

Complex Sleep Apnea Syndrome: Is It a Unique Clinical Syndrome?

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Study Objectives: Some patients with apparent obstructive sleep apnea hypopnea syndrome (OSAHS) have elimination of obstructive events but emergence of problematic central apneas or Cheyne-Stokes breathing pattern. Patients with this sleep-disordered breathing problem, which for the sake of study we call the “complex sleep apnea syndrome,” are not well characterized. We sought to determine the prevalence of complex sleep apnea syndrome and hypothesized that the clinical characteristics of patients with complex sleep apnea syndrome would more nearly resemble those of patients with central sleep apnea syndrome (CSA) than with those of patients with OSAHS.

Design: Retrospective review

Setting: Sleep disorders center.

Patients or Participants: Two hundred twenty-three adults consecutively referred over 1 month plus 20 consecutive patients diagnosed with CSA.

Interventions: NA.

Measurements and Results: Prevalence of complex sleep apnea syndrome, OSAHS, and CSA in the 1-month sample was 15%, 84%, and 0.4%, respectively. Patients with complex sleep apnea syndrome differed in gender from patients with OSAHS (81% vs 60% men, $p < .05$) but were otherwise similar in sleep and cardiovascular history. Patients with complex sleep apnea syndrome had fewer maintenance-insomnia complaints

(32% vs 79%; $p < .05$) than patients with CSA but were otherwise not significantly different clinically. Diagnostic apnea-hypopnea index for patients with complex sleep apnea syndrome, OSAHS, and CSA was 32.3 ± 26.8 , 20.6 ± 23.7 , and 38.3 ± 36.2 , respectively ($p = .005$). Continuous positive airway pressure suppressed obstructive breathing, but residual apnea-hypopnea index, mostly from central apneas, remained high in patients with complex sleep apnea syndrome and CSA (21.7 ± 18.6 in complex sleep apnea syndrome, 32.9 ± 30.8 in CSA vs 2.14 ± 3.14 in OSAHS; $p < .001$).

Conclusions: Patients with complex sleep apnea syndrome are mostly similar to those with OSAHS until one applies continuous positive airway pressure. They are left with very disrupted breathing and sleep on continuous positive airway pressure. Clinical risk factors don't predict the emergence of complex sleep apnea syndrome, and best treatment is not known.

Keywords: Sleep apnea, mixed central and obstructive; sleep-disordered breathing; sleep hypopnea

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INTRODUCTION

A RECENT TASK FORCE SPONSORED BY THE AMERICAN ACADEMY OF SLEEP MEDICINE, THE EUROPEAN RESPIRATORY SOCIETY, THE AUSTRALASIAN Sleep Association, and the American Thoracic Society made recommendations for the classification of sleep-related breathing disorders.¹ They defined 3 disorders: the obstructive sleep apnea hypopnea syndrome (OSAHS) and 2 syndromes with cyclic nonobstructive breathing patterns, the central sleep apnea-hypopnea syndrome (CSA) and the Cheyne-Stokes breathing syndrome. The report acknowledged the “common clinical experience that some patients exhibit predominantly mixed apneas, while other patients exhibit obstructive apneas that seem to change to central events by alterations in body position or application of positive airway pressure.” They suggested that this complex-pattern breathing abnormality might

indicate a shared pathophysiology, but they did not designate a distinct diagnostic category. Little is known about this unclassified group of patients; they lack a common syndromic definition or clinical or pathophysiologic description. For our purposes, we and others term this type of sleep-disordered breathing “complex sleep apnea syndrome” (CompSAS), which will be formally defined below.²

When patients with CompSAS develop frequent central apneas or a Cheyne-Stokes respiratory pattern after initial application of continuous positive airway pressure (CPAP), their sleep often remains severely fragmented by the persistent or emergent breathing abnormalities.²⁻⁵ In a case series involving similar patients who at first appear to have OSAHS, but who develop significant CSA or Cheyne-Stokes respiration after application of CPAP, Thomas et al indicate that no satisfactory CPAP pressure may be found in these patients who, at best pressures, are left with a respiratory disturbance index of approximately 60 per hour.⁵ They have advocated recognition of “complexity” through use of time-series analysis, usually beyond the clinically available techniques. Further, they acknowledge that such complexity may not be unmasked until application of CPAP.² Since these patients do not respond well to CPAP and, in particular, may not be appropriate candidates for autotitrating devices, it would be useful to clinically identify such patients so that alternate therapeutic approaches could be anticipated. A clinical profile may also help in understanding the pathophysiology involved in the development of unstable breathing patterns. Nonhypercapnic repetitive central apneas and hypopneas are most commonly found in patients with concurrent cardiac disease.^{6,7} Multivariate analysis indicates that,

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in such patients referred to a sleep laboratory, symptoms such as snoring, a clinical indicator of upper airway instability, or body mass index are not predictive of OSAHS over Cheyne-Stokes breathing syndrome. Instead, risk factors for Cheyne-Stokes breathing syndrome included male sex, age over 65 years, lower ejection fractions on echocardiographic examination, and atrial fibrillation.⁸

We hypothesized that, since the differentiating respiratory feature in CompSAS was the development of central apneas or Cheyne Stokes pattern mixed in with or superseding the obstructive pattern, the clinical and polysomnography (PSG) patterns seen in patients with this disorder should more nearly match those in patients with the CSA pattern or Cheyne-Stokes breathing syndrome (which for simplicity we together call central sleep apnea, or CSA) than those with the OSAHS. We undertook to determine the prevalence of the CompSAS in a sleep disorders center. Next, we sought to determine the clinical and PSG features of patients with CompSAS and compare or contrast them with those of patients with OSAHS and CSA.

METHODS AND MATERIALS

Patients

We retrospectively recorded data on history, body mass index, hypertension, diabetes, PSG data, and treatment recommendations on consecutive adult patients (age 18 years and older) referred to the Mayo Clinic Sleep Disorders Center during January of 2004. Two hundred fifty-one patients had PSG studies performed; 223 patients were diagnosed with a sleep-related breathing disorder. Among the patients evaluated in January, only 1 patient had CSA (see definition below). In order to enrich our study population with more patients having CSA, we searched all PSG results from February through June 2004 to identify 20 additional patients with CSA. Thus, we examined the clinical and PSG data for a total of 243 patients (Figure 1). We then excluded all patients with a clinical history of congestive heart failure (CHF) or a left ventricular ejection fraction of 40% or less, leaving 219 patients for analysis.

PSG Techniques

All PSG was performed using a digital polygraph (NCI-LAMONT Medical Inc., Madison, Wisc or Bio-logic Systems Corp., Mundelein, IL). Sleep staging and arousals were scored according to standard methods.⁹⁻¹¹ To analyze airflow, we used the Pro-Tech nasal pressure transducer (Pro-Tech Services, Inc., Mukilteo, WA) and respiratory impedance plethysmography during the diagnostic phase and, when CPAP was applied, the flow channel from the CPAP pneumotachometer plus respiratory impedance plethysmography. Apneas were defined as cessation of airflow for at least 10 seconds, and hypopneas were defined as having significant declines in airflow of at least 10 seconds' duration accompanied by at least a 4% oxyhemoglobin desaturation from the local baseline saturation. Central apneas were those apneas unaccompanied by evidence of respiratory effort. Obstructive apneas were apneas with evidence of respiratory effort. Arousals were classified as respiratory-related arousals if they were associated with apneas or hypopneas or if they were preceded by a reduction in airflow with an oxygen desaturation that did not meet the criteria for a hypopnea. The latter was noted by increasing

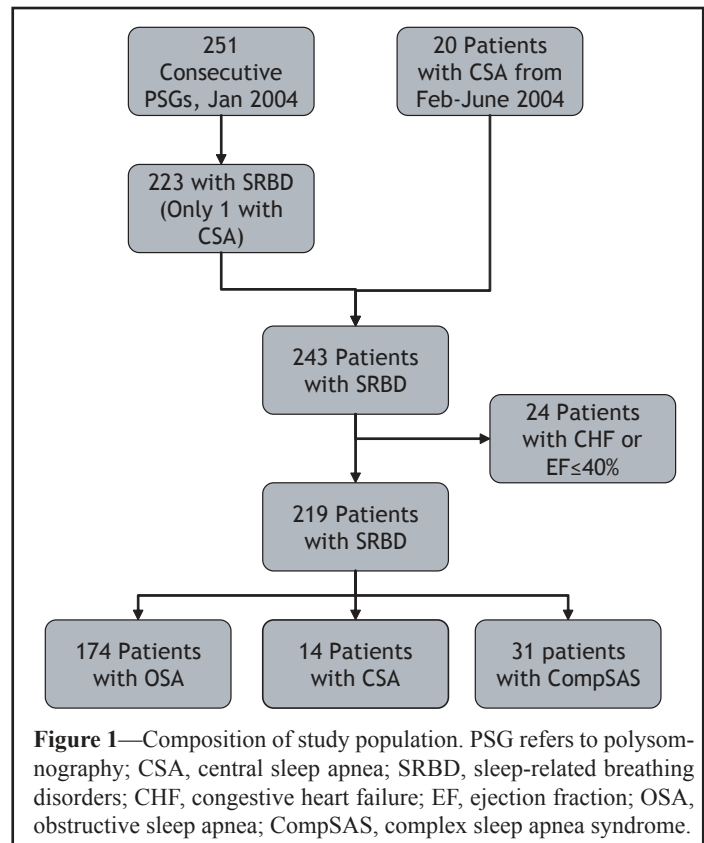


Figure 1—Composition of study population. PSG refers to polysomnography; CSA, central sleep apnea; SRBD, sleep-related breathing disorders; CHF, congestive heart failure; EF, ejection fraction; OSA, obstructive sleep apnea; CompSAS, complex sleep apnea syndrome.

flow limitation on the nasal cannula.^{1,12}

Each study used a “split-night” protocol, starting as a diagnostic study and continuing for a minimum of 2 hours of sleep. At this point, a trial of CPAP was begun if there was either (1) an apnea-hypopnea index (AHI) ≥ 5 (AHI refers to the number of apneas plus hypopneas per hour of sleep) or (2) 10 or more respiratory-related arousals per hour of sleep. A CPAP titration was begun at 4 to 5 cm H₂O and increased in increments of 1 to 2 cm H₂O to eliminate respiratory sleep disturbances. If obstructive events were eliminated but central apneas emerged, pressure was increased up to 5 cm H₂O above the pressure that eliminated obstructive events in order to see if apneas would remit. If this did not succeed in alleviating breathing disturbances, CPAP was returned to the pressure that minimized hypopneas, obstructive apneas, and respiratory-related arousals in both rapid eye movement (REM) and non-REM (NREM) sleep.

Definition of SDBS

Patients were said to have OSAHS if the sum of the obstructive apneas and hypopneas per hour was 5 or greater or if the patient complained of sleepiness and the number of respiratory-related arousals per hour was 10 or greater (consistent with upper airway resistance syndrome). We considered the patients to have CSA when we observed a central apnea index of more than 5 events per hour and at least 50% of the total AHI was purely central in origin, that is, without obstructive components.⁸ Patients were considered to have the CompSAS if CPAP titration eliminated events defining OSAHS, but the residual central apnea index was 5 or more per hour or Cheyne-Stokes respiratory pattern became prominent and disruptive. A typical diagnostic and CPAP-titration PSG tracing of a patient with CompSAS is shown in Figure 2.

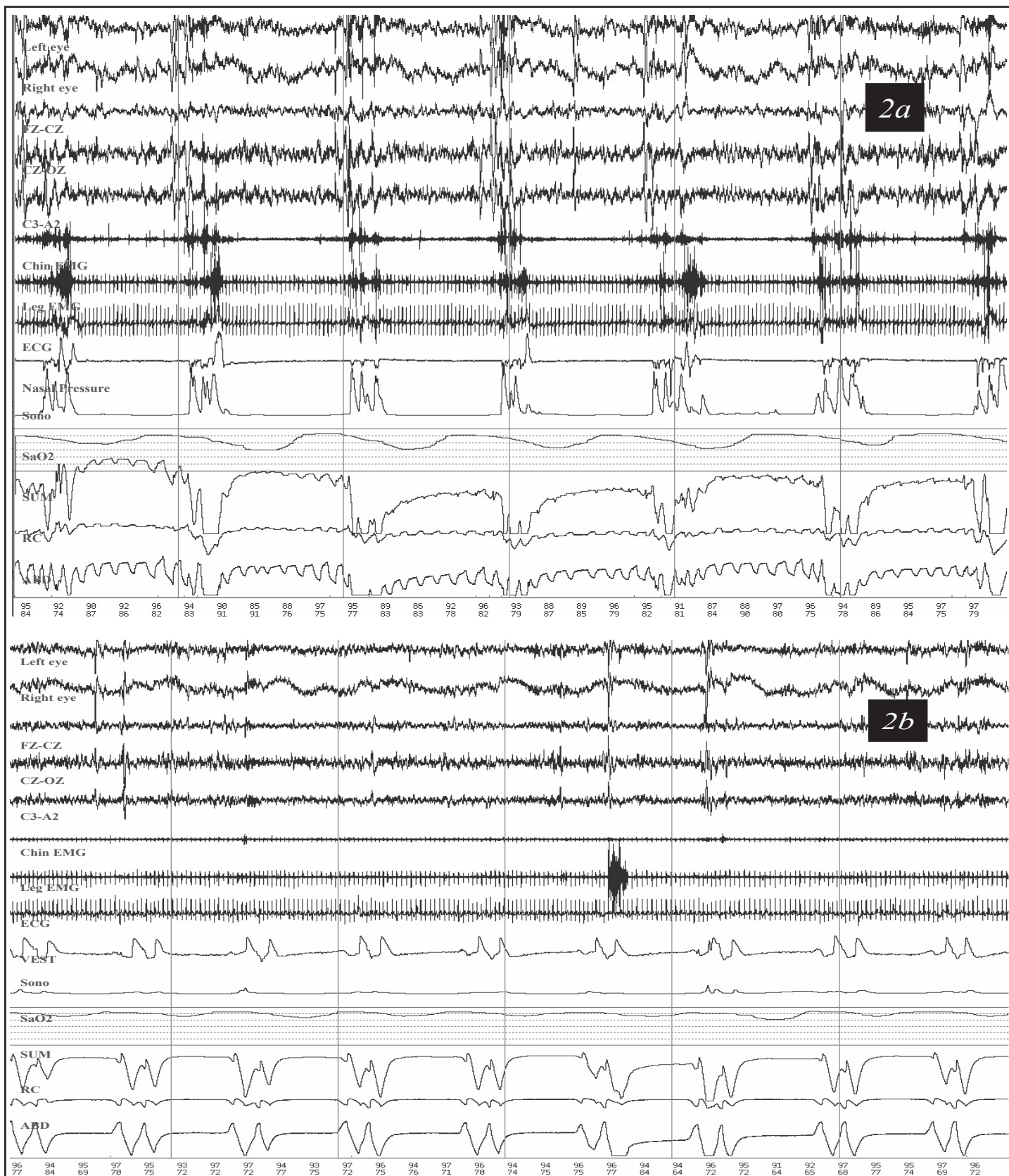


Figure 2—Typical polysomnographic tracings of patient with complex sleep apnea syndrome. 2a: Diagnostic portion (180 seconds) of polysomnogram of patient who fit diagnostic criteria for having obstructive sleep apnea syndrome, with an apnea hypopnea index of 43 per hour (distributed across both rapid eye movement and non-rapid eye movement sleep), and no central apneas. Vertical lines separated by 30 seconds.; 2b: Polysomnographic epochs (180 seconds) from same patient as in 2a but now on 8 cm H₂O pressure. This pressure eliminated all obstructive events, but recurrent central apneas were noted at 28 per hour, mostly in non-rapid eye movement sleep. Higher pressures did not decrease the frequency of respiratory events. Leg EMG refers to right and left leg electromyogram; ECG, electrocardiogram; nasal pressure, pressure via nasal cannula as surrogate for flow; Sono, snore microphone; SaO₂, oxyhemoglobin saturation; RC, rib cage respiratory impedance; ABD, abdominal respiratory impedance; SUM, sum of RC and ABD; VEST, flow from continuous positive airway pressure pneumotachometer.

Statistics

Initially, demographics and physical findings were compared between OSA and upper airway resistance syndrome patient groups using the 2-sample t test for continuous variables and Fisher exact test for categorical variables. After verifying that the groups were similar, these patient groups were collapsed into 1 group—OSAHS. Demographics and physical findings and PSG features during the diagnostic and CPAP-titration phases were compared across the 3 patient groups (OSAHS, CSA, and CompSAS) using the Fisher exact test for categorical variables and analysis of variance for continuous variables. Fisher exact test and linear contrasts were used to perform pairwise comparisons among the 3 groups. In all cases, 2-sided p values of .05 or less were considered statistically significant.

RESULTS

Prevalence of Sleep-Related Breathing Disorders in the Sleep Center

Out of 223 patients tested for suspected sleep-related breathing disorders, 188 patients had OSAHS (84%). The prevalence of CompSAS in the consecutive 1-month sample was 34 or 223 (15%), but the prevalence from the 1-month sample for CSA was very low, at 1 of 223 (0.4%). After enriching the 1-month sample with 20 patients who had CSA and eliminating patients with CHF, as described in the methods (Figure 1), our data included 174 patients with OSAHS, 14 with CSA, and 31 with CompSAS.

Demographics and Clinical Findings

The demographic and clinical findings for these patients are summarized in Table 1. Age among the 3 groups was similar, but there were differences in several measured variables. Male sex was more common in patients with CompSAS than in those with OSAHS or CSA (81% vs 60% vs 43%; $p = .027$) and was the only demographic or clinical feature in which patients with CompSAS significantly differed from patients with OSAHS ($p < .05$). Patients with CompSAS had less sleep maintenance insomnia (32% vs 79%, $p < .05$) than patients with CSA but, in other respects, did not differ significantly from patients with CSA. Patients with OSAHS tended to have higher body mass indexes than did patients with CSA ($p < .05$).

Diagnostic PSG Findings

The findings of the diagnostic portion of the PSG are shown in Table 2. Patients had a similarly elevated total arousal index (mean ranged from 34.2–42.1 per hour, $p = .606$) and respiratory-related arousal index (mean ranged from 24.1–36.9 per hour, $p = .254$).

The total AHI was different between the 3 groups ($p = .005$), with patients with OSAHS having a lower AHI than those with CompSAS or CSA ($p < .050$ in each case). Patients with CompSAS had a higher total obstructive/mixed apnea index than did patients with OSAHS or CSA ($p < .05$ in each case). Central apneas and Cheyne-Stokes patterns were rare in patients with OSA and CompSAS during diagnostic PSG. Finally, there was no statistical difference between the 3 groups for oxygen saturation mean or minimum or percentage of time spent below 90% ($p > .074$, data not shown).

Table 1—Demographics and Physical Findings of Patients with Sleep-Related Breathing Disorders

Characteristic	OSAHS (n=174)	CSA (n=14)	CompSAS (n=31)	p Value ^a
Age, y	56.7±13.1	56.1±15.4	52.3±15.2	.247
Men	105 (60)	6 (43)	25 (81)	.027 ^{bc}
Body mass index, kg/m ²	34.7±9.8	29.3±6.0	33.0±6.0	.083 ^d
ESS score	11.0±5.3	12.1±7.9	11.4±5.5	.728
Hypertension	96 (55)	8 (57)	16 (52)	.935
Habitual snoring	159 (91)	13 (93)	30 (97)	.709
Witnessed apneas	87 (50)	7 (50)	20 (65)	.340
Initial insomnia complaints	45 (26)	5 (36)	8 (26)	.739
Sleep maintenance insomnia	79 (45)	11 (79)	10 (32)	.016 ^{cd}
Nocturnal dyspnea	34 (20)	5 (36)	7 (23)	.323
Peripheral edema	34 (20)	1 (7)	9 (29)	.236
Echo EF	0.60±0.06	0.62±0.04	0.60±0.06	.686
Echo RVSP	36.2±11.0	39.0±14.5	30.3±5.0	.247
Atrial fibrillation, past or present	15 (9)	1 (7)	2 (6)	1.000

Data are presented as mean ± SD or number (%).

^aP values for continuous variables come from analysis of variance. Linear contrasts were used to perform pairwise comparisons among the 3 groups to evaluate whether the groups were significantly different from each other with significance levels noted. P values for categorical variables come from Fisher exact tests. The numbers of patients with data on the right ventricular systolic pressure (RVSP) were 73, 6, and 12 in the 3 groups, respectively; for the data on ejection fraction (EF), the numbers were 42, 6, and 9, respectively. One patient in the central sleep apnea (CSA) group did not have Epworth Sleepiness Scale (ESS) data.

^bObstructive sleep apnea-hypopnea syndrome (OSAHS) vs complex sleep apnea syndrome (CompSAS) $p < .05$.

^cCSA vs CompSAS $p < .05$.

^dOSAHS vs CSA $p < .05$.

PSG Findings on CPAP

The PSG findings during CPAP titration (in patients who successfully completed at least 1 hour of titration) are shown in Table 3. Data shown are summarized over the entire CPAP-titration period (ie, not only at optimized CPAP). Patients with CompSAS had a higher total arousal index (24.8 ± 15.5 vs 18.2 ± 11.2 per hour, $p < .050$) than those with OSAHS but similar to those with CSA (24.5 ± 14.8 per hour).

CPAP led to clear improvement in the AHI for patients with OSAHS but incomplete resolution of sleep-disordered breathing in patients with CSA and CompSAS (AHI = 2.14 ± 3.14 , 32.9 ± 30.8 , and 21.7 ± 18.6 per hour, respectively, $p < .001$). As one would expect from the definition of CompSAS, patients with CompSAS had a higher central apnea index on CPAP than did those with OSAHS ($p < .050$) but a lower central apnea index than those with CSA ($p < .050$). The AHI was more completely reduced in REM than NREM sleep for patients with CompSAS, perhaps reflecting that REM favors obstruction, whereas central apneas are more often seen in NREM sleep. The residual hypopnea index was also higher ($p < .05$) in patients with CompSAS than in those with OSAHS, reflecting residual Cheyne-Stokes pattern. During the CPAP-titration PSG, central apnea duration

Table 2—Polysomnographic Features of Diagnostic Portion of Testing

Characteristic	OSAHS (n=166)	CSA (n=14)	CompSAS (n=31)	p Value ^a
Duration of diagnostic test, min	252±93	301±115	244±59	.118 ^b
Total sleep time, min	175±68	212±118	176±37	.143 ^c
Stage 1	0.17±0.15	0.14±0.11	0.17±0.18	.763
Stage 2	0.55±0.15	0.50±0.20	0.53±0.19	.468
Stage 3/4	0.17±0.13	0.23±0.21	0.20±0.19	.276
Stage REM	0.11±0.08	0.13±0.10	0.10±0.08	.569
Total arousal index, no./h	39.6±24.1	34.2±23.6	42.1±25.4	.606
Respiratory-related arousal index, no./h	31.8±24.1	24.1±23.2	36.9±25.3	.254
Movement-related arousal index, no./h	0.08±0.13	0.03±0.05	0.03±0.08	.047 ^d
Apnea-hypopnea index, no./h				
Total	20.6±23.7	38.3±36.2	32.3±26.8	.005 ^{bc}
NREM	19.1±24.8	40.7±40.0	32.4±27.2	.001 ^{bc}
REM	25.4±30.4	19.4±24.0	26.8±31.2	.733
Central apnea index, no./h				
Total	0.28±1.18	26.9±28.0	0.71±1.32	<.001 ^{bc}
NREM	0.31±1.42	30.2±32.5	0.77±1.38	<.001 ^{bc}
REM	0.03±0.28	8.0±16.6	0.32±1.35	<.001 ^{bc}
Obstructive/mixed apnea index, no./h				
Total	12.2±18.9	6.57±6.55	21.8±23.8	.017 ^{bd}
NREM	11.7±19.6	5.93±6.07	21.8±24.6	.015 ^{bd}
REM	14.1±23.7	9.4±15.2	19.1±26.1	.387
Hypopnea Index, no./h				
Total	8.1±11.6	4.9±6.61	9.7±10.5	.319
NREM	7.1±11.8	4.6±6.79	9.8±11.1	.129
REM	11.3±19.6	2.0±6.39	7.4±14.6	.407
Cheyne-Stokes present (number +) ^e	1 (1)	1 (7)	0 (0)	.144

Data are presented as mean ± SD. REM refers to rapid eye movement; NREM, non-rapid eye movement.

^aP values from analysis of variance. Linear contrasts were used to perform pairwise comparisons among the 3 groups to evaluate whether the groups were significantly different from each other with significance levels noted.

^bCentral sleep apnea (CSA) vs complex sleep apnea syndrome (CompSAS) p < .05.

^cObstructive sleep apnea-hypopnea syndrome (OSAHS) vs CSA, p < .05.

^dOSAHS vs CompSAS p < .05.

^eReviewing sleep specialist assessment.

Table 3—Polysomnographic Features During CPAP Titration

Characteristic ^a	OSAHS (n=153)	CSA (n=11)	CompSAS (n=29)	p Value ^b
Duration of test, min	257±82	240±54	229±51	.167
Total sleep time, min	183±74	169±63	164±71	.382
Stage 1	0.10±0.08	0.18±0.22	0.15±0.11	.004 ^{cd}
Stage 2	0.54±0.14	0.43±0.17	0.52±0.17	.034 ^c
Stage 3/4	0.12±0.12	0.22±0.18	0.13±0.12	.044 ^{cc}
Stage REM	0.23±0.12	0.17±0.16	0.21±0.12	.222
Total arousal index, no./h	18.2±11.4	24.5±14.8	24.8±15.5	.014 ^d
Respiratory-related arousal index, no./h	2.06±3.04	11.5±10.6	12.2±9.4	<.001 ^{cd}
Movement-related arousal index, no./h	0.14±0.18	0.08±0.15	0.06±0.12	.034 ^d
Apnea-hypopnea index, no./h				
Total	2.14±3.14	32.9±30.8	21.7±18.6	<.001 ^{cde}
NREM	1.84±3.37	39.1±40.8	24.8±19.4	<.001 ^{cc}
REM	2.22±5.14	10.7±18.6	4.14±6.12	<.001 ^{cde}
Central apnea index, no./h				
Total	0.75±0.98	31.5±29.8	17.1±15.3	<.001 ^{cde}
NREM	0.68±1.17	37.6±39.7	20.2±16.0	<.001 ^{cc}
REM	0.42±1.04	10.4±18.1	1.93±4.41	<.001 ^{cde}
Obstructive/mixed apnea index, no./h				
Total	0.40±1.08	0.64±1.21	0.93±1.46	.071 ^d
NREM	0.42±1.18	0.82±1.78	1.00±1.58	.069 ^d
REM	0.18±0.81	0=0	0.14±0.44	.714
Hypopnea index, no./h				
Total	1.00±2.22	0.73±1.01	3.66±5.23	<.001 ^{de}
NREM	0.73±2.29	0.64±1.03	3.62±5.80	<.001 ^{de}
REM	1.61±4.75	0.36±0.67	2.07±4.33	.574
Best CPAP pressure, cm H ₂ O ^f	8.99±2.53	8.20±1.87	8.40±1.92	.329

Data are presented as mean ± SD. REM refers to rapid eye movement; NREM, non-rapid eye movement. The numbers of patients with data on the best continuous positive airway pressure (CPAP) were 149, 10, and 29 in the 3 groups, respectively.

^aResults for variables total sleep time through hypopnea index are for total CPAP titration period, including suboptimum pressures.

^bP values from analysis of variance. Linear contrasts were used to perform pairwise comparisons among the 3 groups to evaluate whether the groups were significantly different from each other with significance levels noted.

^cObstructive sleep apnea-hypopnea syndrome (OSAHS) vs central sleep apnea (CSA) p < .05.

^dOSAHS vs complex sleep apnea syndrome (CompSAS) p < .05.

^eCSA vs CompSAS p < .05.

^fReviewing sleep specialist assessment.

was longest in patients with CSA (16.6 ± 2.3 seconds vs OSAHS 14.5 ± 2.8 and CompSAS 16.0 ± 2.4 seconds, p = .007).

DISCUSSION

In our retrospective study, we found that 15% of patients (34/223) consecutively evaluated over 1 month for suspected sleep-disordered breathing had CompSAS. To our knowledge, there are no other published estimates of the prevalence of CompSAS.

The patients with CompSAS begin with quite disturbed sleep, with an average AHI of 32.3 per hour and 42.1 arousals per hour. After CPAP, abnormal respiratory patterns remained, with an average residual AHI of 21.7 per hour and arousals of 24.8

per hour, mostly due to residual central apneas in NREM sleep. This response was qualitatively similar to patients with CSA but markedly different from patients with OSAHS, whose sleep and AHI improved with CPAP (Tables 2 and 3). Our data are derived from split-night studies and, thus, may not adequately represent some stages during diagnostic or CPAP portions of testing. Given these limitations, sleep-stage comparisons are difficult. However, sleep fragmentation and respiratory disturbance are significantly different when comparing patients with CompSAS and with OSAHS. When left with such disturbed sleep, CPAP is not likely an adequate treatment modality for patients with CompSAS unless one speculates that CPAP effectiveness improves with time, something postulated to occur when CPAP is applied to patients

with CHF who have CSA. Whereas some report such improvement, a recent prospective trial did not show improvement in AHI in patients with CSA treated with CPAP after 1 month to a mean of 24 months.¹³ We are not aware of any systematic longitudinal treatment data involving patients with CompSAS.

When patients with apparent OSAHS have a poor response to CPAP, one must question whether an adequate CPAP titration was performed. In clinical trials evaluating various aspects of CPAP efficacy in patients with OSAHS, residual AHI is typically less than 10.¹⁴⁻¹⁶ The residual obstructive apnea index in our patients with CompSAS was very low (0.93) but higher than in the patients with OSAHS. This is probably due to our CPAP-titration scheme. When central apneas and hypopneas emerge on CPAP, they often become more frequent with higher CPAP pressures.³ When this is encountered by our sleep technologists, after first trying higher pressures, they back CPAP down to find the best compromise between central and obstructive abnormalities. The adequacy of CPAP titration may be asserted, given that the same titration protocol is used in all patients, and the mean total AHI in our patients with OSAHS was 2.1, well below levels typically noted in other studies, and that the obstructive apnea index was very low in our patients with CompSAS as well.¹⁴⁻¹⁶

After excluding patients with CHF or left ventricular ejection fraction of 40% or less, we observed only small clinical differences between our patient groups (Tables 1-2). Similar to findings in other reports, our OSAHS patients tended to be heavier and to have less sleep-maintenance insomnia than our CSA patients.^{8,17} Elevated body mass index has been a consistent risk factor for OSAHS.^{18,19} Obesity is thought to increase the likelihood of developing OSA by its deleterious effect on airway configuration and on respiratory control.^{19,20} Our patients with CompSAS had a mean body mass index intermediate between that of patients with OSAHS and CSA, yet was not statistically different from either.

In distinction from conclusions drawn from CHF and stroke populations, in which there is a strong association between male sex and CSA, in our patients, there was no difference in sex prominence between the OSAHS group and the CSA group. In contrast, 81% of patients with CompSAS were men. Male sex has been postulated to be a risk factor for central respiratory events, in part because these events are more commonly observed during lighter stages of sleep and men tend to have more-disrupted and lighter sleep than women.²¹

We had hypothesized that the clinical profile of patients with CompSAS would most nearly resemble that of patients with CSA. Simplistically, we thought that patients with CompSAS might be patients with CSA who had accumulated risk factors for OSAHS, such as obesity or hypertension, combining aspects of respiratory-control instability with airway compromise. The relationships have proven to be more complicated. Apart from a higher proportion of men, there was little to distinguish patients with CompSAS from those with OSAHS on clinical grounds (Table 1). Our hypothesis is not supported, and we must consider other factors to explain why fairly similar patients respond differently to CPAP.

Thomas et al recently reported on a group of patients similar to our own.⁵ In their series, patients meeting criteria for severe OSAHS were categorized into REM- and cyclic alternating pattern-dominant groups. The latter group typically responded to CPAP, with respiratory-instability issues similar to our patients. Like our patients, this group was predominantly male (90%) and was left with marked respiratory disturbance at "best" CPAP. They

selected and categorized their patients somewhat differently, and, in contrast with their patients, our patients had disturbed respiratory patterns in REM and NREM sleep during the diagnostic phase and had a lower mean CPAP pressure (8.4 vs 13.8 cm H₂O) at treatment. Because of marked residual sleep disruption caused by persistent central events, Thomas et al employed supplemental oxygen and benzodiazepines as supplements to CPAP therapy in about half of their patients and later used a novel supplemental CO₂ therapy to assist in management.^{4,5} The proportion of OSA and CSA events was reported to shift from predominantly obstructive to predominantly central when comparing the first and last quarter of the night of PSG recording in 1 study of patients with CHF.²² The shift was attributed primarily to shifts in hemodynamics that occur as a result of obstructive apneas, resulting in increases in minute ventilation and decreasing arterial PCO₂.²² The duration of apneas (both central and obstructive) was longer in patients with CSA than in patients with OSAHS. The tendency toward longer apnea durations in patients with CHF and OSAHS or CSA has been thought to reflect delayed feedback to the respiratory controller due to prolonged circulation times seen with impaired cardiac output.^{22,23} In our study, there was a trend toward longer apnea durations in the patients with CompSAS compared with those with OSAHS. This trend, although not reaching significance, suggests that there may be some difference in either feedback or respiratory chemoreflex gain that predisposes to the different response to CPAP. It is also possible that, in some but not other patients, CPAP induces hypocapnia by suddenly relieving the work of breathing or by improving physiologic shunt. Further investigation of these hypotheses by measuring CO₂ response or analyzing respiratory cycle lengths may further our understanding in this regard.

Our study has several limitations. The retrospective design limited data availability on some patients, and we would have liked to have a more complete set of clinical, pulmonary function, and blood gas information. We are a tertiary center with a large cardiology referral base, and this might be expected to influence our patient population. However, the prevalence of CHF, atrial fibrillation, and hypertension was fairly typical of other sleep-center populations that have been reported in the literature. The use of split-night studies limits our ability to analyze differences in sleep architecture and introduces some potential bias regarding the distribution of events across different sleep stages and circadian cycle. Our study, by design, concerned itself with the presentation of patients with sleep-disordered breathing, but more physiologic studies and longitudinal follow-up data might reveal further similarities or differences between the 3 diagnostic groups. Study of the mechanisms involved in respiratory control and the clinical response to CPAP therapy over time are planned in order to learn more about patients with CompSAS.

CONCLUSION

CompSAS is defined by the emergence of problematic CSA and Cheyne-Stokes respiration with CPAP application sufficient to eliminate obstructive apneas and hypopneas. Patients are left with very disrupted breathing and sleep on CPAP, with respiratory disturbances in the range typically found in patients with moderately severe sleep apnea. We had hypothesized that patients with CompSAS would have clinical profiles more similar to those of patients with CSA than to those of patients with OSAHS. In con-

trast, our data show that, in most respects, their clinical features lie between those of patients with OSAHS and CSA. Patients with CompSAS are mostly similar to those with OSAHS until one applies CPAP. Like patients having OSAHS, they differ from patients with CSA in that they have less sleep-maintenance insomnia. Clinical profiles are not sufficiently characteristic to predict the emergence of CompSAS. The pathophysiologic mechanism underlying the response of patients with CompSAS to CPAP are not well understood but, speculatively, are related to altered chemoreflexes. Optimal treatment of these patients is not certain but merits additional study.

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