Year in Review

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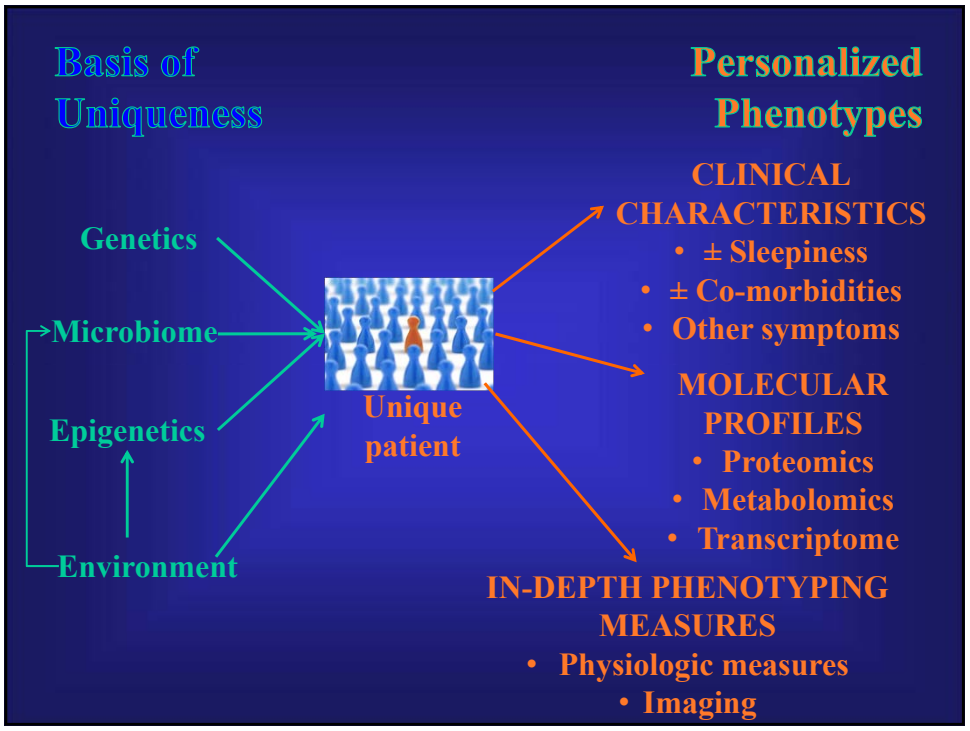
Outline of Lecture

- Personalizing approaches to obstructive sleep apnea
- New approaches to PSG analysis
- OSA and diabetes
- Applying telemedicine approaches



Clinical Subtypes of OSA?

PERSONALIZE

If there are different clinical types…

$$OSA = \sum OSA_1 + \sum OSA_2 + \sum OSA_3$$

Can we assess clinical symptoms by cluster analysis?

Cluster Analysis is Key Tool
What is Clustering?

- Given a specific set of variables, classify individuals into groups such that:
  - Within a specific group, individuals are as similar as possible
    - Minimize "Within Cluster Variance"
  - Individuals falling in different groups are as dissimilar as possible
    - Maximize "Between Cluster Variance"

Predict Using Clinical Features: 3 Distinct Clusters

(Ye L, et al, Eur Respir J 44:1600, 2014)

- Cluster 1 : Insomnia (32.7%)
  - Highest probability of Insomnia-related symptoms
  - Most likely to have frequent awakenings during sleep
  - Epworth Sleepiness Score = 9.5±0.7
    - BMI = 33.3±5.6; AHI = 43.8±20.4
- Cluster 2 : Asymptomatic (24.7%)
  - Highest frequencies of hypertension, diabetes and CVD
  - Most likely to feel refreshed upon awakening (>80%)
    - Epworth Sleepiness Score = 7.9±0.6
    - BMI = 33.0±5.6; AHI = 43.1±18.9
- Cluster 3 : Sleepy (42.6%)
  - Highest probability of falling asleep driving (36%)
  - Most likely to fall asleep during the day
    - Epworth Sleepiness Score = 15.7±0.6
    - BMI = 34.0±5.8; AHI = 46.7±21.7

FROM ICELANDIC SLEEP APNEA COHORT (ISAC)
NO DIFFERENCES IN BMI AND AHI BETWEEN CLUSTERS

Clinical Subtypes of Obstructive Sleep Apnea

PERSONALIZE

$$OSA = \sum OSA_1 + \sum OSA_2 + \sum OSA_3$$

Cluster 1: OSA + Insomnia

Cluster 2: Asymptomatic OSA

Cluster 3: OSA + Excessive Sleepiness

OPPORTUNITY TO ASSESS BROADLY IN CLINICS - ?MINIMAL INFORMATION REQUIRED

Are These Different Clinical Subtypes a Function of Referral patterns in Iceland or Are They Generalizable?[1]

- Have now replicated the clusters in sleep centers across the globe (Sleep Apnea Global Interdisciplinary Consortium—SAGIC)[2] and in population cohort in Korea (Korean Genomic Cohort)[3]

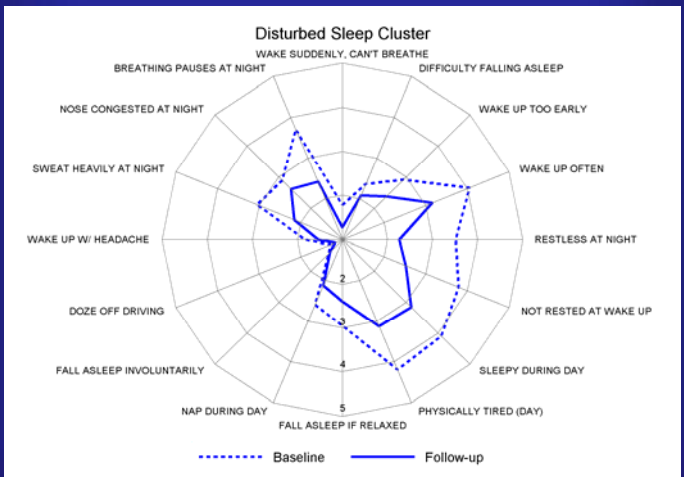
SAGIC is effort to get data on a large number of OSA patients for new analytical strategies (11 international sleep centers)

[1]Ryan CM, et al, Am J Respir Crit Care Med 192:1127, 2015
[2]Keenen, B, et al, Sleep 2018 Jan 5. doi: 10.1093/sleep/zsx214
[3]Kim J, et al, J Clin Sleep Med, in press

Does Clinical Cluster Determine Outcomes of Therapy?

Does Symptomatic Improvement with Therapy Depend on Initial Cluster – Disturbed Sleep

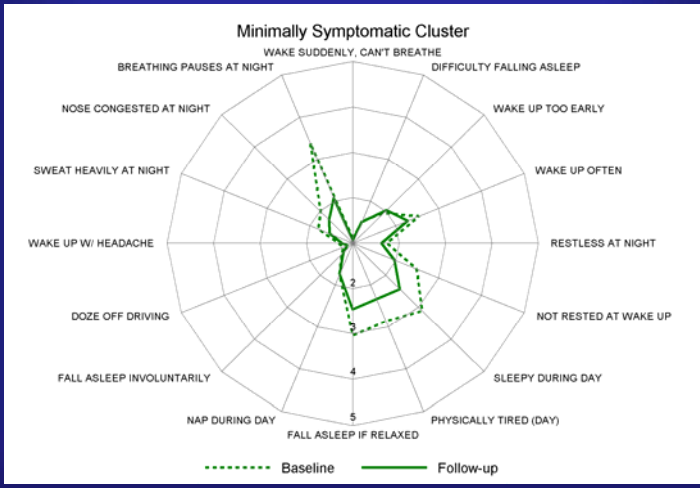
(Pien G, et al, Sleep 2018 Jan 2. doi: 10.1093/sleep/zsx201)



CHANGE IN EPWORTH SCORE = -2.06 ($P<0.001$)

Does Symptomatic Improvement with Therapy Depend on Initial Cluster – Asymptomatic Group

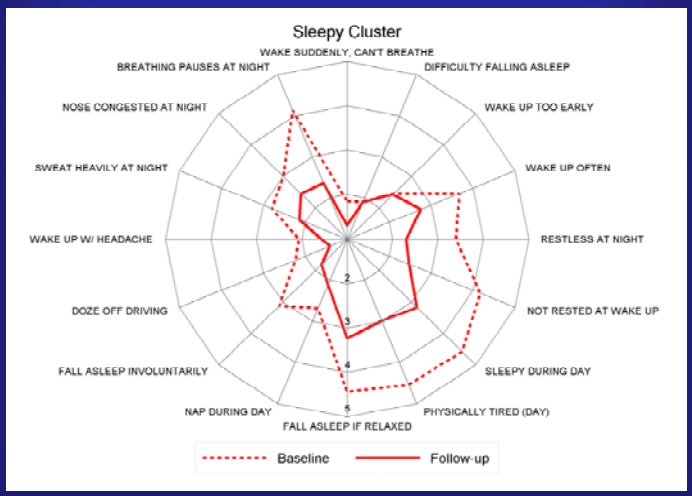
(Pien G, et al, Sleep 2018 Jan 2. doi: 10.1093/sleep/zsx201)



CHANGE IN EPWORTH SCORE = -1.33 (P<0.001)

Does Symptomatic Improvement with Therapy Depend on Initial Cluster – Sleep Group

(Pien G, et al, Sleep 2018 Jan 2. doi: 10.1093/sleep/zsx201)



CHANGE IN EPWORTH SCORE = -5.31 (P<0.001)

Hence, outcome of therapy is cluster-specific.

OPPORTUNITY TO BETTER DETERMINE PERSONALIZED OUTCOMES OF THERAPY AND CONSIDER PERSONALIZED TREATMENT APPROACHES

Classification Based on Physiological Features:

Current AHI Classification Based on Consensus (Chicago criteria)

Current	AHI events/hour
Normal	<5
Mild SDB	5-15
Moderate SDB	15-30
Severe SDB	>30

- **PSG rich in data – most data thrown out**
- **Obtain one number**
  - **why focus only on AHI?**
- **Do other physiological features better inform risk for different outcomes?**

CAN NEW FEATURES ENHANCE VALUE OF PSG?

What About Different Physiological Subtypes Based on Standard Variables Obtained by Scoring PSG

(Zinchuk AV, et al, Thorax Sept 21, 2017)

What About Different Physiological Subtypes Based on Standard Variables Obtained by Scoring PSG

(Zinchuk AV, et al, Thorax Sept 21, 2017)

Description of and labels for the polysomnographic clusters based on distinguishing features

Cluster (n)	Cluster label	Median AHI* (events/hour)	Conventional OSA severity*
A (533)	Mild	4	None/mild
B (119)	PLMS	10	None/mild
C (186)	NREM and poor sleep	19	Moderate
D (168)	REM and hypoxia	19	Moderate
E (75)	Hypopnoea and hypoxia	44	Severe
F (42)	Arousal and poor sleep	68	Severe
G (124)	Combined severe	84	Severe

→ CPAP reduces CV events

→ CPAP reduces CV events

Other Variables That Can Be Extracted from Sleep Study

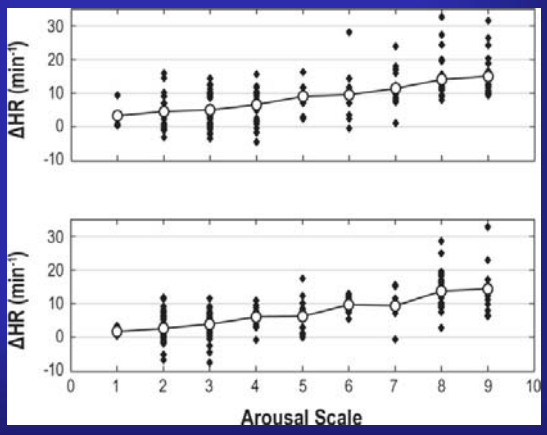
- Arousal intensity – individual trait (scale 1-9)[1]
- Heart rate response to arousal
  - Measure of sympathetic reactivity?
- Odds ratio product – continuous measure of sleep depth[2]
- Different measures of cyclical intermittent hypoxia
- Cardio-pulmonary coupling
- Heart rate variability

[1]Younes M, et al, Sleep 37:1833, 2014
[2]Younes M, et al, Sleep 38:641, 2015

Heart Rate Response to Arousal is Reproducible from Night to Night
(Azarbarzin A, et al, Sleep 38:1313, 2015)

Day One

Day Two



VARIES BETWEEN SUBJECTS

Twin Study Reveals Heritability of Arousal Responses and Heart Rate Response to Arousals

(Gao X, et al, Sleep 2017 Jun 1;40(6). doi: 10.1093/sleep/zsx055)

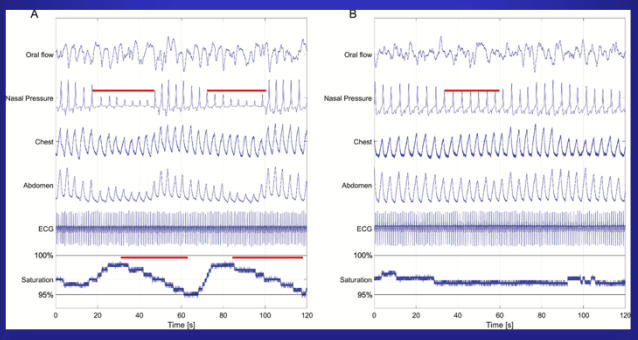
Estimates	Heritability
ΔHR as arousal 5	0.35 (0.56)*
ΔHR at arousal 8	0.91 (0.58)*

IS IT A MEASURE OF SYMPATHETIC RESPONSE?

*ANOVA estimate (maximum likelihood estimates)

Individuals Have Different Types of Events – With and Without Hypoxia

(Koch H, et al, Sleep 2017 Nov 1;40(11). doi: 10.1093/**sleep**/zsx152)



With Desaturation No Desaturation

Events from same patient

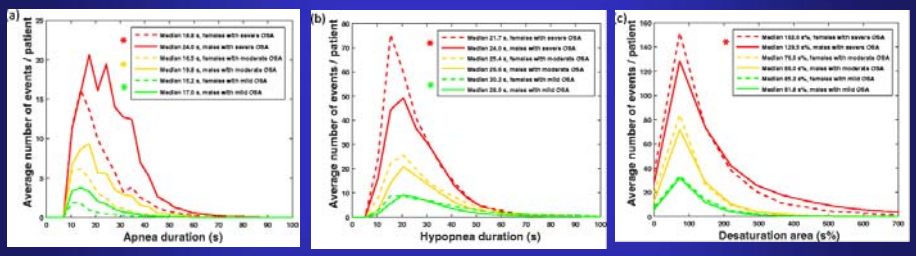
Consequences of Different Types of Events

(Koch H, et al, Sleep 2017 Nov 1;40(11). doi: 10.1093/**sleep**/zsx152)

- Hypoxic events associated with increased hypertension
- Non-hypoxic events increased objective sleepiness (MSLT)

Event Duration and Degree of Desaturation with Events Vary Between Individuals (Differences in Males and Females)

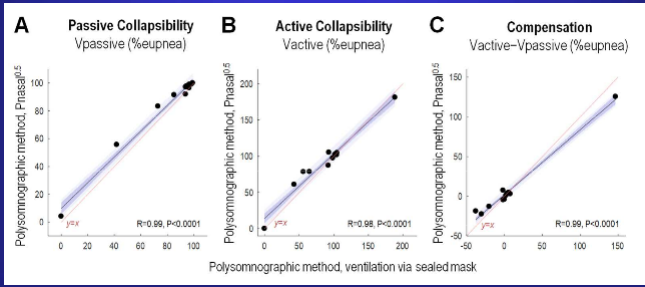
(Leppanen T, et al, Sleep Breath 21:397, 2017)



Obstruction severity parameter = average duration of events x desaturation area

Phenotyping Pharyngeal Pathophysiology Using PSG
(Sands SA, et al, AJRCCM Jan 2018)

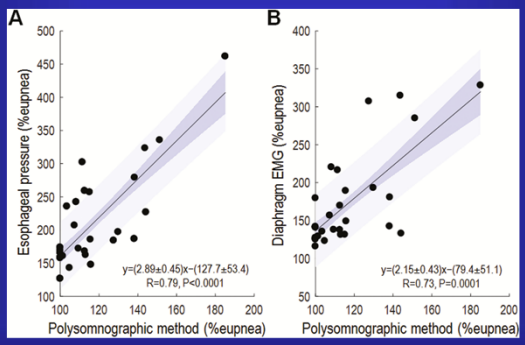
- Can be done using nasal pressure (n=11)



Obtains collapsibility and compensation data

Quantifying the Arousal Threshold Using PSG

(Sands SA, et al, Sleep 2018 Jan 1;41(1). doi: 10.1093/**sleep**/zsx183)



- Correlation with PSG measures and esophageal pressure (A) and diaphragm EMG (B) (n=29)
- Can also be done using nasal pressure (n=11)

Sleep Apnea and Diabetes

Diabetes and Obstructive Sleep Apnea

- Think beyond focus on glycemic control[1]
- OSA is independent risk factor for retinopathy in diabetes[2]
- Could association be due to vascular effects of OSA in retina?

[1]Ip M & Wong D, AJRCCM 196:807, 2017

[2]Altaf QA, et al, AJRCCM 196:892, 2017

- How do we deal with shortage of sleep medicine physicians?
- Is telemedicine part of the answer?

The Past is Prologue: The Future of Sleep Medicine

(Watson NF, et al, J Clin Sleep Med 13:127, 2017)

What are the solutions?

Team approach - integrating PCPs into sleep center programs; widespread application of telemedicine; use of mobile technology

Remote Ambulatory Management of OSA
(Fields BG, et al, Sleep 39:501, 2016)

- Parallel group, randomized trial (n=60)
- Telemedicine compared to in-person care

- No difference in change in self-reported outcomes or CPAP adherence
- Very positive feedback on telemedicine program

TELEMEDICINE MANAGEMENT OF OSA IS FEASIBLE AND GIVES GOOD OUTCOMES

Effects of Telemedicine Education and Tele-monitoring of CPAP Adherence – The Tele-OSA Trial
(Hwang D, et al, AJRCCM 197:117, 2018)

- 4 arm, randomized trial design
- Arms
  a. Usual care (n=129)
  b. Web-based education (n=163)
  c. Automated feedback of CPAP adherence (n=125)
  d. b+c (n=138)
- End-points – CPAP adherence, change in Epworth

Effects of Telemedicine Education and Tele-monitoring of CPAP Adherence
(Hwang D, et al, AJRCCM 197:117, 2018)

	Medicare Adherence (%)	Days Used (%)	Change in Epworth
Usual care	53.5	64.8	-3.7
Web education	61.0	68.6	-2.8
Automated feedback	65.6	76.6	-3.7
Both	73.2	78.3	-3.0
	P<0.001	P<0.001	NS

See also editorial by Farre R, et al, AJRCCM

Conclusions

- Major current research focuses
  - Personalized diagnosis and treatment of OSA
  - Reinventing the PSG – beyond the AHI
  - Applying telemedicine is an area of opportunity