CLINICAL VIGNETTE

Obesity Hypoventilation Syndrome: Are you missing the diagnosis?

Eugenia Wen, M.D., Ravi Aysola, M.D.

Case Report

A 40-year-old woman with morbid obesity, hypo-thyroidism, Behcet's syndrome and seizure disorder presented to the emergency room with worsening dry cough and increased dyspnea on exertion for the past week. The patient denied fever, chills or chest pain. Her arthralgias and myalgias were unchanged from baseline. Her oxygen saturation decreased from 96% baseline to 89% with associated dyspnea walking in the hallway. Physical examination BMI of 43 kg/m2, clear lung fields and trace bilateral lower extremity edema on palpation. Her ABG showed pH 7.41/PCO2 50/PaO2 62/91% saturation on room air. The blood serum bicarbonate was 30 mmol/L. Chest CT angiogram ruled out pulmonary emboli as well as consolidation and pleural fluid. Old platelike atel-ectasis or post-inflammatory changes were noted in her inferior lingula and medial basal right lobe. The main pulmonary artery was enlarged, suspicious for pul-monary arterial hypertension.

The patient denied previous history of smoking, or asthma. She did have a childhood history of gasoline aspiration at 2 years old which required hospital-ization. Subsequent to the episode, she had bouts of recurrent bronchitis, but no further hospitalizations for pulmonary diseases. The patient also complained of sleep fragmentation, snoring and nonrestorative sleep. She is fatigued during the day but denied having unintentional sleep episodes with her usual activities. She denied nocturnal arousals, choking sensation, gasping for air, or palpitations. Her weight had increased over the past years attributed to her use of prednisone for Behcet's syndrome. She had a history of transverse myelitis in 2002 which resulted in severe leg pain. There was no respiratory muscle involvement. A normal MRI of cervical and thoracic spine was noted on her medical records two months prior to admission. Her TSH level was also normal. For her pain control, she uses methadone 10 mg tid and clonazepam 2 mg bid for anxiety.

The patient was admitted for dyspnea secondary to possible infectious etiology vs. cardiac decom-pensation. Echocardiogram showed normal ejection fraction, wall motions and trace tricuspid regur-gitation. Pulmonary function testing showed normal FEV1/FVC ratio of 83%, TLC 82% predicted and DLCO 84% predicted. She was discharged home with outpatient sleep follow up. An overnight poly-somnography showed overall apnea hypopnea index (AHI) of 1 episode/hr and the minimum oxygen saturation of 89% during REM sleep.

Introduction

The United States leads the world with increasing obesity. One third of Americans are obese. Over the past 20 years, extreme obesity defined as BMI >40kg/m2 has increased 5 fold from 1 in 200 adult to 1 in 33 adults[1]. With this rising trend, we as clinicians may be missing an important syndrome that may be mistaken as exacerbation of obstructive lung disease or ischemic cardiac disease with congestion. Patients with decompensating obesity hypoventilation syn-drome often present to the primary care office or the emergency room with complaints of worsening dyspnea or lower extremity edema. If undiagnosed, these patients will continue to have a poor quality of life, increased hospital admissions, intensive care admission, invasive mechanical ventilation, cor pulmonale as well as overall increased mortality rate. Obesity hypoventilation syndrome is a diagnosis of exclusion. In its simplest form, it is defined as daytime hypercapnea with elevated awake PCO2 >45mmHg, BMI >35 kg/m2 with the exclusion of pulmonary, neurologic, neuromuscular disorders, or medications that could result in carbon dioxide retention. In up to 90% of the cases, obstructive sleep apnea is also present.

Epidemiology

Obesity hypoventilation syndrome (OHS), also known as Pickwickian syndrome, was recognized and described earlier than obstructive sleep apnea by Burwell in 1956[2]. The prevalence in patients with

obstructive sleep apnea syndrome (OSA) seen in sleep disorders clinic ranged between 10-20%[3]. A study of hospitalized patients with BMI >35 kg/m2 found OHS in 31%. In patients with BMI >50kg/m2, OHS was found in 48%[4]. As with OSA, Asian patients with OHS tend to have lower BMI than Caucasians due to cephalometric differences in facial and neck structures.

The definition of OHS is evolving as the disease is better understood. The current definition includes the diagnosis of sleep related breathing disorder (SRBD) to the prior criteriae, making a triad of elevated BMI (>35kg/m2), awake hypercarbia (PCO2>45mmHg) and SRBD[3]. Because OHS is a diagnosis of exclusion, pulmonary parenchymal or obstructive disease as well as neurologic disorders, musculo-skeletal diseases, hypothyroidism, medication induced hypoventilation must be ruled out. Sleep related breathing disorder in OHS is mostly OSA in 90% of cases. Ten percent of patients will have a normal polysomnography study with an apnea hypopnea index < 5/hr. Most of these patients have central hypoventilation syndrome which is inferred from nocturnal polysomnography's persistent hypoxemia with saturation <90% despite no evidence of apnea or obstructive hypopnea. Transcutaneous CO2 monitoring had been used in these cases and showed an increase of PCO2 by 10 mmHg from awake to sleep confirming presence of hypoventilation[3].

Comparison of OHS with eucapneic OSA

The presentation of patients with OHS is very similar to patients with OSA. Chief complaints include excessive daytime sleepiness, snoring, unrestorative sleep, nocturnal arousals with or without choking episodes or snore arousals, observed apneas, poor concentration and morning headaches. Unlike the patients with eucapneic OSA, OHS patients have more dyspnea at rest and with exertion. During overnight polysomnography, OHS patients spend more time during sleep with hypoxemia (saturation <90%) than the patients with OSA (59% vs. 19%) despite matching BMI and AHI[5]. OHS patients have higher morbidity and mortality than matching eucapneic OSA patients. OHS patients are hospitalized more frequently with acute super-imposed on chronic respiratory failure, CHF exacerbation, angina pectoris, and cor pulmonale[1]. They are more frequently admitted to the ICU and require invasive mechanical ventilation support. OHS patients who remain untreated have a reported

18 month mortality rate of 23%, vs. 9 % in patients with eucapneic OSA and same BMI[6]. The treatment for OHS is also more complex than OSA.

Pathophysiology

Not all obese patients have OSA and not all OSA patients have OHS despite similar BMI. The pathophysiologic mechanisms behind these disorders is incomplete. OHS patients are capable of voluntarily hyperventilating to eucapnea, placing the defect in the central control mechanism. Obstructive apnea can cause acute hypercarbia if the apnea hypopnea index is high or if the apneic pauses are long with associated short inter-apneic recovery ventilation time. With persistent nocturnal hyper-carbia, renal compensation occurs with increased serum bicarbonate level. Higher serum bicarbonate levels can reduce central ventilatory drive. Another proposed mechanism for hypercarbia is leptin resistance[3]. Leptin is a respiratory stimulant as well as a satiety hormone that is produced by the adipose tissue. Obese patients have elevated levels of leptin which assists in their drive to breathe to compensate for the increased work of breathing associated with increased mechanical load of obesity. Central resistance to leptin is proposed as a possible mechanism since OHS and OSA patients have higher leptin levels than BMI matched eucapneic controls[7]. Lastly, sustained hypoxemia has been demonstrated to raise the arousal threshold with increasing airway resistance loads, in normal non-obese subjects[8]. The elevated arousal threshhold can cause hypoventilation and resultant hypercarbia, especially in a morbidly obese person.

Work up for OHS

Overnight polysomnography is routinely ordered as part of the work up for OHS. An ABG is the gold standard for confirmation of presence of hypercarbia. In its absence, there are 2 factors which can predict presence of OHS. An elevated AHI > 100/hr has a specificity of 85% and sensitivity of 45 % for the presence of OHS[6]. An elevated serum bicarbonate level (>27 mmol/L) had been used to detect of hypercarbia and predict the presence of OHS in patients with OSA with excellent sensitivity of 92% but low specificity of 50%[6]. This allows the evaluation of a patient for possible OHS without the invasiveness of an arterial blood gas. Since OHS is a diagnosis of exclusion, pulmonary function testing and chest imaging are routinely obtained to assess pulmonary reserve as well as for the presence of

parenchymal process. The FEV1/FVC ratio in OHS is generally normal, >77%. Very mild obstructive ventilatory defects may be present due to obesity associated reduction in lung compliance, atelectasis, increased airway resistance, resultant small airway closure and air trapping[7]. Mild restrictive ventilatory defect secondary to reduced ERV (TLC >77%) is often present from relative respiratory muscle weakness as well as an increased abdominal girth displacing the diaphragm upwards. A careful medical history should be taken with focus on the possible presence of neurologic or musculoskeletal disorders as well as a medication history to assess for narcotic or sedative hypnotic use. CBC and TSH are recommended to screen for secondary erythrocytosis and hypothyroidism.

Treatment for OHS

The treatment for OHS is directed at the correction of sleep related breathing disorder and weight reduction. Pharmacotherapy for hypoventilation carries higher risks of complications than the questionable benefits of treatments at this time and will thus not be addressed in this paper. CPAP therapy is the first line of treatment for OHS though its efficacy varies between 57% to 80% in clinical studies, depending on severity of OHS[6,9,10]. Its efficacy is related to patients' hours of adherence to therapy and is maximized after 4 weeks of treatment. Based on Mohklesi's study, PCO2 reduced by 1.8 mmHg/hr of CPAP use with its effect plateau out at 7 hours of use and PaO2 increased by 3 mmHg/hr of CPAP use with its effect plateau out at 4.5 hours of use. Only 6% of the initial 30% of patients on daytime home oxygen therapy prior to PAP treatment continued to need daytime home oxygen therapy after greater than 4.5hr/night use of PAP therapy[11]. There was no clear benefit demonstrated by use of biPAP ventilation over CPAP therapy in patients with mild OHS in the study by Piper et al[10]. Failure of CPAP therapy is generally defined as persistent hypoxemia despite the relief of obstruction/obstructive hypopnea or lack of an improvement of awake PCO2 with continued CPAP treatment. In cases of persistent hypoxemia on CPAP therapy, a change to BiPAP ventilation may further improve oxygen saturation.

Non-responders with persistent daytime hypercarbia were seen in 23% of the patients on CPAP therapy. These patients had lower AHI despite similar BMI than CPAP responders. Central hypoventilation is postulated to be the mechanism behind the non-responders. AVAPS (Average Volume-Assured Pressure Support) ventilation has been shown to be more effective in reducing PCO2 than BiPAP therapy in these non-CPAP repsonders in a small study[3]. AVAPS with BiPAP S/T ventilation has the combined benefit of the comfort of a pressure support mode and the consistency of tidal volume delivery of volume control ventilation. A pre-selected tidal volume (7-10 cc/kg) is chosen by the clinician and set into the machine. With a set EPAP (expiratory positive airway pressure) usually between 4-8 cm H2O, an IPAP (inspiratory positive airway pressure) is titrated by machine as needed at 1 cm H2O/min until the ventilator reaches its goal tidal volume. A back up respiratory rate can be entered at the discretion of the physician though OHS patients' respiratory rate remains high between 15-30 breaths per minutes during sleep[12].

Of note, the autoCPAP should not be used for the treatment of patients with suspected OHS due to its inability to correct the hypoxemia and hypoventilation which may be present in up to 43% of patients. This is important to remember with increasing use of the ambulatory home sleep studies and the subsequent use of an autoCPAP for treatment of OSA. Tracheostomy is a procedure of last resort for patients with severe OSH failing non-invasive positive pressure ventilation therapy. Hypoxemia and hypercarbia post-tracheostomy persist in these patients frequently without nocturnal full ventilator support.

Discussion

Our patient presented to the ER with the most common complaints of patients with OHS: dyspnea, unrefreshing sleep, snoring and daytime fatigue. She met criteria for a clinical diagnosis of obesity hypoventilation syndrome with elevated BMI of 42 kg/m2 and awake hypercarbia of 50 mmHg. Her pulmonary function test and CT chest did not show significant pulmonary pathology to account for the hypercarbia. No significant neurologic disorder or musculoskeletal disease was present to cause CO2 retention. Of interest, she did not have severe obstructive sleep apnea on the overnight poly-somnography. An argument can be made that she had central hypoventilation secondary to her narcotic and sedative hypnotic use. Since her condition did not allow cessation of use of these medications, the treatment remained the same. The patient had a repeat PSG with AVAPS titration study for the treatment of obesity hypoventilation syndrome. In OHS patients without frank obstruction, studies have

shown that CPAP therapy is unlikely to be effective in reducing PCO2. Weight management is also strongly encouraged.

Mokhleski describes OHS as a spectrum of disease, differentiated by the PSG, CPAP titration and the patient's response to CPAP therapy. One extreme has severe OSA with hypercarbia. The obstruction of airway during sleep (OSA) is the primary culprit of hypercarbia. These patient have high AHI that respond to CPAP therapy with relief of obstruction and normalization of PCO2 and PaO2. This composed of the majority (about 65%) of patients with OHS. On the opposite end of the spectrum of OHS, the patients (<10%) have normal PSG with apnea hypopnea index <5/hr, persistent hypoxemia and hypercarbia. In the middle of the spectrum, there are OHS/OSA patients (about 25%) that are not responsive to the CPAP therapy with persistent hypoxemia and hypercarbia due to reduced central receptor sensitivity. The later 2 groups of these patients generally benefit from biPAP S/T or biPAP S/T with AVAPS[3].

Conclusion

Obesity hypoventilation syndrome will increase in prevalence along with the global trend of increasing obesity. Untreated OHS increases mortality and morbidity beyond simple OSA or morbid obesity. These patients not only have a higher risk of death, they also have lower qualities of life, increased health care utilization including frequent doctors' visits, hospitalization, ICU admission, need for invasive mechanical ventilation and increased risk for the development of pulmonary hypertension. Morbidly obese patients with hypercarbia must be evaluated for the presence of obesity hypoventilation syndrome, especially those seen in hospitalized settings.

REFERENCES

1. **Sturm R**. Increases in morbid obesity in the USA: 2000-2005. *Public Health*. 2007 Jul;121(7):492-6. Epub 2007 Mar 30. PubMed PMID: 17399752; PubMed Central PMCID: PMC2864630.
2. **Burnwell CS, Robin ED, Whaley RD, Bickelmann AG**. Extreme Obesity Associated with Alveolar Hypoventilation: A Pickwickian Syndrome. *Am J Med*. 1956; 21(5): 811-818.
3. **Mokhlesi B**. Obesity hypoventilation syndrome: a state-of-the-art review. *Respir Care*. 2010 Oct;55(10):1347-62; discussion 1363-5. Review. PubMed PMID: 20875161.
4. **Nowbar S, Burkart KM, Gonzales R, Fedorowicz A, Gozansky WS, Gaudio JC, Taylor MR, Zwillich CW**. Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. *Am J Med*. 2004 Jan 1;116(1):1-7. PubMed PMID: 14706658.
5. **Kaw R, Hernandez AV, Walker E, Aboussouan L, Mokhlesi B**. Determinants of hypercapnia in obese patients with obstructive sleep apnea: a systematic review and metaanalysis of cohort studies. *Chest*. 2009 Sep;136(3):787-96. Epub 2009 Jun 30. Review. PubMed PMID: 19567489.
6. **Mokhlesi B, Tulaimat A, Faibussowitsch I, Wang Y, Evans AT**. Obesity hypoventilation syndrome: prevalence and predictors in patients with obstructive sleep apnea. *Sleep Breath*. 2007 Jun;11(2):117-24. PubMed PMID: 17187265.
7. **Piper AJ, Grunstein RR**. Obesity hypoventilation syndrome: mechanisms and management. *Am J Respir Crit Care Med*. 2011 Feb 1;183(3):292-8. Epub 2010 Oct 29. Review. PubMed PMID: 21037018.
8. **Hlavac MC, Catcheside PG, McDonald R, Eckert DJ, Windler S, McEvoy RD**. Hypoxia impairs the arousal response to external resistive loading and airway occlusion during sleep. *Sleep*. 2006 May;29(5):624-31. PubMed PMID: 16774152.
9. **Banerjee D, Yee BJ, Piper AJ, Zwillich CW, Grunstein RR**. Obesity hypoventilation syndrome: hypoxemia during continuous positive airway pressure. *Chest*. 2007 Jun;131(6):1678-84. PubMed PMID: 17565018.
10. **Piper AJ, Wang D, Yee BJ, Barnes DJ, Grunstein RR**. Randomised trial of CPAP vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation. *Thorax*. 2008 May;63(5):395-401. Epub 2008 Jan 18. PubMed PMID: 18203817.
11. **Mokhlesi B, Tulaimat A, Evans AT, Wang Y, Itani AA, Hassaballa HA, Herdegen JJ, Stepanski EJ**. Impact of adherence with positive airway pressure therapy on hypercapnia in obstructive sleep apnea. *J Clin Sleep Med*. 2006 Jan 15;2(1):57-62. PubMed PMID: 17557438; PubMed Central PMCID: PMC1894747.
12. **Ambrogio C, Lowman X, Kuo M, Malo J, Prasad AR, Parthasarathy S**. Sleep and non-invasive ventilation in patients with chronic respiratory insufficiency. *Intensive Care Med*. 2009 Feb;35(2):306-13. Epub 2008 Sep 16. PubMed PMID: 18795255.