New Concepts in Sleep Staging and Sleep Physiology

Robert Joseph Thomas, M.D., M.M.Sc.
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts

April 2006
The concept of sleep stability
Sleep stability and the slow oscillation
Phenotyping sleep-disordered breathing
Sleep stability assessment of therapeutic efficacy
The sleep instability in a model of heart failure
The flow of sleep

- **Global dimensions**
  - States: wake, sleep
  - States - abnormal: coma, anesthesia, minimally conscious, persistent vegetative
  - Transitions: falling asleep, awakening, lucid dreaming
  - Transitions - abnormal: sleep walking, night terrors, (maybe REM behavior disorder)

- “Onion” approach to sleep
  - Sleep and circadian interactions
  - REM / NREM cycles
  - Stable / unstable sleep (NREM / REM)
  - Stages, arousals
  - Neurochemical states
  - Gene expression

The stability dimension is at a critical “swing” point.
- Background EEG is Theta (3-7 cps.)
- K-Complexes and Spindles occur episodically.
- Mirrored EEG in the EOG leads.
- High tonic submenthal EMG.
• >50 of the epoch will have scorable Delta EEG activity
• The EOG leads will mirror all of the Delta EEG Activity
• Submental EMG activity will be slightly reduced from that of light sleep.
• Rapid eye movements.
• Mixed frequency EEG.
• Low tonic submental EMG.
Problems with the traditional model

- "Deep" sleep shows dramatic age-related changes
- Depth criteria are arbitrary
- Classic benzodiazepines reduce "depth" despite improving subjective and objective measures of sleep quality
- Poor correlations with disease outcomes
- Poor correlations with subjective assessments of restorative properties of sleep
- Raises the issue of "core" and "optional" sleep
  - Role of sleep with low / minimal delta power
- Does not explain some important clinical features:
  - Periods of stable and unstable respiration in sleep apnea patients
  - Fragmentation of the sleep cycles
Sleep wake stability

Stable wake

Unstable wake

Unstable sleep

Stable sleep
Stable wake - morning
Stable wake - evening
Unstable wake
Physiological unstable sleep
Pathological unstable sleep
Physiological stable sleep
Pathological unstable sleep
A simple but not perfect EEG marker of stability is Cyclic Alternating Pattern (CAP/ n-CAP)
Stage II CAP
Delta CAP
Unstable NREM sleep - normal respiration
CAP period
Non-CAP period
Integrated stage stability

- CAP was described originally as an EEG morphology.
- In reality, it spans all physiology during NREM sleep.
- CAP / n-CAP offered a new path to thinking about sleep
  - Works best in older individuals with low delta power or deep stage
  - Really problematic in the pediatric age group to apply criteria developed in adults
  - EEG can look very different individual to individual (problem)
  - EEG is dramatically modified by drugs (problem)
  - It overlaps but it not identical to stable sleep by other “deeper” measures

- Stability or instability applies equally well to REM sleep

- e.g., EEG is predictable from ECG or respiration, respiration is predictable from EEG or EEG, etc, etc
Unstable sleep
Unstable sleep
Stable sleep
Stable sleep
The slow oscillation and sleep stability

- The < 1 Hz oscillation is the core oscillation of NREM sleep
- Has a traveling wave characteristic
- Has regional distribution characteristics
- What is its relationship to the sleep stability domain?
CLUSTERING PROCESS OF SLOW OSCILLATION

Stage 4 (NCAP)
Continuous slow oscillation - slow wave sleep
Continuous slow oscillation - stage II sleep
Continuous slow oscillation - stage II sleep
Discontinuous slow oscillation - abnormal respiration
How sleep works

- Interactions between sleep and wake promoting networks (modulated by circadian drive) begin to allow expression of sleep (NREM or REM) homeostatic drive.
- For usual NREM sleep onset, the processes underlying the slow oscillation (SO) develops.
- The SO is discontinuous and oscillates at a frequency that has biological constraints but is entrainable (e.g., sleep apnea, timed auditory stimuli).
- This oscillation is expressed vertically through the brain (thalamic, brainstem, etc).
- Increasing homeostatic drive expression reaches a critical stage when the oscillation becomes continuous.
- At this point, there is a relatively abrupt switch to stable NREM sleep.
- These switches are very easily seen in patients with sleep apnea, because the temporal pattern of respiration seems to be a good integrated biomarker of state output.
- After a period of stable NREM sleep, within the same NREM period, there is a transient switch to the discontinuous SO, followed by a return to continuous SO.
- Stable REM sleep is free from wake / NREM intrusions.
- Sleep cycles are dependent on NREM-REM reciprocal inhibition mechanisms.
Is sleep stability important?

- Blood pressure dipping occurs only during stable NREM sleep
- Arousal-triggered arrhythmias
- Unstable sleep may not be restorative
- Circadian mismatch increases unstable NREM sleep
- All effective hypnotics probably increase stable NREM sleep

- As you will see, the oscillatory dynamics of unstable sleep provide profound insights into the interactions of respiratory control and upper airway anatomy
- Sleep stability is the **MOST** powerful influence on sleep respiration, even more than CO2 or O2 or the upper airway
Is unstable sleep important?
To put it all together

- **Stable sleep**
  - n-CAP EEG (usually, not always)
  - Temporal stability of respiration
  - Steady state arousability
  - Blood pressure dipping
  - Tonic sympathetic discharge
  - Protective (?) – arrhythmias
  - High frequency cardiopulmonary coupling
  - Restorative

- **Unstable sleep**
  - CAP EEG (usually, not always)
  - Temporal instability of respiration
  - Fluctuating arousability
  - Non-dipping of blood pressure
  - Bursting of sympathetic outflow
  - Arousal-mediated arrhythmogenesis
  - Intrusions of wake or NREM into REM
  - Low frequency cardiopulmonary coupling
  - Non-restorative

For participants in this course, ECG-HRV signatures are written all over these features.
Let's revisit the sleep spectrogram
Sleep spectrogram in a healthy 22-yr old

High-frequency coupling

Low-frequency coupling
Sleep spectrogram in a healthy 56-yr old

High-frequency coupling

Low-frequency coupling
SDB: Cardiopulmonary Coupling Detector
Measures Treatment Effects

High-frequency coupling

Low-frequency coupling
Summary of sleep stability in an autonomic - HRV context

- States are intensely integrated and modulated
- Integration and modulation are both vertical and horizontal
- Vertical integration ("biospatial")
  - Cerebral cortex-thalamus-brainstem-basal forebrain-limbic
  - The central autonomic network (CAN)
- Horizontal integration (temporal, multicomponent time series analysis)
  - Interactive and integrated flowing biological streams
  - Dissociations possible
- Thus, the ECG is better than the EEG in detecting state stability, but the measures are complementary
Phenotyping sleep-disordered breathing
Sleep spectrogram phenotyping of sleep-disordered breathing

- SDB is really a “spectrum disorder” with **TWO** possible underlying causes: Anatomy and breathing control
- “Complexity” is when breathing control is unstable

Anatomically Vulnerable Airway

Mixed Apnea

“Complex”

Neurologically Unstable Breathing Control
Complexity Is Deceptive

- Complexity has two deceptive features:
  - The events can be mostly or all obstructive
  - It usually goes away or is easier to control in REM sleep
- It can therefore mislead us in two ways:
  - We can confuse it with common obstructive apnea
  - We can think we have defeated it when we have not
NREM-dominant SDB
NREM-dominant SDB
Sleep Spectrograms Make Complexity Simple

**Complex:**
- Short and Regular Cycles, CPAP Failure Likely

**Non Complex:**
- Long and Irregular Cycles, CPAP Success Likely

**Central Apnea**
- Highly Regular: 25 secs
- Irregular: 25-180 secs

**Obstructive Apnea**
Phenotyping sleep-disordered breathing

First level mixed disease
- clues from events, oxymetry, visual timing estimation
Phenotyping sleep-disordered breathing

Control

Anatomy

Second level mixed disease - separate periods of control and anatomy mediated disease
Implication of spectrographic phenotyping of SDB

- Narrow-band low frequency cardiopulmonary coupling strongly predicts failure of positive airway pressure therapy.

- Broadband low-frequency cardiopulmonary coupling increases the probability of success with positive airway pressure therapy.

- Narrow-band low frequency cardiopulmonary coupling is common in the Sleep Heart Health Study database (present in at least 15%).
  - Hypertension association and pathophysiology.

- Our own clinical laboratory experience suggests 20%.

- Standard scoring approaches do not accurately identify complex forms of sleep apnea.
Effect of Enhanced Expiratory Rebreathing Space (EERS)

Before: best PAP + O₂

After: PAP + O₂ + EERS
CHF (EF 20%, on any PAP + O2)
CHF (EF 20%, 50 cc added EERS, BiPAP 17/12)
Treatment efficacy in heart failure with EERS

Failed treatment

Successful treatment
Summary of SDB-complexity in an autonomic/HRV context

- Sleep spectrograms allow phenotyping.
- The phenotypes have pathophysiologic significance.
- Phenotypes can guide therapy.
- Sleep spectrograms can track treatment efficacy, including in the home.
Is sleep stability a fundamental sleep characteristic?
Conserved behaviors
Sleep stability and heart failure
Sleep stability and heart failure

Dahl salt sensitive rat prior to initiation of high salt diet

Dahl salt sensitive rat on a high salt diet, 3-4 days before overt heart failure
Summary stability - CHF relationships

- Interaction between brain, sleep and heart are important
- Conserved characteristics allow application of the sleep spectrogram to animal models of heart failure
- Some questions that can be asked:
  - Is loss of sleep stability an early or late feature during CHF development
  - Role of unstable state in arrhythmia models
  - Can enhancing stable state slow progression to and of heart failure
  - Central correlates of state stability with activation in CAN
Summary

- Sleep works in a stability (bimodal), not graded dimension
- The stability dimension is deeply fundamental – present across species
- The sleep spectrogram is a relatively unbiased, simple, cheap, and automated method to assess state stability
- The sleep spectrogram is a powerful phenotyping tool for sleep apnea with clear clinical implications
- Other HRV/autonomic measures may usefully complement the sleep spectrogram
- Tracking of state stability in heart failure may provide insights into disease pathophysiology and open new avenues for therapy