JCSM
Journal of Clinical Sleep Medicine

PRO/CON DEBATE

Complex Sleep Apnea: It Really Is a Disease

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If failing to recognize the disease complex sleep apnea (CompSA) as a unique entity results in adverse health events to a patient, then a disservice is done and suffering ensues. It must be conceded that ultimately, the only thing that matters is what best serves the patient. There is no argument that one can *lump or split* a description of any disease process as long as you get to the fact of the matter, but no one is proposing a one-size-fits-all solution to this problem. The following will review evidence that a disease definition exists for CompSA, and that it is recognizable, has a potential plausible mechanism, and responds to a treatment process consistent with the underlying problem. However, as this debate progresses, what will be most important is to see what favorable outcomes occur after properly selected treatment choices are applied in long-term randomized trials.

Dorland's Illustrated Medical Dictionary (WB Saunders, Philadelphia) defines disease:

Disease [Fr. *dès* from + *aise* ease] any deviation from or interruption of the normal structure or function of a part, organ, or system of the body as manifested by characteristic symptoms and signs; the etiology, pathology, prognosis may be known or unknown.

A deviation from normal function is well-recognized in patients with CompSA who often have severe sleep-disordered breathing. Several sources provide evidence that CompSA is indeed a defined disease state in the readily accessible literature. Even the website Wikipedia (http://en.wikipedia.org/wiki/Main_Page) states:

Patients with **complex sleep apnea** exhibit OSA, but upon application of positive airway pressure, the patient exhibits persistent central sleep apnea. This central apnea is most commonly noted while on CPAP therapy, after the obstructive component has been eliminated. This has long been seen in sleep laboratories…

Researchers from Harvard University wrote of the disease:[1]

Complex sleep-disordered breathing is a distinct form of sleep apnea. It has recognizable characteristics that are present without, and often worsened during, positive airway pressure treatment.

Finally, in an effort to permit coverage for more specific therapy for CompSA patients in the form of servo-ventilators or bi-level devices with a backup rate, the Centers for Medicare and Medicaid Services or CMS in the Durable Medical Equipment Regional Carrier or *DMERC Region D Supplier Manual* (CMS Pub. 100-03, *Medicare National Coverage Determinations Manual*, Chapter 1, Section 280.1) stated:

Complex sleep apnea (CompSA) is a form of central apnea specifically identified by the persistence or emergence of central apneas or hypopneas upon exposure to CPAP or an E0470 device when obstructive events have disappeared. These patients have predominately obstructive or mixed apneas during the diagnostic sleep study occurring at greater than or equal to 5 times per hour. With use of a CPAP or E0470, they show a pattern of apneas and hypopneas that meets the definition of CSA described above. Revision Effective Date: 01/01/2006.

The appearance of treatment-emergent central apnea is well known and recently described.[2] However the identification of central apnea appearing years after treatment of obstructive apnea is an older observation. Fletcher reported on a patient who four years earlier underwent curative tracheostomy for severe OSA and then had a 23-kg weight gain. He redeveloped hypersomnolence and when restudied, apneas of similar frequency, duration, and depth of desaturation reappeared but were now totally central in origin.[3]

The mechanisms behind this phenomenon and CompSA are not well understood, but some comments can be offered. Presumably there must be dual causation that includes anatomic and physiologic vulnerability to OSA plus a central breathing control instability leading to chemo-reflex dysfunction. High loop gain is required. Loop gain is mathematically defined as the ratio of a corrective response (e.g., hyperpnea) to a disturbance (e.g., apnea). If corrective responses are greater than the disturbance (loop gain >1), then small disturbances can lead to self-sustaining oscillations. In the case of CompSA, we see a typical crescendo-decrescendo respiratory pattern indicative of a high loop gain state. In selected patients with OSA and higher loop gain, application of positive airway pressure in the form of proportional assist ventilation can produce such ventilatory instability leading to periodic breathing.[4] Those patients with persistent CompSA like those with classic Cheyne-Stokes Respiration (CSR) can develop delays in the controller response

Submitted for publication September, 2008
Accepted for publication September, 2008
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during REM sleep. This explains the different behavior during NREM stage where disordered breathing events predominate and when in REM sleep, the events can disappear in patients with CSR or CompSA.[5]

The prevalence and characteristics of CompSA patients was explored in a large retrospective review of 233 adults consecutively referred over 1 month and compared to 20 consecutive patients diagnosed with idiopathic central sleep apnea CSA.[2] The prevalence of CompSA, OSA, and CSA in this 1-month sample was 15%, 84%, and 0.4%, respectively. There were subtle but significant differences in patients with CompSA who were more likely to be male than OSA patients (81% vs 60% men, $p < 0.05$) and had less maintenance insomnia complaints than CSA patients (32% vs 79%, $p < 0.05$). The diagnostic apnea-hypopnea index (AHI) for all groups was moderate to severely elevated, but CompSA was intermediate in rank (CSA = 38.3 ± 36.2 vs CompSA = 32.3 ± 26.8 vs OSAHS = 20.6 ± 23.7 per hour, $p = 0.005$). CPAP suppressed OSA, but the residual AHI, mostly from central apneas, remained high [CompSA= 21.7 ± 18.6 and CSA = 32.9 ± 30.8 in CSA vs in OSA= 2.1 ± 3.1 per hour, $p < 0.001$]. The CompSA patients were most similar to those with OSA until CPAP was applied. In this study, clinical risk factors such as atrial fibrillation or congestive heart failure did not predict the emergence of CompSA.

Another review of polysomnograms (PSGs) and clinical records of 99 consecutive patients with a primary diagnosis of OSA referred for an in-laboratory CPAP titration study found other results.[6] Patients with central apneas ≥5/h at their prescribed CPAP level formed the CSA-CPAP group vs. patients with central apnea <5/h who constituted the CSA-CPAP group. The demographic, baseline, and CPAP titration PSG variables were compared between the two groups. The study found 13 of 99 (~13%) patients had CompSA, and they were almost all male (92%). There was a significant likelihood of congestive heart failure or ischemic heart disease in this group (38% vs 14%), but the details of the clinical diagnoses were not provided.

A most pertinent issue in this debate is how many of these CompSA events are transient and whether patients can quickly use CPAP treatment successfully. Here there are conflicting results. Recently, a retrospective search was done of patients with 2 PSGs between 2003 and 2005 with CompSA evident on the first PSG and a subsequent therapeutic PSG using CPAP.[7] There were 13 such patients with a median follow-up of 195 (49-562) days. The residual AHI on CPAP decreased from 26 (23-40) on the first PSG to 7 (3-21.5) on the follow-up PSG. There were 7 patients who reached AHI <10 and were regarded as "CPAP responders." There were 6 "CPAP non-responders" with AHI ≥10 at follow-up. The latter were sleepier by Epworth Sleepiness Score ($p = 0.03$) and trended toward a lower body mass index ($p = 0.06$), but both groups showed similar adherence to CPAP therapy. The authors concluded that over time in CompSA patients treated with CPAP, the AHI tends to improve. However, nearly half maintained a persistently elevated AHI and remained symptomatic or had abnormal oximetry.

Another retrospective review found 95 of 719 patients who had PSG and used a bi-level positive airway pressure (BLPAP) device for central apnea over a 2-year period.[8] A subgroup of these patients did not have CSR or periodic breathing at baseline, but developed this with BLPAP and/or CPAP. This study did not discuss compliance with therapy or length of individual treatment time precisely but they did note that BLPAP was more likely to worsen central apnea (34% of patients) in those with non-CSR central apneas ($p < 0.001$). During REM sleep, the central apneas improved, while hypopneas and obstructive apneas worsened ($p < 0.001$) suggesting this was not just the result of over-exuberant titration.

In contrast, a cross-sectional analysis of 42 OSA patients with and without CPAP-related CSA after split-night PSG for suspected sleep related breathing disorders was recently done.[9] All CSA patients (n = 21) and control subjects (n = 21) underwent baseline studies; there were no differences by echocardiography, pulmonary function testing, and arterial blood gases. There were 14 patients (7 lost to follow-up) who returned for a follow-up PSG after 2 to 3 months on adequate CPAP therapy. Although sleep quality improved from baseline, sleep efficiency was decreased, stage 1 percentage was increased, and total arousals were increased in CSA patients compared to control subjects. Twelve of 14 patients (85%) in the CSA group demonstrated improvement of CSA events from 20 ± 14.2 to 2 ± 4.5 per hour on follow-up PSG study. The investigators stated that CSA events occurring during CPAP titration are transient and self-limited and might be precipitated by the sleep fragmentation during the initial CPAP titration. They did not find any specific demographic differences compared to OSA patients without CPAP-related CSA. The study was criticized for the large number of dropouts and the persistently compromised sleep quality in these patients. All of the aforementioned studies suffer from the inherent weaknesses of small numbers of subjects and retrospective design. Thus, the jury is still out concerning the percentage of patients with persistent CompSA after more prolonged exposure to CPAP.

Perhaps the most crucial concern for patients with CompSA is whether there is a preferential treatment approach, and what may be lost for failing to achieve success in a timely fashion. Clearly patients who have a bad initial experience with CPAP have a worse adherence to therapy and those that fail with CPAP compliance over longer periods have limited recovery even with alternative devices.[10,11] Benefit of adaptive servoventilation (ASV) has been shown in patients with heart failure and CSR in both short and long-term studies, and editorial comments suggest a future for this technology.[12-15] So is there evidence of treatment benefit with other approaches such as ASV in patients with CompSA? One short-term randomized trial showed equivalence using BLPAP or ASV for correcting obstructive and central events in CompSA patients, most of whom had very large numbers of residual central events on CPAP.[16] The ASV device was superior in eliminating respiratory related arousals and all residual disordered breathing events, and it normalized the AHI. A longer-term retrospective review of a consecutive group of 100 patients treated with ASV included 63 with CompSA.[5] The CompSA patients were younger than CSR patients, 70.7 vs 78.1 years ($p = 0.047$) and had less reported CHF, 25% vs 60% of patients with CSR ($p = 0.036$). There was a notable resolution of the supine NREM central respiratory events (68 vs 5 events/hour) with ASV, and 70.2% of the 47 CompSA patients who underwent a CPAP titration showed at least 2-fold reduction in AHI in non-supine positions

compared to supine positions. Telephone follow-up information was available in 44 patients; 37 (84%) were still using the ASV (median duration of 5 months). The majority of contacted patients (32 of 44 or 73%) reported improvement in sleep quality and/or daytime sleepiness.

So what are we to conclude? As noted above, CompSA fulfills a definition of disease by the simplest criteria, has been defined similarly by multiple authorities and qualifies for CMS reimbursement based on peer-reviewed data. Although admittedly speculative, plausible physiologic mechanisms can help explain the appearance of this disease that is notably different from otherwise uncomplicated OSA. Patients with CompSA have symptoms indicative of the distress attributable to this unique disease process with typically severe residual AHI events with arousals after CPAP titration. Treatment options are available that may rapidly resolve the disorder and relieve the symptoms of this disease, with the potential of increasing early adherence to therapy. Does every CompSA patient need a more expensive and complicated PAP device? Clearly the answer is no but failure to understand and explore further questions in this regard does a disservice to our patients and can create obstacles to a better understanding of CompSA as a unique disease process.

DISCLOSURE STATEMENT

Dr. Gay has received research support from ResMed and has received honoraria for speaking at national and international academic meetings on complex sleep apnea.

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