ± 20.3	23.3 ± 18.8	−0.7 [−5.5, 4.8] 0.794
Arousal index (events/h)	12.9 ± 7.6	13.2 ± 11.8	−0.2 [−1.9, 1.7] 0.818
N1 (%TST)	6.0 ± 4.4	4.6 ± 3.7	−1.4 [−2.5, −0.2] 0.030
N2 (%TST)	73.2 ± 11.0	71.7 ± 12.3	−0.9 [−5.1, 3.3] 0.680
N3 (%TST)	0.9 ± 2.8	1.5 ± 5.2	0.1 [−0.1, 0.4] 0.694
REM (%TST)	19.7 ± 10.7	21.5 ± 11.8	1.0 [−3.0, 5.6] 0.631
SpO2 nadir (%)	90.7 ± 2.7	90.3 ± 3.1	−0.2 [−1.3, 0.8] 0.668
Oxygen desaturation index$_3$ (events/h)	2.2 ± 2.7	1.9 ± 2.5	−0.1 [−0.3, 0.1] 0.224
Oxygen desaturation index$_4$ (events/h)	0.9 ± 1.3	0.9 ± 1.2	−0.1 [−0.2, 0.1] 0.614
T90 (%)	1.4 ± 6.0	2.8 ± 16.3	0.1 [−0.2, 0.3] 0.794

Analyses are adjusted for period and randomization sequence (mixed models). Analysis of respiratory variables are further adjusted for percentage of sleep time spent supine, CPAP levels and mask type. Of note, KPAP increased total sleep (TST) time by almost 6 %. For context, in previous studies, weighted total sleep time increase was around 10 % on hypnotics vs. placebo [19,20]. However, this effect was likely a product of a longer KPAP vs. CPAP administration time (8.8 [1.7, 16] min).
REM, rapid eye movements; T90, percent of sleep time spent under 90 % saturation. Data are means ± SD where appropriate. *Sleep efficiency was calculated without accounting for sleep onset latency (see text for details), hence values are higher than normal.

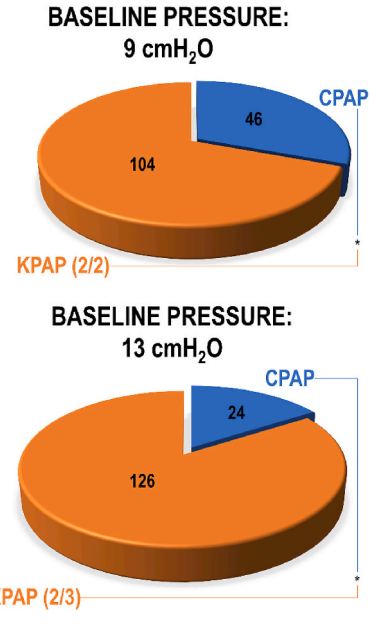

Fig. 4. Individual preferences in the *Comfort* trial: continuous positive airway pressure (CPAP) vs. Kairos PAP (KPAP). The primary outcome of the study was the preference of CPAP vs. KPAP 2/2 (2 + 2 cmH_2O drops in inspiratory PAP) or 2/3 (2 + 3 cmH_2O drops in inspiratory PAP) at baseline pressures of 9 and 13 cmH2O, respectively. Asterisks indicate statistical significance between treatments.

undergoing PAP therapy and may contribute to enhanced long-term tolerability.

For the first time, we also demonstrated that lower inspiratory pressures are more comfortable subjectively than CPAP. Again, this is in line with our previous study [14], which found that a reduction in IPAP through the resistor in the CPAP circuit led to longer usage time, arguably a reflection of enhanced treatment tolerability. The main limitation of CPAP, whose effect on patient outcomes [16] and specific adverse events [17,18] is well-established, is in fact tolerability, which affects adherence rates. A treatment that is as effective as CPAP but more tolerable does not currently exist. Therefore, if these results are confirmed in longer and larger adherence trials, it could importantly change the way OSA is treated.

Our primary goal was to ensure that KPAP vs. CPAP improved comfort during *wakefulness*, which provides patients impetus for improved treatment acceptance and adherence. Our hypothesis, based on our previous pilot study [14], was that breathing with lower IPAP *feels* more natural, closer to normal inspiration, which occurs with lower pressures. Thus, we did not anticipate that KPAP could also improve apparent comfort during *sleep*, such that a measure of objective sleep quality would improve.

4.2. Methodological considerations

First, the main limitation of this study stems from its split-night design. Thus, there was no wash-out period between treatments and a carry-over effect of CPAP treatment cannot be excluded. There was also no washout period between regular CPAP use in the home and this study in the sleep lab. Acute withdrawal of CPAP yields OSA recrudescence [21], but there may still be some residual effect of previous CPAP on upper airway collapsibility after its suspension [22]. However, we would have certainly expected some increase in AHI following the substantial reductions in pressure achieved with KPAP if these decrements in pressure in any way compromised airway patency. Not only was this not observed, but AHI was actually statistically lower on KPAP, although these differences were small. In addition, all our findings withstood adjustments for sequence of randomization and period. Thus we do not believe that our failure to have washout periods in any way nullifies the findings of this study.

Second, we did observe a period effect in the *Comfort* trial, namely an increased preference for the second treatment administered, irrespective of PAP delivery algorithms. This is easily explained clinically, as the participants were all PAP naïve and more susceptible to a negative subjective experience upon the first exposure to PAP. This could arguably affect the interpretability of our results. However, we believe this period effect is an inevitable aspect of any subjective decision-making process where a new exposure is tested. Pre-adaptation time with KPAP or CPAP before the trial might also have skewed preferences toward one treatment or the other and were thus not implemented. Of note, the results at the baseline pressure of 13 cmH_2O were less influenced by this period effect—likely because patients had already been exposed to PAP at 9 cm H_2O. Despite this potential problem, KPAP has consistently found to be more comfortable than CPAP.

Third, the increased preference for KPAP vs. CPAP in the *Comfort* trial was recorded during wakefulness and provides only rough estimates as to real-world acceptance. However, since sleep is by definition an unconscious state, next-morning subjective preferences recollected from a night of sleep would not necessarily reflect increased comfort during sleep. Nonetheless, these data will need to be recorded. Finally, we designed this study to provide preliminary data on treatment equivalence with KPAP and determine with reasonable certainty that decreasing IPAP does not compromise therapy. Again, larger and longer studies will be needed to confirm our findings.

Fig. 5. Continuous positive airway pressure (CPAP) vs Kairos PAP (KPAP) preferences as per the *Comfort* trial. Numbers in bracket denote the individuals who opted for that given preference. Note that the primary outcome for the *Comfort* trial was the difference in comfort between CPAP and KPAP 2/2 (2 + 2 cmH_2O drops in inspiratory PAP for 9 cm H_2O) or 2/3 (2 + 3 cmH_2O drops in inspiratory PAP for 13 cm H_2O). Although comparisons between other KPAP settings and CPAP do not seem meaningfully different, this flowchart illustrates that 139/150 (at CPAP baseline pressure of 9 cmH_2O) and 142/150 (at CPAP baseline pressure of 13 cmH_2O) eventually preferred one of the KPAP settings over CPAP.

5. Conclusions

KPAP, a novel algorithm for OSA treatment that provides pressure at the right time in the respiratory cycle, namely at end expiration, is as effective as CPAP in addressing respiratory events and is subjectively more comfortable.

Data statement

The data used to prepare this manuscript will be available upon reasonable request at: ludovico.messineo@yahoo.it.

CRediT authorship contribution statement

David P. White: Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **Ludovico Messineo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Evelyn Thompson:** Investigation, Data curation. **Bryan Hughes:** Investigation, Data curation. **Wilson D. Lannom:** Investigation, Formal analysis. **Bernard Hete:** Writing – review & editing, Validation, Software, Methodology, Funding acquisition, Conceptualization. **Abinash Joshi:** Validation, Project administration, Methodology, Investigation. **William H. Noah:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: David P White reports a relationship with SleepRes that includes: consulting or advisory. William Noah reports a relationship with SleepRes that includes: board membership. William Noah has patent pending to William Noah. LM received industry grants from Apnimed, Inc and Prosomnus unrelated to this work. DPW received consultancy fees for Bairitone, Cerebra Health, Cryosa, Mosanna, Onera, Philips Respironics, Resonea, Xtrodes, and Apnimed unrelated to this work. If

there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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