Sleep Autonomics

- Overview of autonomic control during sleep
  - Cardiovascular
  - Respiratory
  - Thermoregulatory
- Case presentation

Sleep - Neurology Interface

- Autonomic:
  - Krzyzszak et al. -- Heart rate variability is decreased in pts w/ OSA even in the absence of HTN, CHF, or other disease states. (Circulation 1998)
  - Somers et al. -- Patients with sleep apnea have significantly higher amounts of sympathetic nerve activity. (J Clin Invest 1995)
  - Wing et al., Periodic limb movement during sleep is associated with nocturnal hypertension in children. (Sleep 2010)

- Headaches:
  - Goksan et al. 2009 -- Morning headache prevalence was significantly higher in severe and moderate OSA pts. (Cephalalgia 2009)

- Neurodegenerative Disorders: RBD & circadian rhythm disorders
Sleep & Autonomic System Interactions

- Sleep disorders may affect ANS function
- Autonomic Disorders may influence the physiology of sleep
- Common controls, substrate & functions

- Monoaminergic subgroups most active in wakefulness, become progressively less active in NREM sleep, and virtually cease firing in REM sleep
- Cholinergic neurons are active in both REM & NREM

Cardiovascular Regulation During Sleep

- NREM: Electrocortical synchronization, reduced muscle tone, stable parasympathetic predominance & sympathetic inhibition
  - Tonic decrease in arterial pressure & HR \( \Rightarrow \) reduced CO (Increased parasympathetic)
  - Hypotension secondary to decrease in peripheral resistance (sympathetic inhibition)
  - Hypotension & bradycardia become more pronounced as sleep progresses from N1 to N3 sleep
Cardiovascular Regulation

- Combination of lower arterial pressure, HR & sympathetic NS activities indicate that NREM sleep is accompanied by downward resetting and increased baroreceptor reflex gain.
- This increased baroreceptor gain contributes to the decreased cardiovascular variability in NREM sleep.

- In NREM sleep, arousal stimuli may cause sporadic transient sympathetic activity increase → appearance of K complex
  - Increased HR & respiration
  - Sudden awakening accompanied by more intense autonomic reactions.

- REM Sleep: Electro cortical desynchronization, muscle atonia & phasic motor changes.
- Phasic fluctuations of sympathetic & parasympathetic activities
- Impaired baroreflex & thermoregulation
- Tonic REM: Bradycardia & ↓ peripheral resistance → pressure decrease below that observed in NREM sleep.
- Phasic inhibition of parasympathetic activity & phasic increase in sympathetic discharge
- Large transient increases in arterial pressure & HR during bursts of REM & muscle twitches

CO falls progressively during sleep, with the greatest drop occurring during the last sleep cycle, especially during the last REM sleep.

Respiratory Regulation During Sleep

- NREM: control driven by chemical stimuli
- Hypoxic ventilatory response decreased in NREM sleep in men but not in women. The response is decreased in both genders in REM sleep.
- Hypercapnic ventilatory response decreased in NREM (20-50%) in NREM and further in REM
- Decreased # of functional medullary respiratory neurons during sleep.
Medullary respiratory neurons have a variable behavior in REM sleep → irregular breathing

Thermoregulation During Sleep

- ANS controls temperature regulation by generating responses sweating, shivering, and vasomotor adjustments.
- Thermoregulatory control varies between sleep stages and wake & time of the day

Thermoregulation

- NREM: Downward resetting of thermostat → reduced body core temp & metabolism.
- REM: Impaired hypothalamic regulation of autonomic responses → marked inhibition of thermoregulation → changes in body temp occur passively in relation to surrounding environment.
- Adults don’t sweat or shiver during REM sleep
  - Brown Fat?
Thermal environment can affect sleep architecture & influence amount of arousals
- 0.4°C increase in skin temp suppresses nocturnal wakefulness, increases N3 sleep & decreases the probability of morning awakening.
- Narcoleptics tend to have higher skin temp when asleep & awake

Case 1
- 64yro male w/ dream enactment
  - Likes to sleep naked and hugs wife to sleep. Recently has been scratching wife during sleep drawing blood. Occasionally kicks as if he were fighting. When awakened, he was able to recall dreams that usually involve grabbing & protecting his wife.
  - EDS, nocturnal snoring, and sometimes high pitched sound during inspiration.

Case 1
- 4yr hx of stiffness in b/l UE (R>L)
- Swallowing difficulties, hypophonia, postural instability
- Severe postural light-headedness
- Difficulty looking up when climbing stairs
- Constipation, impotence, difficulty initiating urination.
MSA

- Striatonigral degeneration, olivopontocerebellar atrophy & Shy-Drager Syndrome
- Sleep disorders affect approx. 70% of MSA patients (Ghirayeb et al, 2005)
  - Sleep fragmentation, vocalization, RBD, EDS
  - Nocturnal stridor
- 90% of MSA patients had PSG confirmed RBD
Magnitude of sleep disturbances tend to be associated with severity of motor symptoms and the duration of the disease.

- MSA patients did not show a higher PLMS index compared to matched controls.
- Circadian variation of arterial pressure, HR, body core temp & gastric motility are blunted in MSA patients.

Reduced sleep efficiency, total sleep time, N3 & REM sleep

- Increased sleep latency & recurrent awakenings
- Impaired circadian rhythm of melatonin secretion
- Stable HR & respiratory rate during REM that should be more variable than NREM
- Decreased heart rate variability following EEG arousals.

Laryngeal stridor & OSA

- Cheyne-Stokes respiration, centrally-mediated hypoventilation due to impaired neurons of the pontomedullary networks
- Stridor ➔ impaired breathing & abnormal control of respiratory muscles during sleep (ventrugno, 2004)
  - Important cause of death in MSA
  - Mechanism: laryngeal mm denervation vs dystonic vocal cord
  - Tx: Tracheostomy, CPAP, botox (10U to thyroarytenoid)
Case 2

- 55 yro obese male with PMH of PVD, sciatica, peripheral neuropathy, and poorly controlled DM II presented for syncope evaluation.
- Lightheadedness can be postural but can occur after a large meal.
- Worse with heat & humidity. No sz-like activities
- Diagnosed with vasovagal syncope since 16 yro

- Symmetric burning pain b/l LE up to mid calf. On gabapentin.
- Chronic fatigue, erectile dysfunction, reduced libido x several yrs.
- Gustatory sweating & early satiety
- No sudomotor complaints
- Heroic snorer, gasps out of sleep, EDS

- PE notable for resting tachycardia (~100 BPM, no significant change on standing.
- Supine BP = 160/78; standing BP 130/70
- Autonomic testing confirms OH, abnormal HRV, and abnormal hemodynamic responses to Valsalva maneuver.
• Hx of RLS but unresponsive to Requip and Mirapex
• Urge to move legs while sitting,
  - Crossing/uncrossing of legs, alternate plantar flexion of feet
  - No creepy crawly sensation
• Anytime of the day, not necessarily worse at night
• Worse since orthostatic intolerance worsened

Hypotensive akathisia: Autonomic failure associated with fidgeting while sitting
W P Cheshire Neurology 2000

• 6 pts with autonomic failure from various causes subconsciously perform countermanuevers to reduce symptomatic BP drop.
• When asked to hold legs still, BP declined to the point some have mental claudiness, lightheadedness & fatigue
• Voluntary urge to relieve symptoms → akathesia

Hypotensive Akathesia

• Leg restlessness occurs only when sitting, never recumbent.
• Sleep not disturbed
• Latency to leg movement longer in RLS
• Orthostatic BP drop is the trigger
  - Midodrine, florinef
Diabetic Autonomic Neuropathy

- Diabetic OH due to baroreflex pathway lesions → reduced vagal tone (decreased HRV)
- Predictor of increased mortality and sudden cardiac death (Kleiger et al.)
- Degeneration of sympathetic fibers to the splanchnic mesenteric bed
- Denervation of muscle resistance bed.

DAN

- Autonomic imbalance may trigger ventricular arrhythmias
- Long QT syndrome
- In moderate to severe OSA pts, DAN worsens respiratory event duration and influences severity of desaturation (Bottini et al., Eur Respir J 2003; 22: 654-660)
- OSA alters baroreflex

Case 3

- 31 yro previously healthy F with BMI of 23
- Posturally mediated lightheadedness & “racing heart rate” worse in heat & w/ exercise.
- Unrefreshed sleep, vague daytime fatigue, EDS “mental fog”, unable to stay on the treadmill for as long as before.
- Awakenings out of sleep w/ a rapid heart rate and drenching sweats
- Constipation & sx of gastroparesis
- Symptoms started after a bout of mononucleosis in 1997
Case 3

- Modified M-P class II, mild retrognathia, thyromental distance of 5 cm
- Epworth Sleepiness Scale score = 14. partner reports “heavy breathing” during sleep.

Postural Orthostatic Tachycardia Syndrome

- Orthostatic intolerance accompanied by sustained heart rate of >120 BPM or increase of >30 BPM within the first 10 minutes of Head-Up-Tilt or active stand.
- Pathology is complex and heterogeneous
  - Hyperadrenergic, peripheral denervation, hypovolemia, deconditioning, autoimmune, NE transporter gene mutation, Ehlers-Danlos Syndrome, NO
- Orthostatic intolerance accompanied by sustained heart rate of >120 BPM or increase of >30 BPM within the first 10 minutes of Head-Up-Tilt or active stand.

- Pathology is complex and heterogeneous
  - Hyperadrenergic, peripheral denervation, hypovolemia, deconditioning, autoimmune, NE transporter gene mutation, Ehlers-Danlos Syndrome

- Sleep dysfunction is often an important component of the clinical manifestation of POTS that is often neglected.

- POTS: The Mayo Clinic Experience (Thieben et al 2007)
  - Retrospective study of 152 pts
  - Symptoms abstracted from the medical record
    - 31.6% experienced pronounced sleep disturbance

- Orthostatic intolerance, fatigue, mental fogginess, poor concentration/memory, migraines, tremulousness, and frequent night time awakenings.

- Important to look for SDB in this population
  - SDB generally under-diagnosed in women, a population in which POTS is more common by ratio of 5:1
  - Fatigue, exercise intolerance ➔ cardiovascular decondition, weight gain ➔ SDB
Hyperadrenergic POTS

- Excessive sympathetic discharge due to high NE levels (>600ng/ml)
- Decreased upright NE clearance & increased sensitivity to adrenergic agonist.
- Co-morbid disorders such as SDB that lead to chronic sympathetic activation, if treated, could potentially optimize functional outcome for POTS pts.

Untreated OSA pts have elevated plasma and urine catecholamines (Dimsdale et al, Sleep 1995; 18 (5): 377-81)

- NE release rate is enhanced while clearance is reduced.
- W/ CPAP, circulating plasma and urine NE levels are markedly reduced as daytime NE clearance increased (Mills et al)

Ftal Familia Insomnia

- Rare neurodegenerative prion disease caused by a mutation in the prion protein gene (PRNP)
- Autosomal dominant. Age 40-60
- Affects thalomolimbic system
- Sleep disruption a hallmark
  - Dream Enactment
  - Persistent insomnia
  - Frequent awakenings & EDS
- Motor abnormalities: myoclonus, ataxia, pyramidal signs
- Unbalanced autonomic control w/ preserved parasympathetic activity but higher background & hyperactive sympathetic activity:
  - Excessive salivation & perspiration
  - HTN, tachycardia
  - Temperature dysregulation
- Energy expenditure is up to 60% more than in healthy control → severe metabolic exhaustion

**FFI PSG Findings**

- Progressive reduction in sleep spindles & K complexes
- Spindles not induced by barbiturates or benzodiazepines
- Loss of slow wave sleep
- Reduced total sleep time, severe sleep fragmentation and disruption of architecture
  - Continuous theta interrupted by sudden REM without atonia