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The Complex Sleep Apnea Resolution Study: A Prospective Randomized Controlled Trial of Continuous Positive Airway Pressure Versus Adaptive Servoventilation Therapy

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Introduction: Prior studies show that adaptive servoventilation (ASV) is initially more effective than continuous positive airway pressure (CPAP) for patients with complex sleep apnea syndrome (CompSAS), but choosing therapies has been controversial because residual central breathing events may resolve over time in many patients receiving chronic CPAP therapy. We conducted a multicenter, randomized, prospective trial comparing clinical and polysomnographic outcomes over prolonged treatment of patients with CompSAS, with CPAP versus ASV.

Methods: Qualifying participants meeting criteria for CompSAS were randomized to optimized CPAP or ASV treatment. Clinical and polysomnographic data were obtained at baseline and after 90 days of therapy.

Results: We randomized 66 participants (33 to each treatment). At baseline, the diagnostic apnea-hypopnea index (AHI) was 37.7 ± 27.8 (central apnea index [CAI] = 3.2 ± 5.8) and best CPAP AHI was 37.0 ± 24.9 (CAI 29.7 ± 25.0). After second-night treatment titration, the AHI was 4.7 ± 8.1 (CAI = 1.1 ± 3.7) on ASV and 14.1 ± 20.7 (CAI = 8.8 ± 16.3) on CPAP (P ≤ 0.0003). At 90 days, the ASV versus CPAP AHI was 4.4 ± 9.6 versus 9.9 ± 11.1 (P = 0.0024) and CAI was 0.7 ± 3.4 versus 4.8 ± 6.4 (P < 0.0001), respectively. In the intention-to-treat analysis, success (AHI < 10) at 90 days of therapy was achieved in 89.7% versus 64.5% of participants treated with ASV and CPAP, respectively (P = 0.0214). Compliance and changes in Epworth Sleepiness Scale and Sleep Apnea Quality of Life Index were not significantly different between treatment groups.

Conclusion: Adaptive servoventilation (ASV) was more reliably effective than CPAP in relieving complex sleep apnea syndrome. While two thirds of participants experienced success with CPAP, approximately 90% experienced success with ASV. Because both methods produced similar symptomatic changes, it is unclear if this polysomnographic effectiveness may translate into other desired outcomes.

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Keywords: complex sleep apnea, central sleep apnea, positive airway pressure, adaptive servoventilation

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INTRODUCTION

Complex sleep apnea syndrome (CompSAS) describes the coexistence or appearance and persistence of central apneas or hypopneas, often associated with a periodic breathing pattern, in patients with coexistent obstructive sleep apnea (OSA) that is most evident upon successful restoration of airway patency.[1–4] Based on international reports, this pattern is seen in patients with clinical and polysomnographic features of OSA between 4% and 19% of the time.[2,3,5–8] The acute response to continuous positive airway pressure (CPAP) in patients with CompSAS is poor by definition, with a residual central apnea index (CAI) ranging between 5–30/h, and a residual apnea-hypopnea index (AHI) ranging between 16–49/h.[2,6,7,9–18] In contrast, several studies have shown acute efficacy of adaptive servoventilation (ASV) in the treatment of CompSAS, with residual AHI less than 10 and concurrent improvements in arousal indexes.[9,11,12,14,15,17,19] Efficacy of ASV is also suggested by the subjective reports of benefit and subjective adherence, with more than 80% of patients reporting improvement in symptoms.[9]

Although ASV clearly reduces the AHI more than CPAP, there remains controversy regarding the role of ASV versus CPAP in chronic treatment of CompSAS. Limited data show that patients with CompSAS demonstrate increased difficulties tolerating CPAP compared with ASV, but long-term data are sparse.[20] Additionally, the natural history of central respiratory events that emerge on CPAP over time is not entirely clear.[3,6,8,16,21] In a study evaluating 21 patients with central sleep apnea (CSA) events occurring during CPAP titration and again 2–3 mo after CPAP commencement concluded that the CSA events were transient and self-limited in 12 of 14 patients.[8] These data must be interpreted with caution, because 33% of patients were lost to follow-up and may be those in whom CSA events did not resolve and who subsequently experienced more difficulties with CPAP; their absence may seriously alter the results and conclusions in this study. Javeheri et al. showed in a large retrospective cohort study that of those 6.5% showing initial CompSAS, 89% showed resolution of the condition over 5–6 w.[6] However, in this study, there was again only approximately 50% follow-up of CompSAS cases, and 11.9% of those first identified were being treated with bilevel positive airway pressure (BPAP). Cassel et al. noted that of the 12.2% initially

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Table 1—Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
• Adults ≥ 18 years of age • Diagnosis of CompSAS. Patients who, during PSG had a CPAP titration eliminating events defining OSA, **but had a residual CAI ≥ 10 events/hour** or residual CSR pattern that was predominant and disruptive. • Requiring CPAP less than or equal to 15 cm H_2O to eliminate obstructive apneas and flow limitation. • Able to understand and comply with protocol	• Unstable CHF or CHF III-IV • Requires supplemental O_2 • Cognitive impairment that renders unable to answer questionnaires • Night shift or transport workers • Conditions that may affect patient's ability to use therapy, such as primary claustrophobia, or significantly impaired nasal patency; pre-existing primary pulmonary disease (COPD, asthma), or neuromuscular disease

CompSAS, complex sleep apnea syndrome; PSG, polysomnography; CPAP, continuous positive airway pressure; CAI, central apnea index; CSR, Cheyne-Stokes respiration; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

found to have CompSAS, 26% still had the condition after 3 mo of treatment. [3] Additionally, in their patients with CompSAS, 34% were lost to follow-up.[3] In another study evaluating residual sleep apnea in patients treated with CPAP for 3 mo, the authors found that 25% had a residual AHI ≥ 10, and of those, 73% had either periodic breathing or a CAI ≥ 5/h.[21] A retrospective study of 13 patients from our institution documented persistently elevated AHI in approximately 50% of patients treated with CPAP, but the retrospective design also suffered from inherent selection bias, probably overestimating the proportion of patients who have persistently increased central respiratory dysfunction.[16] These studies show variable CompSAS resolution rates, and possibly a tendency for less compliance with CPAP in patients with CompSAS.

Because ASV devices are more expensive than CPAP, it is desirable to determine what proportion of patients may be treated effectively with CPAP, and more importantly, whether clinical or laboratory features might predict long-term response. We conducted a multicenter randomized prospective trial to determine (1) what proportion of patients identified with CompSAS and treated with either CPAP or ASV experience resolution of sleep disordered breathing (SDB) over 3 mo of treatment, and (2) the clinical or laboratory features that might predict a given patient's response to CPAP or requirements for ASV.

METHODS

Design

This was a prospective, randomized, single-blind, multicenter trial. The primary objective was to compare the efficacy of ASV to CPAP in resolving CompSAS over a 90-day period. Using *a priori* methods, we determined that the goal of treatment was an AHI of ≤ 10/h, and that a meaningful difference in AHI would be 10/h. The secondary objectives were to assess the effect of positive airway pressure (PAP) treatment on quality of life; determine the proportion of patients in whom SDB has resolved; and determine, if possible, which clinical parameters may be associated with CPAP response versus the requirement for treatment with ASV.

Participants were recruited by investigator invitation and via signage placed in participating sleep centers after clinically indicated diagnostic and CPAP titration polysomnograms (PSGs). Inclusion and exclusion criteria are shown in Table 1. Although many studies have previously used a residual CAI ≥ 5 on best CPAP as the defining characteristic, we wanted to ensure that participants who might have only slight elevations of CAI because of, for example, arousals from other causes were not included, so we used a residual CAI ≥ 10. Interested participants meeting criteria in Table 1 gave consent to participate, and their PSGs were sent to the Core Lab for review. After candidate participants were confirmed to have CompSAS, a total of four visits were to be completed, with three in-person clinic visits and a follow-up phone call within a timeframe of approximately 90 days. The study was approved by the internal review boards of each participating center (supplemental material).

The protocol is summarized in Figure 1. Visit 1 was used to confirm the inclusion and exclusion criteria and to obtain a baseline Epworth Sleepiness Scale (ESS) score[22] and the Calgary Sleep Apnea Quality of Life Index (SAQLI).[23] Participants were then randomized to either CPAP or ASV therapy. Titration on assigned therapy was performed over a full night of PSG and participants began therapy at best settings (supplemental material). All titration procedures, participant instructions, and equipment settings were blinded to the participants. Two weeks after the start of treatment, participants were contacted by phone to inquire about and respond to problems (visit 2). Visit 3 was conducted in person, and served to download 30-day PAP data, obtain the SAQLI, and obtain the participants' evaluation of sleep quality via a visual analog scale (VAS) (supplemental material), reinforce importance of adherence, and address encountered problems with adaptation. Visit 4 occurred 90 days after the start of treatment. Participants completed a final PSG on their treatment mode and settings, and completed a final PAP Comfort, ESS, and SAQLI questionnaire. PAP usage data were downloaded one final time, and subsequent treatment after the study was discussed with the site sleep specialists. The study procedures are detailed in the supplemental material.

Measurements and Data Management

Three to four attended PSGs were acquired for each participant: diagnostic and initial CPAP titration PSG (some split night), research titration PSG, and final PSG. All PSGs were recorded at the local sites, and were subsequently analyzed and scored by registered PSG technologists on Gamma software (Grass Technologies Corporation, West Warwick, RI) at the Core Lab (Center for Sleep Medicine, Mayo Clinic, Rochester, MN) according to standardized criteria.[24] Between-technologist scoring agreement was tested in an ongoing fashion

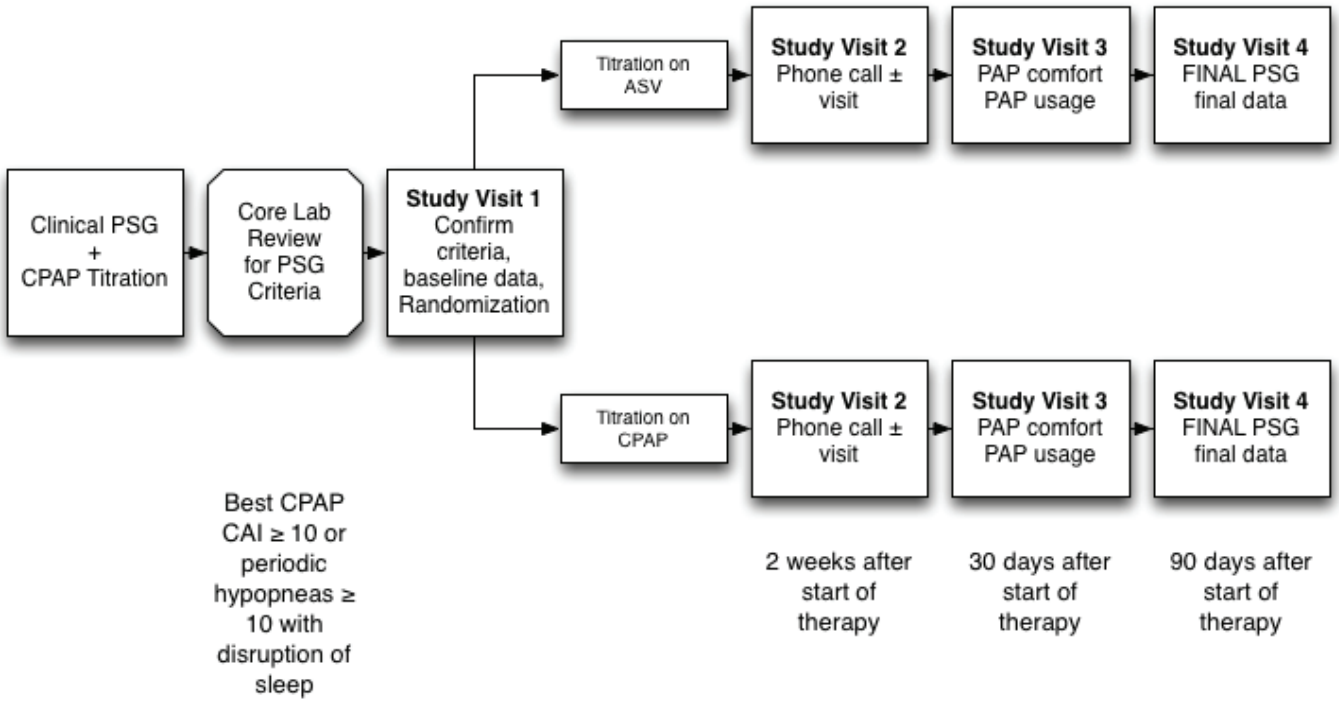

Figure 1—Schematic of study protocol. PSG, polysomnography; CPAP, continuous positive airway pressure; ASV, adaptive servoventilation; PAP, positive airway pressure; CAI, central apnea index.

to affirm reproducibility. One board-certified sleep specialist (TIM) provided confirmatory clinical review and audit for each PSG. PSG reports were sent back to the sites after each review, and discrepancies in scoring, if any, were discussed between the Core Lab sleep specialist and the site sleep specialist until agreement was achieved. The supplemental material contains details about measurement and data management.

CPAP and ASV were titrated according to a standardized protocol at each facility, and the Core Lab determined optimal treatment settings for the 90-day treatment period. At the final PSG, SDB was considered resolved if the AHI was ≤ 10 and there was no significant residual periodic breathing as detected by inspection of the summation of respiratory impedance plethysmography and/or the pressure signal from the flow generator in the case of participants treated with ASV.

Statistical Methods

Data summaries are presented for all participants randomized to the study (Randomized), and for evaluable participants (Evaluable). The evaluable group included all participants who used the study device for 4 h or more a night, at least 70% of the nights during the 90-day study period. In addition, evaluable participants must have completed the final PSG at the 90-day visit.

Primary efficacy was assessed by comparing the change in total AHI from the baseline diagnostic PSG to the visit 4 PSG (90-day visit) between the two treatment groups (CPAP versus ASV). Secondary endpoints included SAQLI at 90 days, CompSAS resolution, respiratory arousal index, average daily usage over the study period, and the assessment of ESS and VAS scores over the study period. All endpoints were compared between the treatment groups. Where appropriate, the change from baseline was also assessed.

All statistical comparisons between the treatment groups were generated using a two-sample *t*-test or the Wilcoxon rank-sum test, depending on the normality of distributions. Categorical comparisons were generated using chi-Square and Fisher exact tests, as appropriate. In all cases, P values were based on a two-sided test with a type I error of 0.05. All statistical calculations were performed in SAS®, Version 9.2 (SAS Institute Inc., Cary, NC).

Sample Size

Using the results of prior studies as a guide, we calculated that a sample size of 21 in each group would have 90% power to detect a difference in means of 10 AHI events/h, and would also take into account a dropout rate of 40%. Over the course of the study (because enrollment was slower than anticipated) it was determined that a study powered to 80% would be sufficient to assess study objectives, thus requiring 16 evaluable participants per treatment arm, for a total of 32 participants.

Equipment

The positive airway treatment device used was the VPAP Adapt SV™ flow generator (ResMed Inc., San Diego, CA), and depending upon allocation arms, devices were set in the ASV or CPAP mode. The HumidAire 2i™ (ResMed Inc., San Diego, CA) was uniformly used to enhance comfort, and ResLink™ (ResMed Inc., San Diego, CA) devices were also used in conjunction with the VPAP Adapt SV flow generator in order to record compliance and respiratory event data (supplemental material).

RESULTS

A total of 140 participants were screened for the study, of which 69 enrolled. Three patients withdrew prior to

Table 2—Demographic and medical data of 66 participants randomized in the trial.

Characteristic/comorbidity	All Patients Randomized ASV (N = 33)	CPAP (N = 33)	P-value
Age at enrollment (years)	59.1 ± 14.2	59.4 ± 11.7	0.93
Male gender	78.8%	90.9%	0.17
Body mass index (kg/m^2)	34.8 ± 7.5	35.1 ± 8.5	0.88
ESS score	10.3 ± 5.6	9.6 ± 4.5	0.67
Myocardial infarction	12.1%	12.1%	1.00
Hypertension	48.5%	54.6%	0.62
Heart failure	3.0%	15.2%	0.20
Atrial fibrillation	21.2%	18.2%	0.76
Restless legs syndrome	9.1%	15.2%	0.71
Insomnia	18.2%	24.2%	0.55
Chronic opioid use	15.2%	12.1%	1.00

Data are presented as means ± SD or percentages, as appropriate. ASV, adaptive servoventilation; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale.

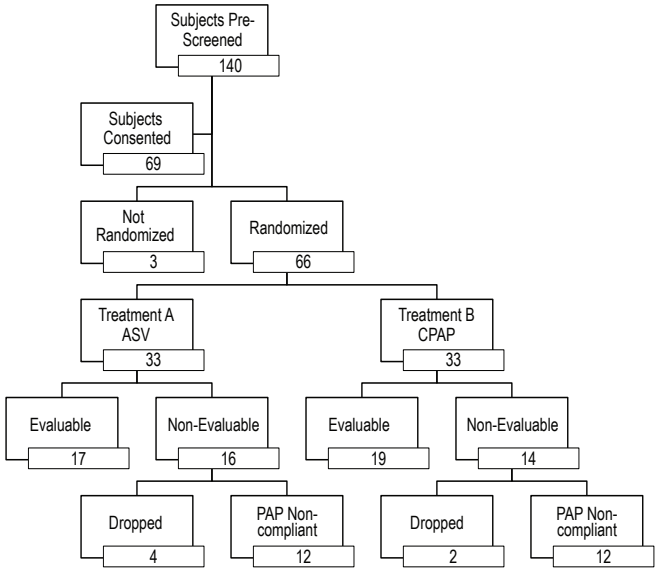

Figure 2—Participant flow chart. ASV, adaptive servoventilation; CPAP, continuous positive airway pressure; PAP, positive airway pressure.

Table 3—Polysomnographic variables in 60 participants with complex sleep apnea randomized into adaptive servoventilation (ASV) and continuous positive airway pressure (CPAP) groups who completed the study (ASV n = 29, CPAP n = 31).

Variable	Polysomnographic Data: Diagnostic Study ASV	Diagnostic Study CPAP	Cpap Titration ASV	Cpap Titration CPAP	Randomization Study ASV	Randomization Study CPAP	Final Study (90 days) ASV	Final Study (90 days) CPAP
Total sleep time (min)	213.9 ± 120.8	186.0 ± 103.7	204.3 ± 103.0	187.8 ± 90.4	336.3 ± 86.0	356.2 ± 62.6	363.5 ± 55.9	373.1 ± 65.5
Sleep efficiency (%)	75.1 ± 15.2	72.3 ± 16.7	71.8 ± 15.3	70.2 ± 16.2	73.5 ± 16.0	77.0 ± 13.8	80.5 ± 10.1	80.7 ± 13.4
Apnea-hypopnea index (h^{-1})	35.1 ± 25.3	37.9 ± 29.3	35.7 ± 23.6	33.2 ± 17.9	10.9 ± 14.8*	19.5 ± 17.6*	4.4 ± 9.6*	9.9 ± 11.1*
Central apnea index (h^{-1})	2.7 ± 4.6	3.0 ± 5.5	25.2 ± 19.1	22.2 ± 12.6	2.0 ± 5.8*	11.5 ± 15.1*	0.7 ± 3.4*	4.8 ± 6.4*
Obstructive-mixed apnea index (h^{-1})	13.4 ± 18.0	16.0 ± 19.7	2.0 ± 4.4*	3.8 ± 5.5*	0.7 ± 3.2*	1.7 ± 2.6*	0.4 ± 1.3*	0.9 ± 1.8*
Total arousal index (h^{-1})	46.3 ± 29.1	43.4 ± 25.2	36.9 ± 25.8	38.7 ± 19.2	29.4 ± 20.3	29.7 ± 14.2	25.9 ± 13.5	24.4 ± 15.4
Respiratory arousal index (h^{-1})	35.0 + 27.0	31.7 ± 25.4	21.8 ± 15.4	27.3 ± 18.0	9.6 ± 13.5*	14.9 ± 11.9*	5.7 ± 9.7*	8.5 ± 7.2*
Total sleep time at SpO_2 < 90% (% of TST)	12.7 ± 16.1	14.2 ± 25.7	5.4 ± 9.3	6.3 ± 10.3	6.7 ± 10.2	5.9 ± 10.3	6.2 ± 14.9	7.9 ± 14.0
CPAP/EEP setting (cm H_2O)							8.3 ± 2.3*	9.6 ± 2.6*

Data are presented as means ± SD or percentages, as appropriate. * P < 0.05 for difference between ASV and CPAP. TST, total sleep time; EEP, end-expiratory pressure.

randomization. Sixty-six participants (age 59.2 ± 12.9 y, body mass index [BMI] 35.0 ± 8.0, ESS 10 ± 5) were randomized. Thirty-six participants (17 randomized to ASV and 19 participants to CPAP) were considered evaluable. Demographic data and comorbidities of participants in the trial are shown in Table 2. No statistical differences were noted.

At baseline, participants had severe OSA with a mean AHI of 37.8 ± 27.8 (CAI 3.2 ± 5.8). The AHI on best CPAP was 37.1 ± 24.9, with a residual CAI 29.7 ± 25.0 (Table 3). Following the randomization into the treatment groups, the baseline AHI on ASV decreased to 4.7 ± 8.1 (CAI 1.1 ± 3.7) and on CPAP to 14.1 ± 20.7 (CAI 8.8 ± 16.3) (AHI, P = 0.0003; CAI, P < 0.0001). Additional information about CompSAS resolution is available in the supplemental material.

Figure 2 shows participant dropout and retention within the study arms. Six participants dropped out of the study. Additional information about dropped participants is in the supplemental material. Device usage monitoring for all 60 participants with data at visit 4 showed similar compliance in ASV and CPAP groups (4.7 ± 2.2 h versus 4.5 ± 2.5 h, respectively; P > 0.05).

Both the AHI and CAI were significantly lower at final PSG for the ASV group than the CPAP group: (4.4 ± 9.6 versus 9.9 ± 11.1, P = 0.0024 and 0.7 ± 3.4 versus 4.8 ± 6.4, P < 0.0001, respectively), but the difference in these means was not ≥ 10 (Figure 3). In an intention-to-treat analysis, using AHI < 10 as a clinically relevant objective, control of SDB was attained in 26 of 29 participants (89.7%) of the ASV group and in 20 of 31 participants (64.5%) in the CPAP group (P = 0.0214, Figure 4). Among evaluable (compliant) participants, 16 of 17 (94.1%) of those in the ASV group and 14 of 19 (73.7%) in the CPAP group (P = 0.1821) had AHI < 10. Similarly, among the 36 evaluable participants, AHI and CAI were lower in the ASV group than in CPAP group (2.4 ± 3.8 versus 8.1 ± 12.1, P = 0.0487 and 0.1 ± 0.2 versus 2.8 ± 4.3, P < 0.0001, respectively).

We obtained PAP download estimates of the residual AHI from the ResLink™ data card at day 30 and day 90. These results were

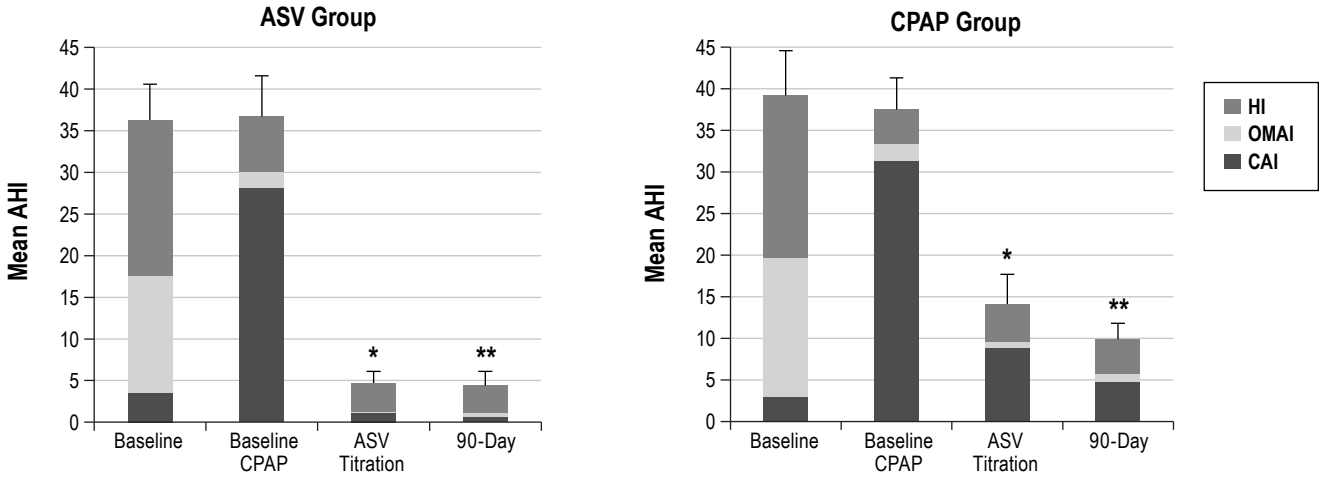

Figure 3—Polysomnographic variables in participants with CompSAS prior to therapy, at randomization, and after 90 days of treatment, with either continuous positive airway pressure (CPAP) or adaptive servoventilation (ASV). AHI, apnea-hypopnea index; HI, hypopnea index; OMAI, obstructive/mixed apnea index; CAI, central apnea index. * Mean AHI at Titration, ASV vs CPAP, P = 0.0003. ** Mean AHI at 90-day, ASV vs CPAP, P = 0.0024.

partitioned into periods to possibly determine the timing of apnea resolution. The residual AHI from days 1–7, days 22–30, and days 61–90 for the evaluable CPAP participants was 14.9 ± 8.8, 9.7 ± 4.9, and 11.5 ± 9.2, respectively. For evaluable participants undergoing ASV, the corresponding values were 7.6 ± 6.6, 5.8 ± 5.9, and 5.1 ± 4.9, respectively. Figure 5 shows individual AHI values across the four PSGs. These data show that participants randomized to ASV gain better and more reliable control of AHI at titration and for the remainder of 90 days. This finding is even more evidenced in evaluable participants (supplemental material).

Participants in both groups experienced a significant improvement in daytime sleepiness, and there were no statistical differences in ESS or VAS scores between the ASV and CPAP group either at randomization or at 90 days of therapy. In both groups, there were similar and minimal changes in health-related quality of life, as measured by SAQLI (Table 4).

In search of the predictors of adequate response to CPAP, defined as attaining an AHI < 10 at final PSG, we correlated demographic data of all participants randomized into the CPAP group with the AHI at the final PSG. None of the baseline clinical or PSG frequency indices (AHI, CAI, obstructive apnea index, arousal index) correlated to the AHI at the final PSG; the only variable that correlated with suboptimal CPAP response was higher saturation of oxygen during the diagnostic study.

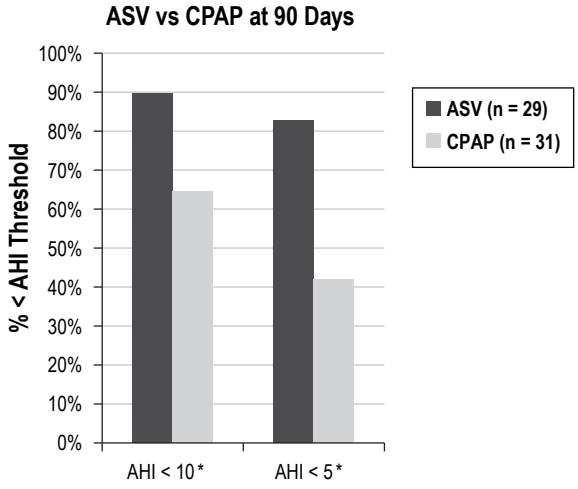

Figure 4—Total AHI at 90 days in participants randomized to adaptive servoventilation (ASV) and continuous positive airway pressure (CPAP). AHI, apnea-hypopnea index. * P < 0.05.

DISCUSSION

Since the description of complex disordered breathing pattern by Gilmartin et al. in 2005[1] and coining of the term "complex sleep apnea" by Morgenthaler et al.,[2] there has been much debate about optimal treatment for these patients. Numerous studies have confirmed that, in patients with CompSAS, CPAP is inferior to bilevel devices (especially those equipped with adaptive servo technology) in acutely controlling sleep disordered breathing.[9–12,17,18,25] However, others have raised an argument that use of adaptive servo technology is not warranted, given a fourfold higher price than CPAP on average[26] and a tendency for complex sleep apnea to resolve over time in many patients with CompSAS who use CPAP.[27]

We supply important information for this debate. In a randomized, single-blind, prospective study carried out over a 3-mo period, we have shown that compared to CPAP, application of ASV led to better control of all SDB both acutely, and after 3 mo of therapy. Furthermore, we showed that 35.5% of participants treated with CPAP did not achieve an AHI < 10 at 3 mo of therapy. We further demonstrated that inadequate improvement in AHI in many participants treated with CPAP was evident from 1 w to 90 days (Figure 5). These are novel findings that were obtained in a wide spectrum of patients with CompSAS. In contrast to the prior studies, these data were obtained in a prospective, randomized, controlled trial, and were less subject to selection and dropout bias.[6,8] Additionally, in contrast to these prior retrospective studies,[6] we had a relatively lower dropout rate (9.1%). Compliance rates in our study were comparable to that in other studies.

Table 4—Secondary outcome comparisons in patients treated with adaptive servoventilation (ASV) and continuous positive airway pressure (CPAP).

	ASV		CPAP		
Measured Variable	**Mean ± SD**	**Median (N)**	**Mean ± SD**	**Median (N)**	**P-value**
Δ ESS	-2.7 ± 6.1	-2.0 (28)	-2.0 ± 5.2	-3.0 (31)	0.97
Δ SAQLI	0.1 ± 1.0	0.2 (30)	0.1 ± 0.8	0.0 (31)	0.77
Average daily usage (h)	4.7 ± 2.2	5.6 (31)	4.5 ± 2.5	5.1 (33)	0.75
How refreshed did you feel after waking in the morning? (VAS) (0 = Exhausted, 100 = Very Refreshed)	68.8 ± 21.3	70.0 (30)	65.2 ± 19.7	65.0 (31)	0.50
How restful was your sleep? (VAS) (0 = Very Restless, 100 = Very Restful)	67.9 ± 20.5	68.5 (30)	62.1 ± 23.9	63.0 (31)	0.31

Δ ESS, change in Epworth Sleepiness Scale score; Δ SAQLI, change in Calgary Sleep Apnea Quality of Life Index; VAS, visual analog scale.

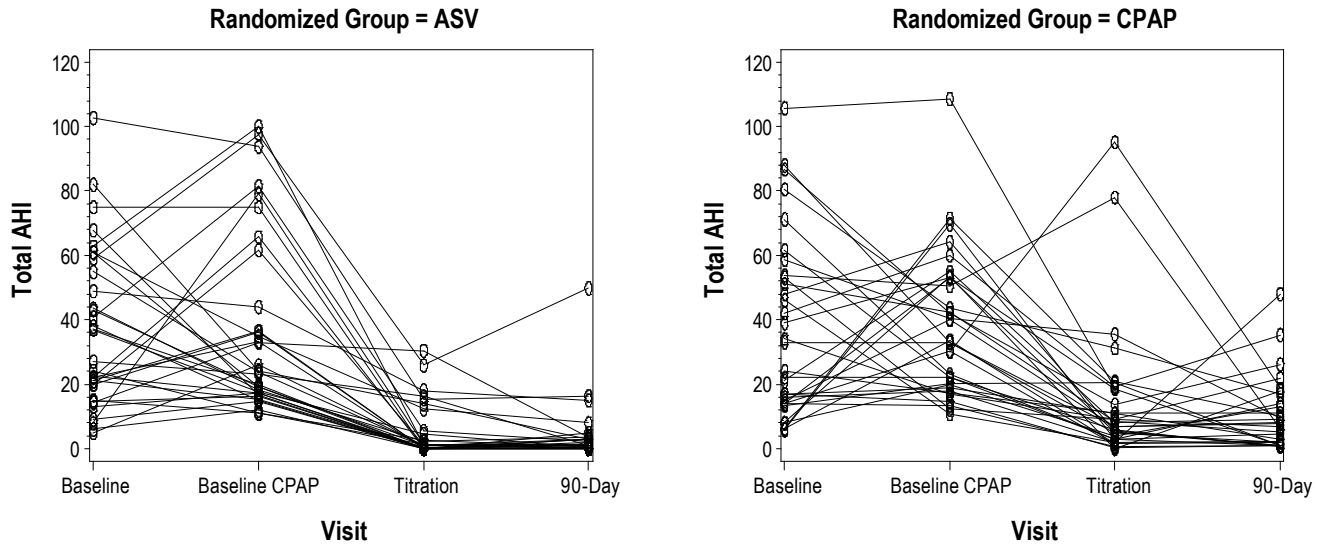

Figure 5—Total apnea-hypopnea index (AHI) at each polysomnography visit for participants randomized to adaptive servoventilation (ASV) and continuous positive airway pressure (CPAP).

One of the goals considered important in treating sleep apnea is normalization of indices of SDB. In studies of patients with OSA, optimally controlled SDB had better health outcomes than those with residual SDB.[28–30] In patients with heart failure and CSA, subgroup analysis indicated that patients with controlled SDB had improved cardiovascular outcomes.[31] Finally, incomplete control of SDB may be associated with worse subjective tolerance of therapy.[20] These arguments suggest a premium on ensuring that patients with CompSAS obtain control of SDB. Based on our data, one may expect that approximately one third (with a goal AHI ≤ 10) to two thirds (with goal AHI ≤ 5) of patients in whom management is attempted with CPAP alone may remain inadequately controlled (Figures 4 and 5).

We looked for patient characteristics that might predict an ultimately good control of SDB in those patients with CompSAS who are treated with CPAP. Unfortunately, in our analyses we were unable to identify any clinical or PSG features that would predict resolution of CompSAS on CPAP. We believe that the analysis of other variables or physiological responses that are not currently collected during typical clinical and PSG evaluation, such as the measurement of apneic threshold, carbon dioxide (CO_2) reserve, controller gain, gain margin via measurement of end-tidal CO_2, addition of dead space, or responses to hyperventilation by conventional bilevel device or proportional-assist device may be needed to predict this reponse.[32–34]

Another important question is the time course of CPAP response in those patients who ultimately do respond to it. From the literature, this response, based on an improvement of chemoresponsiveness, is probably centrally and not peripherally mediated,[35] and takes days to weeks. If this process were shorter, then a series of supervised nightly trials with CPAP to determine its efficacy might turn out to be more effective than supplying the patient with a more expensive ASV device. In our participants, some improvement in central activity was already seen on the randomization PSG (second night of exposure to PAP). Additionally, participants who were compliant with their therapy (ASV or CPAP, "adherent" group) had a higher rate of treatment success. Both obstructive and central events were reduced more with ASV versus CPAP, possibly because of improvement in sleep stage stability and reduction in respiratory arousal index.

Our study had several limitations. The small and heterogeneous sample did not allow for subgroup analysis of

phenotypes, and thus we were unable to address many important issues. We had a slower accrual rate than anticipated because of our conservative CompSAS inclusion criteria and the rigorous requirements of the protocol, and the effects of the economic recession on patients' utilization of sleep services. The small size and design also does not allow evaluation of how economic issues might affect treatment decisions. However, the main goals of this study were actually centered on effectiveness. Patients in both groups experienced similar improvements in ESS, but minimal improvement in SAQLI. We are not sure why our patients did not experience the expected improvements in quality of life. This is the first report of patients with CompSAS evaluated with SAQLI, and perhaps our population had a different disease burden than usual patients with OSA. Finally, our patients were enrolled in a protocolized care plan, and although we allowed adjustment of interfaces and headgear, we did not adjust pressures after initial set-up. In clinical practice, one might consider adjustment of CPAP or EEP if one encountered new or different breathing patterns, such as persistent obstructive apneas. In our patients, the final mean obstructive-mixed apnea index was 0.9 for CPAP group and 0.4 for ASV group at 90 days (Table 3), making it fairly unlikely that many adjustments would have been needed.

In conclusion, we have shown that CompSAS resolves in only about one third to two thirds of patients treated with CPAP, and that ASV is superior to CPAP in both acute and long-term control of SDB. Further research should focus on expanding clinical and physiological evaluation of patients with CompSAS to better define the subset of patients that are unlikely to benefit from CPAP and who require more advanced forms of PAP therapy.

ABBREVIATIONS

AHI, apnea hypopnea index
AI, arousal index
ASV, adaptive servoventilator, adaptive servoventilation
BMI, body mass index
BPAP, bilevel positive airway pressure
CAI, central apnea index
CompSAS, complex sleep apnea syndrome
CPAP, continuous positive airway pressure
CSA, central sleep apnea syndrome
ESS, Epworth sleepiness scale
OAI, obstructive apnea index
OSA, obstructive sleep apnea syndrome
PAP, positive airway pressure
PSG, polysomnograms, polysomnography
SAQLI, sleep apnea quality of life index
SDB, sleep disordered breathing
VAS, visual analogue scale

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DISCLOSURE STATEMENT

This work was supported by a grant from the ResMed Science Center, ResMed Corp. Other than this work, Drs. Morgenthaler, Kuzniar, McLain, and Goldberg have indicated no other financial conflicts of interest. Dr. Wolfe has served as a consultant for ResMed Inc. and Hill-Rom. Leslee Willes has served as a consultant for ResMed, Inc., and was contracted to perform the statistical analysis for this work.

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SUPPLEMENTAL MATERIAL

PARTICIPATING CENTERS AND PATIENT ACCRUAL

This was a randomized, controlled, single-blind multicenter study. Table S1 lists the sites, principal investigator at those sites, and accrual rates for each site.

STUDY PROCEDURES

Visits

Clinical visit(s) preceding enrollment

Participants were recruited from center patients referred for suspected obstructive sleep apnea. Patients underwent clinically motivated interviews and polysomnograms (PSGs), many of which were split-study PSGs (first portion diagnostic, second portion continuous positive airway pressure [CPAP] titration). Patients meeting clinical criteria for CompSAS and generally meeting inclusion and exclusion criteria were invited to participate in the study. Once consent was obtained, the qualifying PSGs were sent to the Core Lab for individual analysis to confirm the presence of CompSAS according to the study criteria (see Methods section in manuscript).

Visit 1

After the Core Lab confirmed the CompSAS diagnosis, participants completed a site visit and confirmed all inclusion and exclusion criteria, and completed the Epworth Sleepiness Scale (ESS) and the Calgary Sleep Apnea Quality of Life Index (SAQLI).[1,2] Candidates were provided education regarding sleep apnea, mask fittings, daytime acclamation to positive airway pressure (PAP), site contact information for any needed troubleshooting, and were then centrally randomized in blocks of two to a treatment group. They completed a full-night titration PSG on the therapy mode to which they were randomized. We attempted to conceal allocations from the participants, instructing technologists and study coordinators to remain vague regarding type of settings applied to the positive airway pressure device. Following the titration PSG, participants were set up with their PAP therapy and instructed to use their therapy over the next 3 mo.

Visit 2

Visit 2 was a follow-up phone call by the site completed 2 weeks after PAP set-up. Acclimation to PAP use was reviewed; any issues with the mask, VPAP Adapt SV, or HumidAire 2i (both ResMed Inc., San Diego, CA) were discussed. If needed, participants could return to the site to assess any other issues with treatment.

Visit 3

Visit 3 was to be completed within 30 days of PAP set-up. Participants were to return to the site and complete a PAP Comfort Questionnaire (Visual Analog Scale) and the SAQLI. PAP usage was downloaded through the data card attached

Table S1—Accrual rates at participating centers

			# of Participants					
			Randomized			Evaluable		
Site #	Principal investigator	Site Name	ASV	CPAP	Total	ASV	CPAP	Total
01	Timothy Morgenthaler, MD	Mayo Center for Sleep Medicine, Rochester, MN	15	15	30	8	11	19
02	William McLain, MD	SleepMed-Columbia SC	4	3	7	2	2	4
03	Tomasz Kuzniar, MD; Shilpa Rahangdale, MD	NorthShore University Healthcare Research Institute, Evanston, IL	7	7	14	5	3	8
04	Lisa Wolfe, MD	Northwestern University, Chicago, IL	4	3	7	1	2	3
05	Rochelle Goldberg, MD	REM Medical, Phoenix, AZ	1	2	3	0	0	0
06	June Fry, MD, PhD	Center for Sleep Medicine, Lafayette Hill, PA	2	3	5	1	1	2
Total			33	33	66	17	19	36

ASV, adaptive servoventilation; CPAP, continuous positive airway pressure.

Table S2—Epworth Sleepiness Scale results

	Randomized					Evaluable				
	ASV		CPAP			ASV		CPAP		
ESS	Mean ± SD	Median (N)	Mean ± SD	Median (N)	P value	Mean ± SD	Median (N)	Mean ± SD	Median (N)	P value
Baseline	10.3 ± 5.6	9.0 (33)	9.6 ± 4.5	9.0 (33)	0.67	9.2 ± 5.1	9.0 (17)	9.6 ± 4.3	10.0 (19)	0.81
30 Days	7.8 ± 5.2	7.5 (32)	7.6 ± 3.5	8.0 (33)	0.77	7.1 ± 5.1	6.0 (17)	7.1 ± 3.0	7.0 (19)	0.85
90 Days	7.4 ± 5.5	6.5 (28)	7.6 ± 5.3	6.0 (31)	0.83	6.9 ± 4.7	7.0 (15)	8.1 ± 6.3	6.0 (19)	0.82

ASV, adaptive servoventilation; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; SD, standard deviation.

to the VPAP Adapt SV and reviewed with the participants. Adverse events and any other concerns with PAP therapy were discussed and recorded.

Visit 4

The final visit was to be completed within 90 days of PAP set-up. Participants completed a final PSG on their treatment mode and final PAP Comfort, ESS, blinding assessment, and SAQLI questionnaires. PAP usage data were downloaded one final time, and subsequent treatment after the study was discussed with the site investigator.

Measurement Questionnaires and Results

At visits 1 and 4 participants were asked to complete the ESS and the Calgary SAQLI.[2] The ESS is an eight-question instrument that seeks to gauge the degree of subjective sleepiness in the recent weeks prior to filling out the questionnaire, and has been found responsive to interventions in patients with obstructive sleep apnea (OSA.)[3] The results from the ESS are shown in Table S2. ESS improved with treatment a similar amount with both treatments.

The SAQLI results for all randomized subjects are shown in Table S3. The mean change from baseline in SAQLI for both

Table S3—Calgary Sleep Apnea Quality of Life Index results for randomized participants

	Baseline			30 Days		90 Days	
SAQLI Results	**ASV (N = 33)**	**CPAP (N = 33)**	**P value**	**ASV**	**CPAP**	**ASV**	**CPAP**
Domain A	4.7 ± 1.3	4.8 ± 1.2	1.00	5.4 ± 1.1 (32)	5.3 ± 1.1 (33)	5.6 ± 1.1 (30)	5.3 ± 1.2 (31)
Domain B	5.5 ± 1.3	5.4 ± 1.1	0.37	6.0 ± 1.1 (32)	5.9 ± 1.2 (32)	6.1 ± 0.9 (30)	6.0 ± 1.0 (31)
Domain C	5.2 ± 1.4	4.8 ± 1.2	0.12	5.6 ± 1.2 (32)	5.4 ± 1.2 (33)	5.7 ± 1.0 (30)	5.4 ± 1.2 (31)
Domain D	3.1 ± 1.5	3.0 ± 0.8	0.72	3.1 ± 1.3 (30)	3.2 ± 1.3 (32)	3.2 ± 1.3 (29)	3.1 ± 1.3 (31)
Total SAQLI	4.6 ± 1.2	4.5 ± 0.9	0.36	4.6 ± 1.0 (32)	4.5 ± 1.3 (32)	4.7 ± 0.9 (30)	4.6 ± 1.1 (31)

ASV, adaptive servoventilation; CPAP, continuous positive airway pressure; SAQLI, Sleep Apnea Quality of Life Index.

Table S4—Positive airway pressure comfort visual analog scale results for randomized participants

	30 Days			90 Days		
	ASV	**CPAP**		**ASV**	**CPAP**	
Parameter (mm)	**VAS ± SD Median (N)**	**VAS ± SD Median (N)**	**P value**	**VAS ± SD Median (N)**	**VAS ± SD Median (N)**	**P value**
How satisfied were you with positive airway pressure? (0 = Very Dissatisfied, 100 = Very Satisfied)	59.6 ± 24.5 57.0 (31)	67.6 ± 22.7 75.0 (31)	0.19	68.3 ± 19.9 71.5 (30)	70.4 ± 21.3 76.0 (31)	0.69
How satisfied were you with the mask? (0 = Very Dissatisfied, 100 = Very Satisfied)	51.9 ± 26.2 49.0 (31)	57.9 ± 25.1 55.0 (31)	0.35	61.7 ± 25.9 64.5 (30)	60.7 ± 21.0 63.5 (30)	0.87
How refreshed did you feel after waking in the morning? (0 = Exhausted, 100 = Very Refreshed)	63.3 ± 20.8 58.0 (31)	58.1 ± 23.6 59.0 (31)	0.36	68.8 ± 21.3 70.0 (30)	65.2 ± 19.7 65.0 (31)	0.49
How restful was your sleep? (0 = Very Restless, 100 = Very Restful)	60.9 ± 21.0 57.0 (31)	56.8 ± 21.5 61.0 (31)	0.45	67.9 ± 20.5 68.5 (30)	62.1 ± 23.9 63.0 (31)	0.31
Did you have trouble getting to sleep? (0 = No Trouble, 100 = Severe Trouble)	33.9 ± 28.6 26.0 (31)	23.2 ± 22.5 15.0 (31)	0.11	27.4 ± 22.9 23.5 (30)	25.0 ± 24.1 16.0 (31)	0.69
Did you have trouble staying asleep during the night? (0 = No Trouble, 100 = Severe Trouble)	35.8 ± 23.4 30.0 (31)	47.7 ± 27.0 44.0 (31)	0.07	34.8 ± 22.4 35.0 (30)	40.6 ± 29.6 41.0 (31)	0.40
Did you have trouble with mask leak? (0 = No Leak, 100 = Severe Leak)	43.7 ± 25.8 36.5 (30)	38.2 ± 24.6 35.0 (31)	0.40	42.8 ± 26.9 49.0 (30)	38.2 ± 24.3 34.0 (31)	0.48
Did you have discomfort with the pressure? (0 = No Discomfort, 100 = Severe Discomfort)	30.1 ± 25.9 20.0 (31)	25.7 ± 23.5 18.0 (31)	0.49	19.8 ± 21.0 12.0 (30)	25.1 ± 24.2 18.0 (31)	0.36

ASV, adaptive servoventilation; CPAP, continuous positive airway pressure; SD, standard deviation; VAS, visual analog scale.

Table S5—CompSAS physiologic resolution in participants randomized to CPAP or ASV

	Randomized			Evaluable		
	ASV	**CPAP**	**P value**	**ASV**	**CPAP**	**P value**
CompSAS physiologic resolution (%)	77.4% (24/31)	51.5% (17/33)	0.02	94.1% (16/17)	63.2% (12/19)	0.04

ASV, adaptive servoventilation; CPAP, continuous positive airway pressure.

the randomized and evaluable groups at 90 days was not statistically significant.

At visit 3 and visit 4, patients were assessed using a PAP Comfort Questionnaire (Visual Analog Scale construct). The questionnaire was composed of eight questions, and the subject could mark their answers to the questions along a continuous scale ranging from 0 to 100. The results for randomized participants are shown in Table S4. There were no statistically significant differences across any of the questions between the adaptive servoventilation (ASV) and CPAP group at 30 or 90 days.

Polysomnographic Data Management

Core Lab

A Core Lab (Mayo Clinic, Rochester, MN) was utilized for the study, to review all PSG studies completed. Specifically, the Core Lab reviewed the following PSGs:

- Clinical diagnostic (completed prior to visit 1 to confirm inclusion/exclusion criteria)
- Clinical CPAP titration (completed prior to visit 1 to confirm inclusion/exclusion criteria)
- Research PAP titration (completed at visit 1 using the randomized treatment)
- Final (completed at visit 4)

Before centers were enrolled in the trial, we affirmed that standard recommended signals were acquired,[24] and that data could be shared with the Core Lab (Mayo Clinic Center for Sleep Medicine), and that site scoring agreed with the Core Lab within set specifications. Sites converted PSGs to European Data Format (EDF) and electronically conveyed them to the Core Lab, along with copies of the corresponding technician notes. The PSGs were analyzed and scored by registered PSG technologists on Gamma software (Grass Technologies Corporation, West Warwick, RI) at the Core Lab, adhering to standardized scoring criteria.[24] Between-technologist scoring agreement was tested in an ongoing fashion to affirm reproducibility. One board-certified sleep specialist (TIM) provided confirmatory clinical review and audit for each PSG. PSG reports were sent back to the sites after each review. Discrepancies in scoring, if any, were discussed between the Core Lab sleep specialists and the site specialist until agreement was achieved. The Core Lab confirmed final complex sleep apnea syndrome (CompSAS) diagnosis and that the CPAP pressure required to treat the participants was less than 15 cm H_2O prior to visit 1 of the protocol.

Subsequent treatment titrations were scored by the Core Lab, who determined the optimal treatment settings for assigned modalities. CPAP and ASV were titrated according to a standardized protocol at each facility. Determining best pressure settings was a pragmatic process that involved choosing a pressure setting to efficiently treat obstructive events and respiratory effort-related arousals, and as low as possible in order to minimize the emergence of central apneas (in the event that they are exacerbated by pressure).

The Core Lab review of the final PSG determined CompSAS physiologic resolution. Sleep disordered breathing was considered physiologically resolved if the apnea-hypopnea index (AHI) was ≤ 10 and there was no significant residual periodic breathing as detected by inspection of the summation of respiratory inductance plethysmography (RIP) and/or the pressure signal from the flow generator in the case of participants treated with ASV.

All PSG and clinical data were collected on standardized forms and entered into a protected database.

Equipment

The VPAP Adapt SV's algorithm works with minute ventilation. By monitoring an individual's minute ventilation, target ventilation is calculated and maintained. In conjunction with the target minute ventilation, pressure support is adjusted as needed. If ventilation decreases from the target, pressure support increases and is monitored for its effect on minute ventilation. Through the early detection and response to changes in

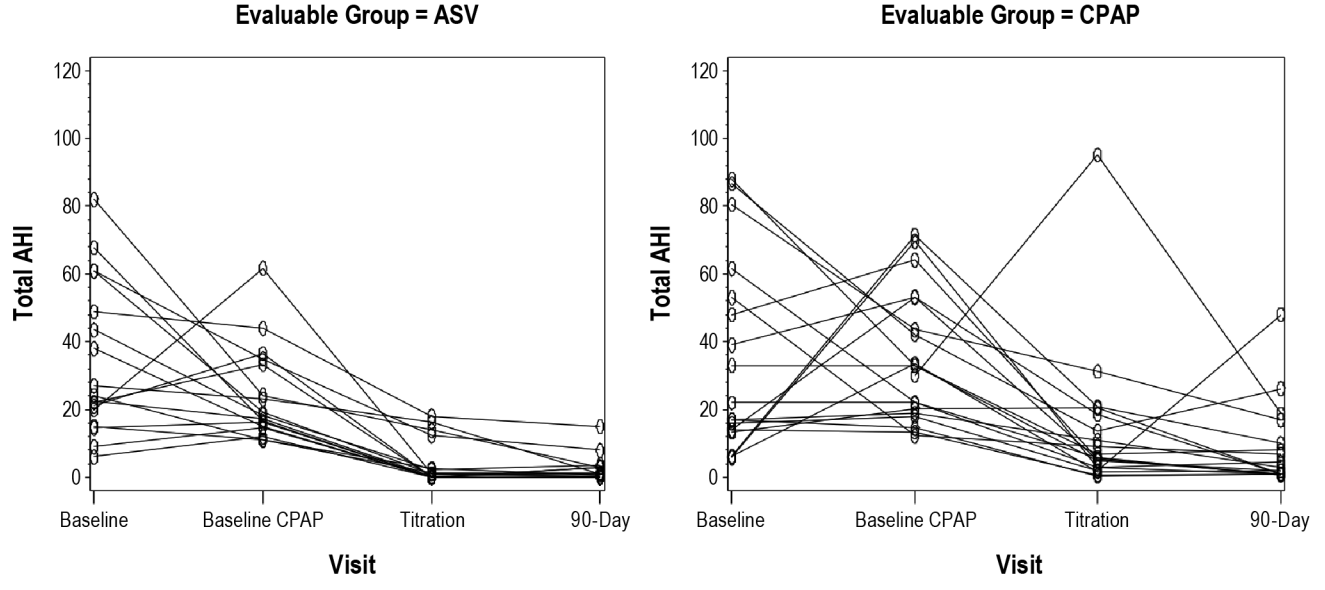

Figure S1—Improvement in AHI in evaluable participants assigned to adaptive servoventilation (ASV) or continuous positive airway pressure (CPAP).

Table S6—Treatment adherence in study participants

	Randomized					Evaluable				
	ASV		CPAP			ASV		CPAP		
Day range = 1–90	Mean ± SD	Median (N)	Mean ± SD	Median (N)	P value	Mean ± SD	Median (N)	Mean ± SD	Median (N)	P value
Average daily usage	4.7 ± 2.2	5.6 (31)	4.5 ± 2.5	5.1 (33)		6.4 ± 1.1	6.0 (17)	6.4 ± 1.1	6.3 (19)	
Median	5.7 ± 1.8	6.1 (31)	5.2 ± 2.4	5.5 (33)		6.9 ± 1.0	6.9 (17)	6.9 ± 1.0	6.9 (19)	
% Used days ≥ 4 h	63.6 ± 30.5	74.0 (31)	60.0 ± 35.4	76.0 (33)		87.2 ± 10.5	88.0 (17)	86.4 ± 8.6	86.0 (19)	
Apnea index (events/h)	0.4 ± 1.0	0.0 (31)	2.9 ± 4.9	1.1 (32)	< 0.0001	0.2 ± 0.6	0.0 (17)	2.3 ± 3.0	1.3 (19)	< 0.0001
AHI (events/h)	8.7 ± 10.9	5.7 (31)	11.3 ± 7.6	10.2 (32)	0.0158	5.5 ± 5.3	3.9 (17)	10.6 ± 6.2	10.1 (19)	0.0078
Mask interface										
Oronasal	58.1% (18)		45.5% (15)			47.1% (8)		36.8% (7)		
Nasal	41.9% (13)		54.5% (18)			52.9% (9)		63.2% (12)		

AHI, apnea-hypopnea index; ASV, adaptive servoventilation; CPAP, continuous positive airway pressure.

Table S7—Reasons for participant withdrawal

Reason	Not Randomized	ASV	CPAP	Total
Difficulty with mask/ unable to tolerate device	–	2	1	3
Not interested	3	1	1	5
Did not complete final PSG	–	1	0	1
Total	3	4	2	9

ASV, adaptive servoventilation; CPAP, continuous positive airway pressure; PSG, polysomnography.

Table S8—Internal review board data

Site	Internal Review Board Numbers
Mayo Center for Sleep Medicine, Rochester, MN	08-007228
SleepMed-Columbia SC	00000533
NorthShore University Healthcare Research Institute, Evanston, IL	IRB00000549, IRB00005002, IRB00006333
Northwestern University, Chicago, IL	IORG0000247
REM Medical, Phoenix, AZ	00000533
Center for Sleep Medicine, Lafayette Hill, PA	00000533

ventilation, desired ventilation levels can be maintained, thus removing the occurrence of central breathing disorders.

The ResLink™ (ResMed Inc, San Diego, CA) is an accessory to ResMed flow generators. When connected to the flow generator, it collects PAP usage data through a data card. The data cards were downloaded and viewed through ResScan™ software (ResMed Inc, San Diego, CA).

RESULTS

CompSAS Resolution and Control of Sleep Disordered Breathing

We gauged the response to therapy in two different kinds of analysis: improvement in the AHI, and CompSAS physiologic resolution (according to the method described previously). We found that ASV led to CompSAS physiologic resolution significantly more commonly than CPAP (Table S5).

The AHI also improved earlier and more reliably in evaluable participants randomized to ASV than to CPAP (Figure S1). Note the wide variability in AHI among patients assigned to CPAP compared with ASV.

ResScan™ Data (Treatment Adherence and Estimated Residual Sleep Disordered Breathing)

The VPAP ADAPT SV continuously monitors patient breathing patterns and detected events are stored and indexed to time on therapy. We retrieved these data at various intervals within the 90- day trial. Our hope was to detect when CompSAS resolved. Unfortunately, the output from this version of the flow generator does not permit an accurate assessment of the proportion of periodic breathing nor of the percent of apneas that are central. The results of these downloads from the flow generator are shown in Table S6.

Dropped Participants

Six dropped out of the study: two participants had difficulty with masks, two participants lost interest in the study, one participant was unable to tolerate the device, one for personal reasons. See Table S7.

ETHICAL CONSIDERATIONS

See Table S8.

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APPENDIX: TITRATION PROTOCOLS FOR COMPSAS RESOLUTION STUDY

All study sites used these protocols for titration of PAP.

Initiation of Titration

Initial pressure

CPAP or end-expiratory pressure (EEP) should be set at 5 cm H_2O at the initiation of all studies. In adults who complain about pressure at 5, the initial pressure may be 4 H_2O (if possible). The patient's comments about pressure should be explicitly documented.

Adjustment of pressure prior to sleep onset

Some patients may feel that 5 cm H_2O fails to provide sufficient airflow and experience discomfort resulting in interference with sleep onset. For these patients, titration may commence prior to sleep onset. Pressure should be advanced in the manner described in the next section. If this procedure is done and effective pressure has been reached at sleep onset, then, after sleep has been solidly established, the pressure should be reduced in decrements of 1 cm H_2O at intervals of 2 min until hypopnea or snoring returns or the patient awakens. Pressure should then be incremented again to the optimal level.

Titration of CPAP

Titration of CPAP Protocol

Advancement of pressure: See Figure S2. When the patient is asleep, CPAP pressure should be incremented by 1 cm H_2O at intervals of no less than 2 min until all apnea, hypopnea, snoring, and respiratory effort-related arousals are eliminated. Pressure may be increased to a maximum of 18 cm H_2O (higher pressures require express orders from the physician). If brief arousals continue, pressure should be increased 1-2 cm H_2O to demonstrate whether the arousals are the result of increased upper airway resistance and can be reduced by CPAP. If further increases in pressure increase the frequency of, or lengthen arousals, then pressure should be decreased to a level at which a good compromise is reached between the continuity of sleep and the amount of disordered-breathing events (DBEs) and snoring. If central apnea occurs as pressure is increased, optimize pressure for obstructive events and allow at least 10 min for breathing to stabilize. If the central apnea continues, increment pressure up to an additional 5 cm H_2O (do not exceed 18 cm H_2O) until the central apnea stops. If increasing pressure is not successful, decrease pressure until the central apnea stops or a good compromise is reached between central and obstructive events.

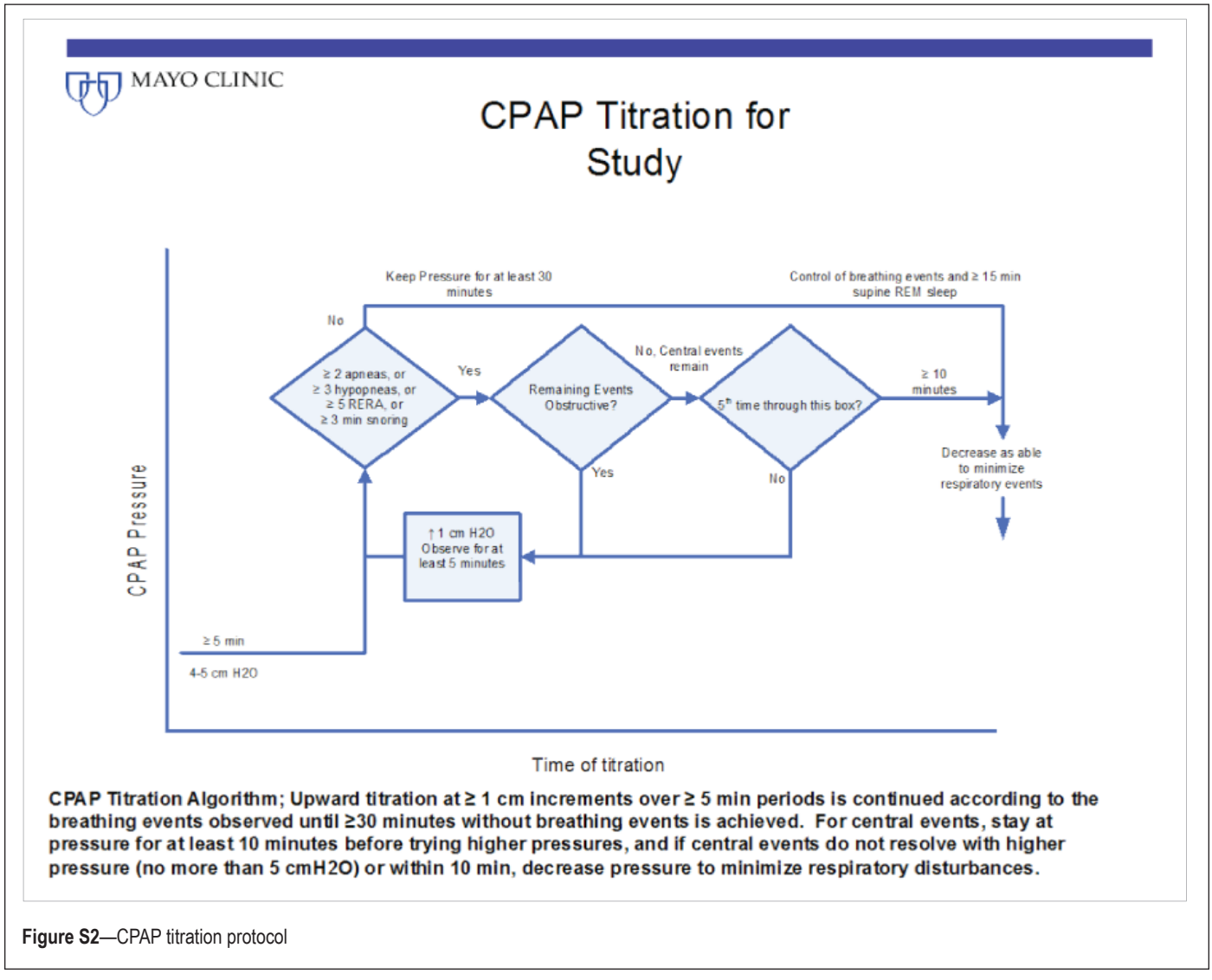

Figure S2—CPAP titration protocol

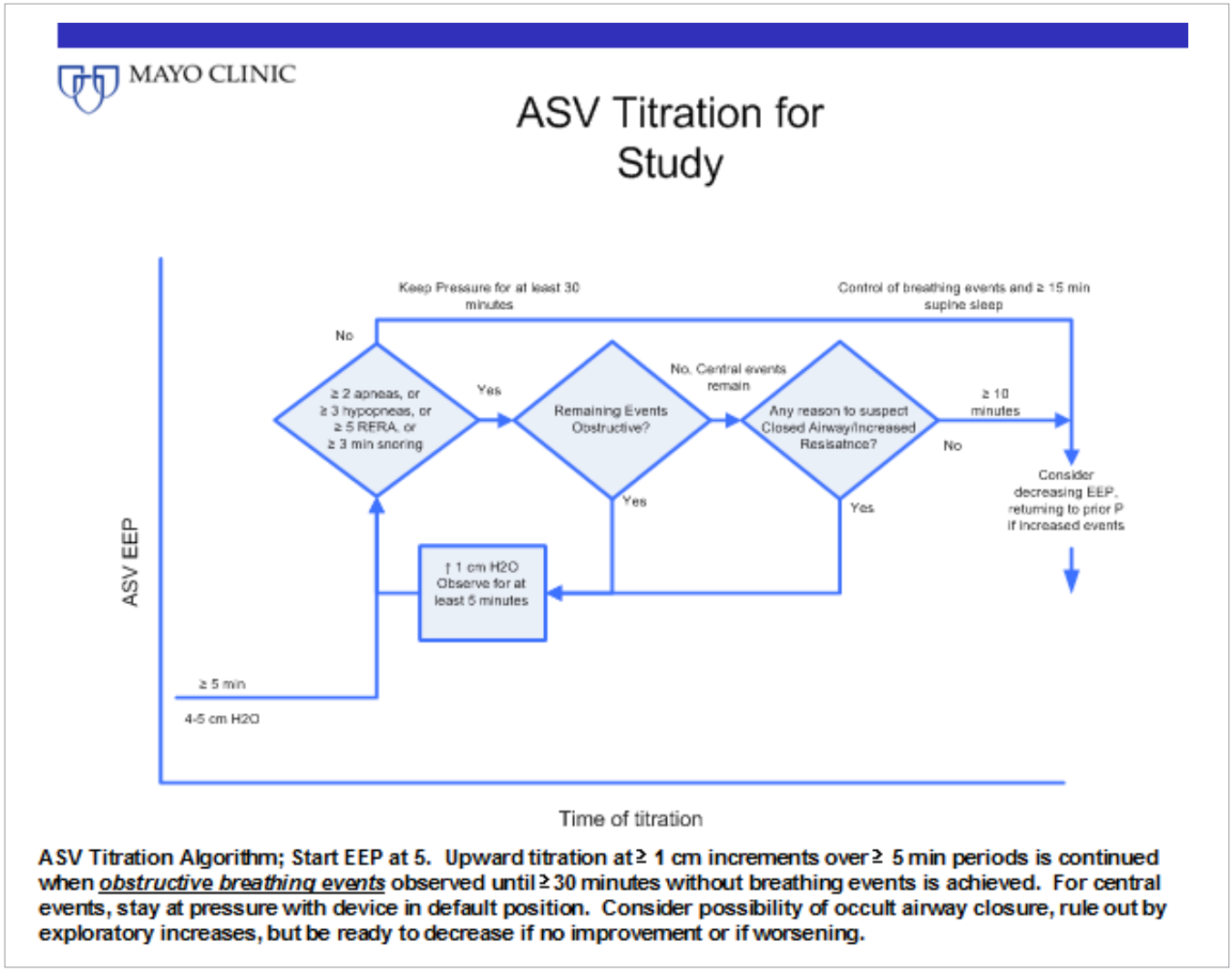

Figure S3—ASV titration protocol

Body position and sleep stage: Have the patient begin the CPAP trial in the supine position, if this is not possible, then after the optimal CPAP pressure is determined, the patient should be asked to sleep on his or her back, if he or she does not do so spontaneously. At least two attempts should be made to have the patient roll on his or her back until a total of at least 10 min is spent on the back (ideally with a portion of that time during rapid eye movement).

Use of chinstraps and full-face masks: Patients should wear whichever style mask that is preferred (nasal versus oronasal). Patients using a nasal interface may experience discomfort, or CPAP may not be effective because of open-mouth breathing. A chin strap may be used on these patients to position the jaw for more effective sealing of the lips. If the chin strap does not reposition the jaw effectively or after resumption CPAP remains ineffective, then a full face mask should be used. Certain patients may have a problem with mouth breathing which is apparent on pre-study evaluation. This information should be noted on the "tech sheet" so that use of a chin strap or full face mask can be initiated at the beginning of the CPAP trial.

ASV Titration

Titration of ASV protocol

See Figure S3. When the patient is asleep, EEP should be incremented by 1 cm H_2O at intervals of no less than 2 min until all obstructive events (clearly obstructive apneas or hypopneas with snoring) are eliminated. Pressure may be increased to a maximum of 15 cm H_2O to achieve this goal. If brief arousals continue, pressure should be increased 1–2 cm H_2O to demonstrate whether the arousals are the result of increased upper airway resistance and can be reduced by EEP. If further increases in pressure increase the frequency of, or lengthen arousals, then pressure should be decreased to a level at which a good compromise is reached between the continuity of sleep and the amount of DBEs and snoring. If central apnea occurs or continues as pressure is increased, allow at least 10 min for breathing to stabilize. If the central apnea continues, explore decreases in pressure until the central apnea stops or a good compromise is reached between pressure and breathing events.