

Sleep HealthCenters® Newsletter

David P. White, MD, Editor June 2004

Dear colleague,

In the last several years, great strides have been made in understanding the health consequences of sleep apnea. In this edition of the Sleep HealthCenters® Newsletter, Drs. Malhotra and Fang present the current knowledge on how sleep apnea contributes to the development of hypertension and other cardiovascular diseases. Patients with congestive heart failure are particularly susceptible to sleep-disordered breathing, which can exacerbate their cardiac disease. Fortunately, as described in the accompanying article, treatment of sleep apnea improves both sleep and heart function making it important to recognize patients with sleep and breathing problems as early as possible. We hope this information will prove valuable in helping you manage your patients with cardiovascular disease.

Sincerely,
David P. White, MD
Corporate Medical Director
Sleep HealthCenters®, LLC




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Cardiovascular Consequences of Sleep Apnea

Atul Malhotra, M.D. and James Fang, M.D.


Dr. Malhotra is an Assistant Professor of Medicine at Harvard Medical School, board certified in Internal Medicine, Pulmonary and Critical Care Medicine and a staff physician at Sleep HealthCenters®. Dr. Fang is an Assistant Professor of Medicine at Harvard Medical School, Medical Director of Heart Transplantation and Circulatory Assistance, Director of Cardiovascular Fellowship Training Program at Brigham and Women's Hospital and board certified in Cardiovascular Medicine.

Case Study: A 55 year old woman presented to her primary care physician for management of hypertension. She had no other cardiac risk factors and her review of systems was negative. Physical exam revealed a blood pressure of 160/100 but no other evidence of cardiovascular disease. Her lungs were clear to auscultation. Her body mass index was 28kg/m². Over the course of the next 6 months, she was started on three different anti-hypertensive medications (hydrochlorothiazide 50 mg, atenolol 100mg, amlodipine 10mg). However, her blood pressure remained persistently elevated at 150/95. The patient was rather concerned, and was adamant that she was compliant with her medications. A 24 hour ambulatory blood pressure monitoring revealed a mean blood pressure of 148/93, with no major fluctuations over the course of the 24 hours. There was no overnight fall in blood pressure observed ("non-dipper").

Questions: What underlying etiologies for hypertension should be sought? What is the most common cause of refractory hypertension among compliant patients?

Case Study (continued): Hypertension that is resistant to therapy should trigger an evaluation for other conditions that can cause hypertension. An underappreciated primary cause of hypertension is obstructive sleep apnea (OSA). In fact, the Joint National Committee on Hypertension (JNC VII) lists sleep apnea first under "identifiable causes" to consider in the hypertensive patient (JAMA 2003; 289:2560-2572). OSA is a common disorder with major neurocognitive and cardiovascular sequelae. It is defined by recurrent collapse of the pharyngeal airway during sleep with associated hypoxemia, hypercapnia and surges in catecholamines. The fragmentation of sleep can lead to substantial daytime sleepiness including a reduced quality of life, marital discord, and a seven fold increased risk of motor vehicle accidents. Treatment can alleviate the symptoms. The usual first line therapy for the treatment of OSA is continuous positive airway pressure (CPAP). Other treatment options include weight loss, oral appliances or upper airway surgery.

A causal relationship has now been demonstrated between obstructive sleep apnea and systemic hypertension. The evidence for this relationship is based on rigorous mechanistic animal studies, large well-controlled epidemiological studies, longitudinal prospective epidemiological studies, and most recently interventional studies. Several studies have also demonstrated a high prevalence of OSA among patients with refractory hypertension. In a recent study by Logan et al (ERJ 2003; 21:241-247), the authors demonstrated a greater than 80% prevalence of OSA among patients who had persistent hypertension despite being on at least three anti-hypertensive medications. Moreover, the authors showed a robust decrement in blood pressure over the course of two months of CPAP therapy. This decrement was more pronounced for nocturnal blood pressure (14.4 mmHg fall) in contrast to daytime blood pressure (9.3 mmHg). There was no control group in this paper; however, several other papers have now demonstrated important reductions in blood pressure with the treatment of sleep apnea, compared to untreated controls. The data suggest that the biggest decrements in blood pressure occur for individuals with baseline hypertension (or those on anti-hypertensive medications). There are also cross-sectional data suggesting an important association between OSA and myocardial infarction, stroke, and congestive heart failure (Shahar et al, AJRCCM 2001; 163:19-25). Whether treatment of sleep (continued on page 2)


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In this issue of the Sleep HealthCenters® Newsletter...

- ▶ Cardiovascular Consequences of Obstructive Sleep Apnea
- ▶ CEO Corner: Sleep HealthCenters® Welcomes Roger Smith, D.O.
- ▶ Research Activities
- ▶ Announcements

Locations:

- ▶ Newton, MA - affiliated with Brigham and Women's Hospital
- ▶ Bedford, MA - affiliated with McLean Hospital
- ▶ Malden, MA - affiliated with Hallmark Health
- ▶ Boston, MA - affiliated with Beth Israel Deaconess Medical Center
- ▶ Jamaica Plain, MA - affiliated with Faulkner Hospital

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Sleep HealthCenters® Newsletter

(continued from page 1) apnea prevents the occurrence of myocardial infarction, stroke and congestive heart failure is the subject of ongoing investigation.

Case Study (continued): Further questioning of the patient revealed a nightly pattern of loud snoring and complaints of daytime sleepiness. The patient was sent for an overnight sleep study and found to have severe OSA, with 52 obstructive events per hour that also produced oxyhemoglobin desaturation, with a low of 83% seen.

This case also emphasizes that the stereotype of the OSA patient as an "older obese male with substantial alcohol and tobacco intake" can be misleading. At least 30% of OSA patients are non-obese, although many practitioners still limit screening to morbidly obese men. In addition, menopause is a major risk factor for OSA in women. Thus, the diagnosis of OSA should be considered even in patients that do not meet the conventional stereotype.

Case Study (continued): Before the patient could be started on therapy for OSA, she developed a myocardial infarction and was treated in a coronary care unit. The patient was seen in follow-up by a cardiologist to have her medications optimized and was put on carvedilol 25mg bid, lisinopril 40mg, furosemide 40mg b.i.d., atorvastatin 80mg, aspirin 81mg. She continued to have dyspnea on exertion of more than one block, and had a measured LVEF=30% on Echocardiography. She occasionally awakens in the middle of the night with paroxysmal nocturnal dyspnea.

Questions: What further diagnostic testing and therapy is appropriate? What is the impact of ventricular dysfunction on sleep and breathing?

Paroxysmal nocturnal dyspnea (PND), a classic symptom of heart failure, is a common manifestation of volume overload and Cheyne-Stokes Respirations (CSR). Features of CSR on polysomnography include a waxing and waning pattern of breathing, fluctuations in oxygen saturation, recurrent arousals from sleep when breathing is maximal, and surges in catecholamines as a result of hypoxemia and arousals. PND is usually related to the hyperpneic phase of the CSR breathing pattern. Although less common in women, CSR is seen in approximately 30-40% of patients with systolic heart failure (Javaheri et al, Circulation 1998; 97:2154-9). Risk factors for its development in this population include atrial fibrillation, hypocapnia, male gender, and age. It is seen more commonly in those with ischemic left ventricular dysfunction as compared with those with idiopathic dilated cardiomyopathy. The mechanisms underlying this cyclic pattern of breathing are complex but involve instability in the ventilatory control system due to high ventilatory drive and circulatory delays from the lungs to chemoreceptors (carotid bodies and brainstem).

The presence of CSR in heart failure has important prognostic and therapeutic implications. For example, when the presence of CSR is compared to other potential predictors of mortality (such

as demographic variables, echocardiographic indices, autonomic function, and ventricular arrhythmias) in a chronic heart failure population, only CSR (as quantified by the apnea-hypopnea index) and left atrial size were independently predictive of mortality. Such data strongly suggest that CSR is not only a marker of severe heart disease but has independent prognostic utility as well.

The first line treatment for CSR is the optimization of medical therapy, especially directed at relieving congestion. Aggressive management with angiotensin converting enzyme inhibitors, betablockers and diuretics can help resolve CSR and overall symptoms. When medications are already optimized, as in the case of our patient, nasal continuous positive airway pressure (CPAP) is the treatment of choice. CPAP works through several mechanisms, including improvement in arousals from sleep, improvement in oxygenation and reductions in cardiac preload and afterload.

Transmural pressure across the left ventricle (pressure inside minus pressure outside) is an important determinant of left ventricular afterload. Typically, the fall in pleural pressure during inspiration increases transmural pressure or left ventricular afterload. The inspiratory fall in pleural pressure during the hyperpneic phase of CSR may be exaggerated by the low compliance of the congested lungs and can therefore have substantial negative hemodynamic consequences. In a similar manner, the large falls in pleural pressure that occur during OSA can produce profound increases in transmural wall tension when OSA complicates heart failure. Treatment of either CSR or OSA with CPAP decreases the transmural wall tension by increasing the pressure around the heart (i.e., increasing the intrapleural pressure). CPAP also decreases cardiac preload by reducing thoracic venous return. Finally, CPAP acts to stabilize the breathing pattern and prevent the sympathetic surges associated with hypoxemia, hypercapnia, and frequent arousals. Together, these effects of CPAP can cause marked reductions in cardiac afterload and adrenergic tone, leading to improvements in cardiac function. For example, data suggest suppression of catecholamines, reductions in myocardial oxygen consumption, reduced ventricular ectopy and improvements in exercise tolerance as a consequence of treatment of CSR with CPAP. Most impressively, Sin, et al. (Circulation 2000; 102:61-66) reported improvement in transplant free survival in patients with systolic heart failure and CSR treated with CPAP when compared with controls. This preliminary observation has led to a larger multicenter trial called the CANPAP (Canadian Positive Airway Pressure) Study that is examining the impact of nasal CPAP therapy in heart failure. Until these data are available, we recommend a patient/physician discussion regarding the use of nasal CPAP for the medically optimized CHF patient with CSR.

Case Study (continued): A repeat sleep study showed both OSA and CSR. Treatment with CPAP eliminated both disorders. The patient's blood pressure was controlled with the use of medication and her PND resolved. (continued on page 3)

Summary: Breathing patterns during sleep can both affect cardiovascular function and be influenced by cardiac dysfunction. OSA is a known cause of hypertension, should be suspected in patients with difficult to treat or refractory hypertension and is not limited to overweight elderly males. Central sleep apnea, particularly CSR, occurs frequently in patients with congestive heart failure and can contribute to worsening of cardiac function if not treated. Both OSA and CSR can be easily diagnosed with overnight sleep studies and respond to treatment with CPAP.

For a fully referenced version of this article, visit the Sleep HealthCenters® website at www.sleephealth.com.

Research Activities

Sleep HealthCenters® and their related research affiliations are actively recruiting patients for the following studies:

Apnea Positive Pressure Long-Term Efficacy Study (APPLES)

A NIH-funded study examining the long-term effects on quality of life, neurocognitive function, sleepiness and mood of using Continuous Positive Airway Pressure (CPAP) to treat sleep apnea. The Sleep HealthCenter® affiliated with Brigham and Women's Hospital is recruiting patients age 18 or older who suspect they may have sleep apnea but have not been previously treated with CPAP or surgery. Subjects will be enrolled for six months (maximum of 7 months) and will receive extra medical attention as well as monetary compensation. Study contact: Denise Clarke 617-527-3501 ext. 146.

Heart Failure and Cheyne-Stokes Respiration

A research study investigating a new mode of positive pressure therapy for the treatment of Cheyne-Stokes respiration during sleep. The Sleep HealthCenter® affiliated with Brigham and Women's Hospital is recruiting patients age 21-80 with congestive heart failure (LVEF< 40%). The study involves one home study and up to four overnight studies in our sleep lab.

Study contact: Mary MacDonald 617-527-3501 ext. 162.

Restless Legs Syndrome

A placebo controlled, double blind, crossover trial to investigate the effectiveness of levetiracetam (Keppra®) in the treatment of Restless Legs Syndrome. The Sleep HealthCenter® affiliated with Brigham and Women's Hospital is recruiting patients age 18-85 who suffer from Restless Legs Syndrome (achy, creepy-crawly sensations in the legs, which get worse at night). Participation in this study involves clinic visits and four overnight sleep studies over a 14-week period. Compensation is available.

Other studies of Restless Legs Syndrome using other medication treatments do not require sleep studies.

Study contact: Lindsay Johnston 617-527-3501 ext. 115.

CEO Corner

Paul S. Valentine
President and Chief Executive Officer

We are pleased to announce the addition of another full-time physician at Sleep HealthCenters®. Roger Smith D.O., started on June 1st. Dr. Smith is board certified in sleep medicine, family practice, and psychiatry. He completed a sleep medicine fellowship at Stanford University and has been working in sleep medicine for over 10 years. His most recent position was as Medical Director of the Sleep Clinic of San Francisco. Dr. Smith is an Adjunct Clinical Instructor at Stanford University School of Medicine and a physician consultant for the U.S. Olympic Committee. As Sleep Medicine Consultant for the 1998 Winter Games in Nagano Japan and the 2000 Summer Games in Sydney Australia, Dr. Smith was author of the USOC travel strategies and jet lag guidelines documents. In addition to treating the entire range of sleep disorders, he has particular interest in sleep deprivation, circadian disorders, and insomnia.



At Sleep HealthCenters®, we strive to offer a quick turnaround time for patient appointments in both our sleep labs as well as in our clinics. Dr. Smith will strengthen the organization's ability to care for the increasing number of patients seen in our existing facilities, as well as prepare the organization for the opening of new comprehensive sleep disorders centers. Dr. Smith will also assume the medical directorship of our Bedford facility, Sleep HealthCenter® affiliated with McLean Hospital. Please welcome Dr. Smith to the Sleep HealthCenters® medical team.

Announcements

- Would you like to provide your patients with a screening tool for Obstructive Sleep Apnea (OSA)? Copies of Dr. David White's OSA screening tool can be ordered from SHC, free of charge, by contacting Jennifer Feldman at (617) 527-2227 ext.177.
- Sleep HealthCenters® recently signed a lease for a new comprehensive sleep disorders center in Weymouth, Massachusetts. We look forward to welcoming patients into the new facility between August and September 2004.



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