More: Recognizing and Treating Excessive Sleepiness in Primary Care

Selection from: Recognizing and Treating Excessive Sleepiness in Primary Care: Reports From 2007

Central Sleep Apnea in a Patient Presenting With Daytime Fatigue and Sleepiness CME

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Disclosures

History of Present Illness

The patient is a 52-year-old black man who comes to our sleep clinic with the chief complaint of waking up because of difficulty breathing. He also reports that he snores on a regular basis.

The girlfriend who accompanied him to the clinic reports frequently witnessing pauses in his breathing when he sleeps, and that these are bothersome enough that she has actually awakened him, fearful that he has died. In general, he sleeps flat on his back but occasionally wakes up gasping for air. He only rarely feels refreshed and ready to go upon waking up in the morning, and frequently feels tired during the day. He sleep-talks rarely but denies sleepwalking. He also denies any symptoms of sleep paralysis, hallucinations, or cataplexy, or ever acting out during dreams. He has no symptoms suggestive of restless legs syndrome or bruxism, and no history of epilepsy or head trauma.

He smokes 1 pack of cigarettes per day. He denies drinking alcohol or using illicit drugs. He generally goes to bed at 10 PM, and has no difficulty falling asleep but often watches TV before sleeping. He reports a usual waking time around 7 AM. He occasionally worked nights in the past, but has no job currently.

Past Medical History

This patient is known to have type 2 diabetes mellitus and hypertension. He also is known to have stage 3 NYHA class II congestive heart failure related to nonischemic dilated cardiomyopathy. He receives carvedilol, digoxin, and lisinopril. He has no history of lung, thyroid, or neurologic diseases. His family history is not significant for any sleep disorders.

Clinical Evaluation

The patient is overweight with a body mass index of 28.3 kg/m^2. He has a Mallampati class 4 oropharyngeal airway, indicating a relatively narrowed oropharyngeal passage (the higher the class, the greater the risk). Lung auscultation reveals few inspiratory crackles at the bases bilaterally but otherwise is clear to auscultation without wheeze. A 2/6 holosystolic murmur is audible and heard best at the apex. The patient's extremities demonstrate chronic stasis changes with 1+ edema bilaterally but no clubbing or cyanosis. His Epworth sleepiness score is 15 out of 24 (a score of < 10 is considered normal; above that suggests hypersomnolence). His most recent echocardiogram shows left ventricle ejection fraction of 25% to 30% with severe global hypokinesis.

An overnight polysomnography (PSG) shows an apnea-hypopnea index of 47.5 per hour (< 5 per hour are normal) and minimal snoring (Figures 1, 2, and 3). The apnea-hypopnea events caused desaturations but no hypoxia or arousals, and the apneic events were predominantly central in

type. The breathing pattern showed continuous cycles of crescendo and decrescendo changes in breathing amplitude, ending in hypopneas and apneas with arousals occurring at the hyperpnea stage. The sleep latency was shortened at 3 minutes, suggesting sleep pressure, but the REM sleep latency was normal. The periodic limb movement index was 0.0 per hour. The mean sleep oxygen saturation was 98%.

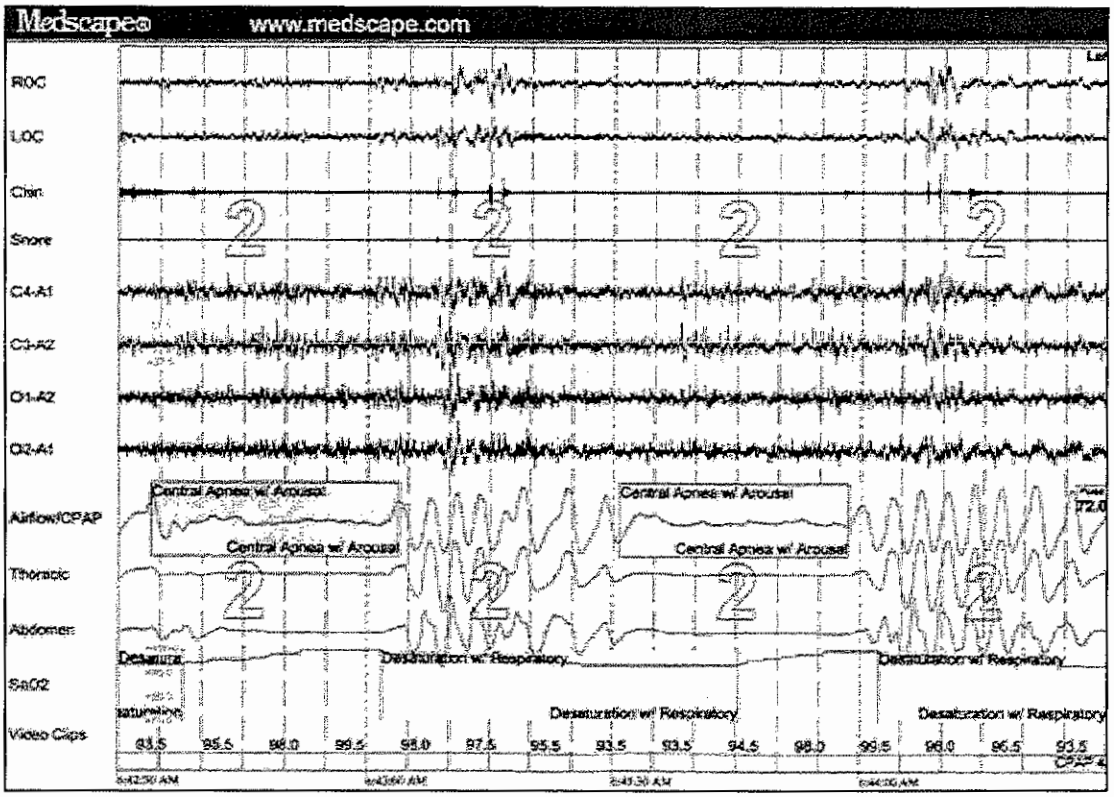

Figure 1. 120-second epoch of PSG showing 2 central apneas (flat line in airflow, thoracic and abdominal channels; in central apnea, the absence of airflow is without respiratory effort, unlike obstructive apnea where there is presence of effort but no airflow). Note the fall in oxygen saturation which lags after the occurrence of event.

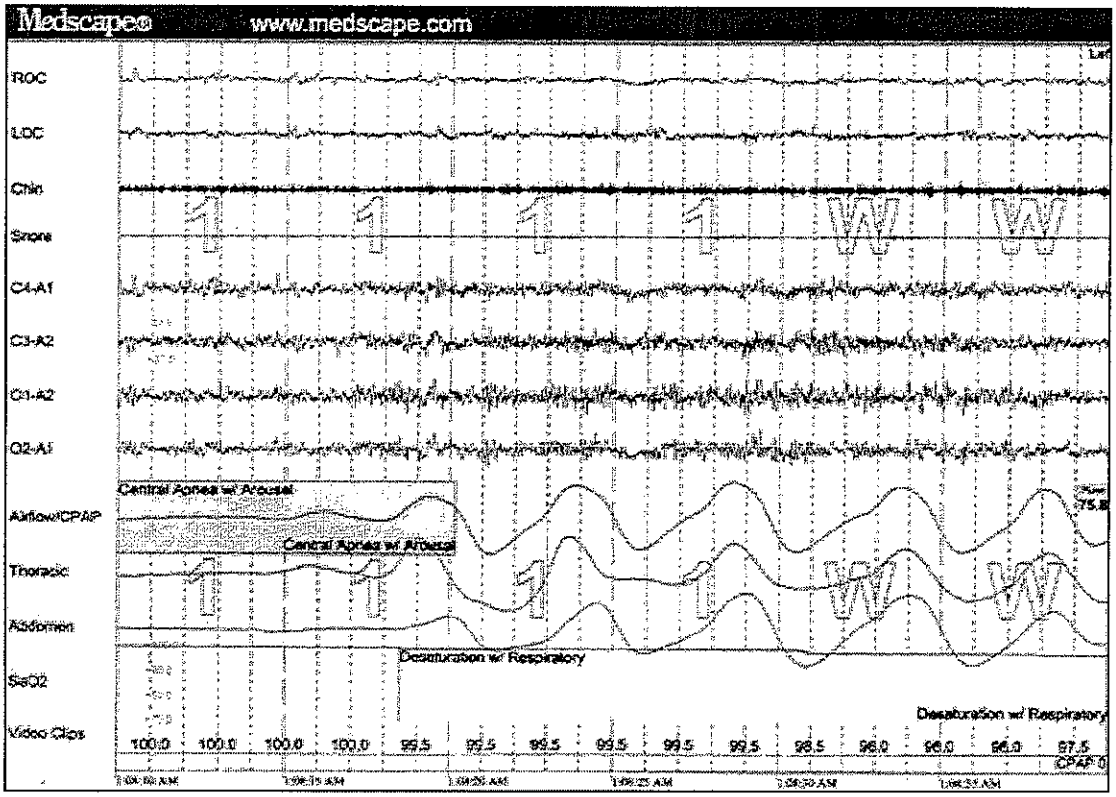

Figure 2. Overlapped epoch of 30 seconds showing arousal secondary to central apnea. Note low amplitude mixed frequency EEG of Stage 1 sleep changing to high amplitude alpha frequency EEG of arousal (alpha frequency 8-12 Hz are more prominent in occipital channels O2-A1 and O1-A2 than in central channels C4-A1 and C3-A2, although still nicely seen in C3-A2).

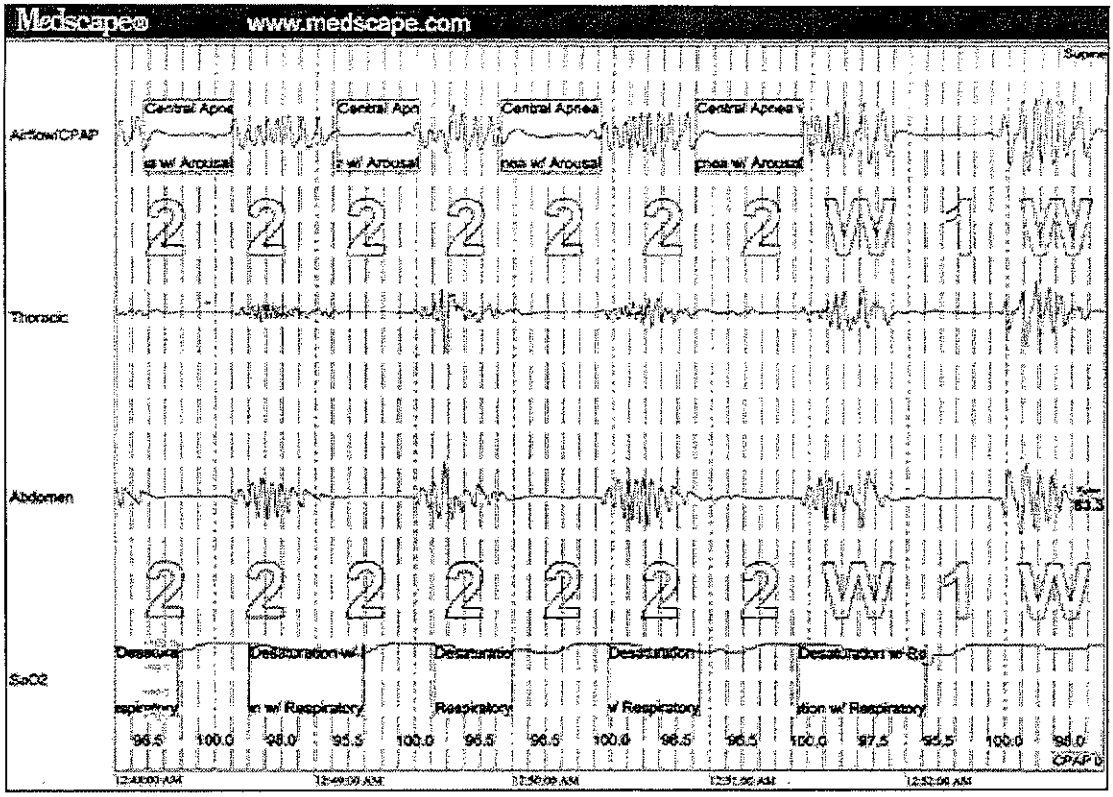

Figure 3. A limited polygraph recording of 300-second epoch showing only the airflow, thoracic, abdominal, and oxygen saturation channels. Note the abrupt cessation and appearance of airflow waveform. In pure Cheyne-Stokes breathing pattern, there is a crescendo-decrescendo hyperpnea interspersed among central apneas, and cycle lasts more than 45 seconds. Here, this typical pattern is missing and cycle lasts less than 30 seconds.

Management and Clinical Course

The patient's symptoms and PSG result support the diagnosis of central sleep apnea (CSA) syndrome most likely related to his heart failure. Initially, he is prescribed CPAP, but he is unable to tolerate it and is switched to bilevel positive airway pressure (BiPAP) therapy in addition to his existing medical therapy. He is also instructed to maintain a regular sleep/wake schedule as much as possible, avoid watching TV in bed, and aim for a minimum of 8 hours of nighttime sleep. In addition, he meets with a nutritionist who counsels him about a healthy diet to encourage weight loss.

One month later, at a follow-up visit, the patient reports that he is sleeping better. He generally feels good and no longer suffers daytime fatigue to the extent that he had in the recent past.

Heart Failure and Associated Sleep Disorders

Cardiovascular diseases remain the most common cause of both morbidity and mortality in the industrialized world.[1,2] Sleep disorders are also highly prevalent, estimated to affect more than 40 million Americans.[3] Hence disorders of sleep and cardiovascular disease frequently coexist.

Sleep-related breathing disorders (SRBD) are by far the most common sleep disorders encountered at the sleep centers. There are 2 major types of SRBD in the general population, namely obstructive (OSA) and CSA, with the former being more common.[4]

The Sleep Heart Health Study has shown the importance of SRBD as a contributing factor in the pathogenesis of myriad metabolic and cardiovascular disorders.[5] The widespread implications of

SRBD on the cardiovascular system are summarized in Table 1.

Table 1. Cardiovascular Manifestations of Sleep Related Breathing Disorders (SRBD)[5-10]

Systemic hypertension
Pulmonary hypertension
Left ventricular hypertrophy
Left ventricular systolic and diastolic dysfunction
Congestive heart failure
Arrhythmias (atrial fibrillation)
Nocturnal angina
Increased platelet aggregability
Ischemic cardiovascular/cerebrovascular events
Sudden cardiac death (questionable)

In the context of heart failure, SRBD occurs with markedly greater frequency[8,9] compared with the general population, especially in patients with left ventricular ejection fraction (LVEF) < 40%.[11-13] Epidemiologic studies demonstrate a prevalence of 40% to 70% in ambulatory male patients with NYHA Class II & III.[12] There is compelling evidence that SRBD contributes to the pathophysiology and progression of this devastating disorder.[14-16] Thus, prompt recognition, appropriate diagnosis, and early institution of treatment is vital to improve the overall prognosis and quality of life in patients with heart failure. The 3 primary SRBDs are listed in Table 2. In the context of the case patient, our discussion will focus on CSA.

Table 2. Sleep-Related Breathing Disorders in Heart Failure[17]

Central sleep apnea (Cheyne-Stokes respiration)
Obstructive sleep apnea
Mixed type (combination of both central sleep apnea and obstructive sleep apnea)

Central Sleep Apnea

CSA with Cheyne-Stokes respiration (CSR) is a form of periodic breathing in which central apnea or hypopneas alternate with periods of hyperventilation. Although used interchangeably sometimes, the American Academy of Sleep Medicine recommends differentiating pure CSA from CSA that is associated with CSR because no crescendo-decrescendo breathing is seen in primary CSA. The distinctive feature of CSR is its long recovery period which reflects the long circulation time indicative of systolic heart failure. This differentiates CSR from other periodic breathing with CSA conditions (idiopathic form), in which the recovery arm is abrupt and short rather than smooth and prolonged.[11]

Clinical Features

Patients with CSA are usually thin and do not snore heavily, and despite having fragmented sleep due to arousals, most of the time they do not complain of excessive daytime somnolence.[11] For this reason, the Epworth Sleepiness Scale is probably not useful in evaluating heart failure patients. Patients who awaken during the peak of ventilation after apnea may complain of paroxysmal nocturnal dyspnea which, again, can be easily attributed to heart failure rather than SRBD. Moreover, the symptoms resulting from CSA usually overlap with the classic heart failure symptoms, such as orthopnea, cough, neurocognitive problems, nocturia, waking up unrested, nocturnal dyspnea, sleep fragmentation, and fatigue.[11] Thus, in heart failure patients, CSA remains occult.[12]

Pathophysiology of Central Sleep Apnea Related to Heart Failure

The left ventricular filling pressures are increased in heart failure along with enhanced central and peripheral chemosensitivity. This results in pulmonary congestion that activates the J receptors (vagal irritant receptors), ultimately stimulating hyperventilation and hypocapnia. Central apnea comes about because the increase in ventilation causes the $PaCO_2$ to be driven below the threshold for ventilation. Apnea persists until $PaCO_2$ rises above the threshold, require stimulating ventilation.[17] CSA will elicit chemical, neural, and homodynamic oscillations similar to those observed in OSA.

Diagnosis

A high index of suspicion is required to adequately recognize CSA and CSR in patients with heart failure patients because the clinical picture may not be entirely clear. Standard overnight PSG is the diagnostic modality of choice. It can differentiate different forms of SRBD and is also helpful in gauging severity by measuring the apnea- hypopnea index. PSG should be considered if risk factors CSR are present in patients with heart failure (Table 3).

Table 3. Risk Factors for Cheyne-Stokes Respirations in Patients With Heart Failure[11,17]

Male sex
Age greater than 60
Presence of atrial fibrillation
Hypocapnia (awake $PaCo_2$ of 38 mm Hg or less)
Ventricular tachycardia
Low left ventricular ejection fraction (< 40%)
Higher NYHA Class (III & IV)
Excess premature ventricular beats and couplets
Refractory congestive heart failure with standard medical management

Note: Obesity is not a risk factor; women with heart failure rarely develop CSR, which may explain better prognosis compared with men.

Implications for Heart Failure

The 3 largest studies of CSA in patients with heart failure reported a CSA prevalence of 28% to 40%.[8,9,13] CSA remained an independent risk factor for death or cardiac transplantation.[11] This pathologic relationship may be attributed to marked neurohumoral activation, surges in blood pressure and heart rate, and a greater propensity for lethal arrhythmias induced by CSA.[15,16]

Treatment

CSA is likely arising as a consequence of heart failure, so its presence should alert the astute physician to optimize the pharmacologic treatment for heart failure, which includes the combination of angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, digoxin, and diuretics. Patients with heart failure who are on beta-blockers have a lower prevalence and severity of CSR than those who are not receiving beta-blockers.[18]

If CSA persists, however, a variety of therapeutic options are available:

Pharmaceuticals. Acetazolamide is a carbonic anhydrase inhibitor and causes a mild metabolic acidosis. This in turn stimulates the chemoreceptors in the carotid bodies and central chemoreceptors, thus acting as a respiratory stimulant.[19] It has been successfully used in the treatment of idiopathic CSA and periodic breathing at higher altitude. However, it cannot be recommended for therapy for CSA in heart failure patients because its long-term safety and effectiveness in such patients remains to be demonstrated.

Theophylline is a phosphodiesterase inhibitor, but its competitive nature with adenosine is what drives increased ventilation. Studies have shown efficacy in CSA[20] but potential arrhythmogenic effects and phosphodiesterase inhibition are major concerns for their long-term use.

Oxygen. Multiple studies have shown that nocturnal oxygen supplementation with a flow of 2-3 L/min improves the quality of sleep, sleep-related breathing events, and oxygen desaturation.[21] It also reduces the sympathetic activity and urinary norepinephrine excretion.[21] We need prospective, placebo-controlled, long-term studies to determine whether this form of treatment has the potential to improve the morbidity and mortality of patients with heart failure.

Positive airway devices. Nasal continuous positive airway pressure (nCPAP) has shown promising results in treating CSA from systolic heart failure. Several studies have demonstrated the benefit of nCPAP on LVEF, reducing urinary epinephrine secretion, increasing the distance walked in 6 minutes, and reducing cardiac sympathetic activity.[22] The largest randomized controlled trial to date (CANPAP) failed to show a benefit on the transplantation-free survival,[23] but the main limitation of the trial was the inability to reduce the apnea-hypopnea index (AHI) to below 15, which was the inclusion criterion. Later, the same group performed a post-hoc analysis and showed that early suppression of CSA to an AHI below 15 per hour may improve both LVEF and transplant-free survival.[24]

Pressure support ventilation such as bilevel positive airway pressure (BiPAP) or adaptive servo-ventilation (ASV) treatment should be offered to patients who are refractory, noncompliant, or unable to tolerate CPAP. Whereas CPAP operates at the same pressure level during expiration and inspiration, pressure support ventilation acts at a lower pressure during expiration and a higher pressure during inspiration, which actively supports it. ASV is a newer form of noninvasive pressure support treatment that has shown excellent results in open-label studies.[25,26]

Heart transplantation. Heart transplantation can eliminate CSR by virtue of reversing the homodynamic features of heart failures responsible for generation of CSA.[27] Unfortunately, follow-up studies have shown that patients develop OSA related to steroid treatment and obesity.[28]

Addressing Excessive Fatigue and Sleepiness in Patients With CSA

Maximizing pharmacotherapy for underlying cardiac disease, along with CPAP and BiPAP, are the only therapeutic modalities that have been studied for CSA. In most cases, improving the patient's cardiac and respiratory status and sleep will also ameliorate the patient's fatigue and daytime sleepiness. Arousals occur at the height of the hyperpnea phase, leading to sleep fragmentation and subsequent daytime symptoms of sleepiness. Treatment with CPAP or BiPAP is aimed at breaking this cycle and thus eliminating arousals, with consequent consolidation of sleep and improvement in daytime symptoms. Wake-promoting agents may be potentially risky in patients with CSA. If symptoms of fatigue and excessive sleepiness persist despite optimal treatment as described, exploring other causes for fatigue, such as secondary depression, hypothyroidism, and noncompliance, should be pursued.

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References

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Wallace Mendelson, MD (Expert Column, December 28, 2008)

2. Central Sleep Apnea in a Patient Presenting With Daytime Fatigue and Sleepiness
   What cardiac manifestations are associated with sleep-related breathing disorders? How is CSA distinguished from OSA?
   Faisal Khan, MD; Ataf Chaudry, MD; Sabin Bista, MD (Case Vignette, December 28, 2008)

3. Sleepy in America: Findings of the National Sleep Foundation's 2007 Survey of Women
   What factors are robbing women of sleep in the United States? What are the consequences of this epidemic of sleepiness?
   Paul P. Doghramji, MD (Article, December 28, 2008)

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