SLEEP DISORDERED BREATHING IN ADULT NEUROLOGY PATIENTS

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Sleep is a daily stress test for the human ventilator. Normally, upon falling asleep the musculature in the upper airway relaxes and neuronal groups in the ventral medulla raise thresholds for tolerable carbon dioxide levels leading to (slightly) decreased gas exchange. These physiological processes evolve through the sleep cycle. In the lighter stages of NREM sleep (N1, N2) individuals are at risk of mixed events (combination of central and obstructive apneas and hypopneas) due to an inability to consolidate either sleep or wakefulness. Later during deep NREM sleep (N3) at risk individuals may develop the prolonged creshendo-decreshendo oscillations of Cheyne-Stokes periodic breathing. Ultimately, during REM sleep, due to the skeletal muscular paralysis that characterizes this fascinating cholinergic state, patients have the greatest tendency for both upper airway collapse as well as hypoventilation.

Sleep disordered breathing is reciprocal with neurological disease. Various pathologies of the brainstem or respiratory musculature can cause or exacerbate these disorders. Conversely sleep-related breathing disorders can lead to neurological disease. Examples include stroke with chronic untreated obstructive sleep apnea (OSA) or morning encephalopathy in hypoventilation syndromes. Additionally, sleep disordered breathing can be misattributed to an incidental brain lesion when the etiology stems from another systems pathology. The most frequent example of this is Cheyne-Stokes periodic breathing in the setting of stroke where there is (often undiagnosed) co-morbid cardiovascular disease.

Here we will review four disorders commonly seen in clinical neurology. They are: OSA, Opioid Induced Central Sleep Apnea, Hypoventilation, and Cheyne-Stokes periodic breathing.

Obstructive Sleep Apnea

Obstructive Sleep Apnea is a common disorder and increases with age. The NIH funded Sleep Heart Health Study (SHHS) reported a PSG confirmed diagnosis of OSA (AHI >15) in 18% of adult subjects (Young et al 2002). Prospectively, the Cleveland Family Study (CFS) demonstrated a 30%-40% increase in AHI over 5 years that was, not surprisingly, primarily related to BMI. The greater the BMI at baseline the greater the increase in AHI was half a decade later (Redline et al 2003).

However, numerous age-dependent, and primarily weight independent factors lead to progressive upper airway collapse. These include: 1) increase fatigability in pharyngeal relative to diaphragmatic musculature, 2) decreased genioglossus strength, 3) decreased thyroid function, 4) edentulism, and 5) decreased oral vibratory sensation and two-point discrimination. In addition, increasing sleep fragmentation leads to more mixed (combination of central and obstructive) apneas and hypopneas (Bliwise 2005). Thus disrupted sleep not only is a consequence of sleep-disordered breathing but leads to it among the elderly who have a predominance of light NREM sleep.

OSA increases the risk of cardio and cerebrovascular disease through several mechanisms: 1) Obstructive apneas lead to striking changes in intrathoracic pressure impairing both diastolic filling (preload), as well as systolic performance (afterload). 2) The respiratory events with cortical arousal lead to a hyperadrenergic state. 3) The intermittent upper airway collapse causes large fluctuations in cerebral perfusion. 4) Intermittent hypoxemia, more neuronal toxic then sustained hypoxemia, activates inflammatory cytokines and free radicals. 5) The combination of intermittent hypoxemia with hypo/hyperperfusion leads to cerebral vascular endothelial dysfunction and impaired vascular autoregulation. 6) Induction of stearoyl coenzyme desaturase leads to dyslipidemia and atherosclerotic lesions (Redline et al 2010).

After following subjects for 8 years, the SHHS confirmed that severe OSA in men leads to a threefold increase risk of stroke. In addition, SHHS data showed that OSA increases the risk of Afib, itself a reversible stroke risk factor, by fourfold. In women a link between OSA and stroke was seen but only in those with the highest OSA burden (AHI of > 25). The most likely explanation the sex-discrepancy in OSA risk is related to the nature of the

SHHS study and the fact that OSA does not typically manifest in women until after menopause. As the SHHS enrolled individuals over the age of 40 many of the women were premenopausal. Thus many of the women who would go on to develop OSA were not recognized at the time of the baseline sleep study (Redline et al 2010).

In general, the clinical significance of sleep disordered breathing decreases with age.

The strength of association between sleep apnea and several adverse outcomes all weaken. These include: cognitive dysfunction, cardiovascular disease, cerebrovascular disease and mortality. This is related in large part to the survivor effect, as many individuals, particularly obese subjects who had young-onset sleep apnea, do not survive into old age.

Clinically however, it is important to recognize that individual patients will demonstrate great variability and many elderly and patients do well with therapy and thus management should be customized to each individual patient.

As OSA is a mechanical problem it requires a mechanical solution. The most common therapy, nasal positive airway pressure (PAP) operates as a pneumatic splint holding the upper airway open throughout sleep. It is highly effective among individuals who can tolerate it and is considered first-line treatment among patients with severe disease. Additionally, PAP (when used) has been demonstrated to reduce recurrent vascular events in stroke patients (Martinez-Garcia et al 2005).

Unfortunately, only approximately 50% of individuals are still using the therapy after one year. Recently, an article in the New England Journal of Medicine provided further detail regarding the limited efficacy of this treatment. It showed, in an intention-to-treat analysis, that continuous PAP (CPAP) was not effective in decreasing cardiovascular events. The reason for this was a poor adherence to therapy (mean CPAP usage of only 3.3 hours per night) in the treatment arm (McEvoy et al 2016).

Clearly other options are needed.

As obesity is a strong predictor of upper airway collapse supervised weight loss is an important component of OSA management. Beyond weight loss and CPAP, alternative therapies include: dental appliances and upper airway surgery. Dental appliances look like an athletic mouth guards that, through mandibular stabilization help hold the airway open. These devices are often well tolerated but may not fully resolve all respiratory events and thus are best considered for patients with either mild to moderate disease or as salvage therapy among severe OSA patients who cannot tolerate CPAP. Various surgical procedures on the upper airway can be helpful to maintain a patent upper airway. These include: nasal turbinate reduction, uvulopalatopharyngoplasty, maxilomandibular advancement, and hypoglossal nerve stimulation, among others. These procedures are performed by otolaryngologists and like dental appliances are most effective in the setting on non-obese patients with mild to moderate OSA. However in the setting of treatment refractory severe OSA, these procedures can also be helpful as salvage therapy.

Additional strategies include avoiding ethanol and supine sleeping both of which promote upper airway collapse.

Opioid Induced Central Sleep Apnea

Since the turn of the millennium few medical trends have had such a profound impact upon public health as the growth in prescription opioids. Over half a million opioid prescriptions are dispensed in the United States each day. While these agents are effective at temporarily relieving pain their use has quadrupled the rate of overdose deaths. Since 1999 over 165,000 people have died from prescription opioid overdoses (Department of Health and Human Services 2016). More recently, since 2014, clinical practices have begun to change and opioid prescriptions have decreased in frequency. That drop however coincides with a rise in heroine and other synthetic available “black market” compounds such as fentanyl. On an individual level the opioid epidemic has destroyed lives as measured by employment, family happiness, and financial savings. On a macroeconomic scale, in the United States the health and social cost of opioids is $55 billion per year (CDC 2015).

During this time sleep physicians interpreting polysomnograms, have witnessed the rise in opioid induced central apneas. These events are characterized by intermittent, irregular pauses in respiratory effort and are typically of short duration, about 10-15 seconds. They are caused by the effect of opioids on the ventral and dorsal respiratory groups (VRG and DRG) of the medulla. Normally the steady rhythm of inspiration and expiration is coordinated through the pre-Botzinger complex of the VRG. These neurons form the respiratory pacemaker

generating a consistent respiratory rhythm. Respiratory dysrhythmias, characterized by pauses followed by normal tidal volumes, develop when the pre-Botzinger complex is exposed to opioids even at low doses. Higher opioid doses affect CO2 thresholds leading to decreased tidal volume and hypoventilation (Pattinson 2008).

Opioid induced central apneas differ from other respiratory events on polysomnography. Since central apneas are caused by an absence of neuronal activation to ventilator musculature there is a clear absence of respiratory effort; there is no snoring or thoracic/abdominal movements that would be seen in obstructive or mixed events. Unlike Cheyne-Stokes periodic breathing opioid induced central apneas occur at irregular intervals consistent with their dysrhythmic etiology. Cheyne-Stokes Periodic breathing (see below) demonstrates consistent creshendo-decreshendo respiratory effort and airflow that stems from a delay in circulation time (cardiovascular disease) (Eckert et al 2007, Yumino et al 2008).

Despite our insight into the mechanisms that lead to opioid induced central apneas we have only a superficial understanding in regards to the clinical meaning of these events. Central apnea is frequently conflated with OSA; the degree to which one has central events (measured by AHI) is equivalent to a similar degree of OSA. This is not the case. An example: if someone has an opioid induced central apnea index of 30 (AHI=30) they do not suffer the same cardiovascular, cerebrovascular, and cognitive consequences as an individual who suffers from an a similar degree of OSA (AHI=30). In general the evidence would suggest, that in the absence of intermittent hypoxemia, central apneas are far less consequential then a similar degree of obstructive events. For example, while the SHHS has helped quantify the risk of OSA on later cardiovascular disease, central apneas (in the absence of Cheyne-Stokes periodic breathing) has not been linked to cardiovascular disease (Yayan et al 2015). Further, patients with central apneas, once controlled for other factors, do not demonstrate the typical daytime consequences of OSA, such as daytime sleepiness (Yayan et al 2015).

Treatment data on opioid induced central apneas is even more limited. CPAP is not helpful as this therapy only serves to hold open an airway that in the case of central apneas is already open. Bi-level PAP therapy when used in a spontaneous mode may worsen central apneas by lengthening their duration. This occurs as the additional pressure support serves to excessively drive down CO2 during eupneic periods. Then during the subsequent apneas it takes a longer period of time without ventilation (waiting for the CO2 to rise and reach the respiratory threshold) to trigger the brainstem to initiate breathing. Bi-level PAP therapy with backup rates, along with related therapies such as adaptive servo ventilation (ASV), can minimize the number and duration of central events by ventilating the patient during apneas however it is not clear that decreasing central apneas leads to improved clinical outcomes (Javaheri et al 2014). Further we have no long-term cardiovascular outcome data and while one recent study of ASV treatment noted a drop in daytime sleepiness the majority of the events in this study were in fact obstructive, not central apneas (Javaheri et al 2015).

In conclusion, opioid induced central apneas are distinctly different from obstructive events and other central phenomena (Cheyne-Stokes periodic breathing). Their clinical relevance should not be conflated with nor quantified in the same manner. Further, treatment strategies need to be customized to each patient and in the setting of persistent daytime sleepiness other etiologies should be explored (sleep restriction, circadian misalignment, medication effect on daytime wakefulness, etc.).

Sleep Related Hypoventilation

Sleep related hypoventilation is a state dependent impairment in gas exchange. Unlike OSA, Central Sleep Apnea or Cheyne-Stokes periodic breathing, hypoventilation is not characterized by distinct respiratory events measured in seconds, but instead a prolonged failure in oxygen inhalation and carbon dioxide exhalation.

In a population of neurology patients the most common causes of hypoventilation are restrictions to chest wall excursions, either from obesity or neuromuscular disease such as Amyotrophic Lateral Sclerosis (ALS). Gas exchange is most severely impaired during REM sleep when accessory muscles of respiration are paralyzed and breathing is solely dependent upon the diaphragm.

Among patients with ALS hypoventilation is nearly universal. Fortunately, bi-level PAP treatment in a spontaneous mode is an effective therapy. This treatment provides the needed pressure support to improve gas exchange, decrease the work of breathing, and promote sleep continuity, all of which lead to improved daytime function and quality of life.

It is important to start bi-level PAP therapy early in patients with ALS as it prolongs survival (Lechtzin et al 2007, Carrati et al 2009, Radunovic et al 2013) and its effect upon quality of life can be dramatic.

Some ALS patients are hesitant to start bi-level PAP due to a concern about possibly becoming dependent upon it. These patients can be categorically reassured. In fact, by providing patients with decreased work of breathing at night their respiratory musculature is stronger during the day (Radunovic et al 2013).

Cheyne-Stokes Periodic Breathing

Few myths in medicine are as persistent as the idea that brain lesions cause Cheyne-Stokes periodic breathing (CSPB). This is not the case in the overwhelming number of patients with CSPB. CSPB is caused by a delay in circulation timing.

Under normal circumstances the lung-to-brainstem circulation time is less than 15 seconds. However in the setting of heart disease such as failure (diastolic or systolic), arrhythmia, or valvular disease the circulation can becomes delayed. In these cases alterations in CO2 or O2 fail to trigger an immediate appropriate response to the aberrant signal (either an increase or decrease in tidal volume). Thus the signal that would normally activate respiration with a rise in CO2 arrives late. The brain stem then begins sending output that increases tidal volume but continues to lag behind the rising CO2 until the patient with CSPB hyperventilates and then conversely begins to excessively drive down CO2. At this point the circulation delay fails to send the signal to avoid hyperventilation until CO2 has been excessively driving below the respiratory threshold and the cycle begins again.

While CSPB is seen in patients with stroke this is most commonly due to coexisting cardiovascular disease. Cardiovascular disease is often undiagnosed in cases of cerebrovascular disease and clinical investigations such as transesophageal echocardiography as well as prolonged EKG monitoring can help identify cryptic cardiac causes of CSPB.

CSPB can be treated with adaptive servoventilation (ASV) however it's utility has been curtailed in recent years because of reports indicating that this therapy can increase mortality among patients with reduced ejection fraction (Cowie et al 2015). The best therapy for CSPB is reversing, if possible, the underlying cardiac disorder.

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