

Journal Scan

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1. *PLoS One. 2012;7(12):e53481.*

Energy types of snoring sounds in patients with obstructive sleep apnea syndrome: a preliminary observation.

Lee LA(1), Yu JF, Lo YL, Chen YS, Wang DL, Cho CM, Ni YL, Chen NH, Fang TJ, Huang CG, Li HY.

BACKGROUND: Annoying snore is the principle symptom and problem in obstructive sleep apnea syndrome (OSAS). However, investigation has been hampered by the complex snoring sound analyses.

OBJECTIVE: This study was aimed to investigate the energy types of the full-night snoring sounds in patients with OSAS.

PATIENTS AND METHOD: Twenty male OSAS patients underwent snoring sound recording throughout 6 hours of in-lab overnight polysomnography. Snoring sounds were processed and analyzed by a new sound analytic program, named as Snore Map®. We transformed the 6-hour snoring sound power spectra into the energy spectrum and classified it as snore map type 1 (monosyllabic low-frequency snore), type 2 (duplex low- & mid-frequency snore), type 3 (duplex low- & high-frequency snore), and type 4 (triplex low-, mid-, & high-frequency snore). The interrator and test-retest reliabilities of snore map typing were assessed. The snore map types and their associations among demographic data, subjective snoring questionnaires, and polysomnographic parameters were explored.

RESULTS: The interrator reliability of snore map typing were almost perfect ($\hat{\kappa} = 0.87$) and the test-retest reliability was high ($r = 0.71$). The snore map type was proportional to the body mass index ($r = 0.63$, $P = 0.003$) and neck circumference ($r = 0.52$, $P = 0.018$). Snore map types were unrelated to subjective snoring questionnaire scores (All $P > 0.05$). After adjustment for body mass index and

neck circumference, snore map type 3-4 was significantly associated with severity of OSAS ($r = 0.52$, $P = 0.026$).

CONCLUSIONS: Snore map typing of a full-night energy spectrum is feasible and reliable. The presence of a higher snore map type is a warning sign of severe OSAS and indicated priority OSAS management. Future studies are warranted to evaluate whether snore map type can be used to discriminate OSAS from primary snoring and whether it is affected by OSAS management.

2. *J Clin Sleep Med. 2012 Dec 15;8(6):673-9.*

Sleep related expiratory obstructive apnea in children.

Haupt ME, Goodman DM, Sheldon SH.

STUDY OBJECTIVES: We describe the respiratory, cardiac, and sleep-related characteristics of two types of sleep-related respiratory pauses in children that can fulfill current criteria of pathological apnea, but often seem to be benign: prolonged expiratory apnea (PEA) and post-sigh central apnea (PSCA).

METHODS: All outpatient comprehensive overnight polysomnography completed on children without significant underlying medical conditions completed during an 18-month period were retrospectively reviewed for the presence of augmented breaths followed by a respiratory pause. Events were identified as a PEA or PSCA based on characteristic features. Physiologic parameters associated with the respiratory events were recorded and compared.

RESULTS: Fifty-seven (29 PEA and 28 PEA) events were identified in 17 patients (8.5 ± 3.5 years old). Median durations of PEA and PSCA were not significantly different. For both PEA and PSCA, average heart rate (HR) during the augmented breath before the respiratory

pause differed from lowest instantaneous HR during the first half of the pause. When compared to each other, the lowest instantaneous HR recorded in the first half of PEA was lower than that for PSCA (63.9 [59.41-68.3] vs 66.75 [61.7-80.75]) beats per min, $p = 0.03$. No PEA or PSCA event was associated with an oxygen desaturation more than 3% from baseline.

CONCLUSION: PEA and PSCA have stereotypic HR changes and resemble pathologic apneas but appear to be benign. Clinical significance of PEA and PSCA is yet to be determined. Consistent recognition of the events is required, given their frequency of occurrence and potential for misclassification.

3. *Chronobiol Int.* 2012 Dec;29(10):1358-65.

Health-related quality of life in adolescent chronotypes—a model for the effects of sleep problems, sleep-related cognitions, and self-efficacy.

Roeser K, Brückner D, Schwerdtle B, Schlarb AA, Kübler A.

In adolescence, the circadian preference shifts toward eveningness orientation. Eveningness seems to be negatively correlated with quality of life. The present study investigates influencing factors of this association and proposes a model for the mediating effects of sleep, sleep-related cognitions, and self-efficacy according to chronotype. The sample comprised $N = 280$ adolescents (172 girls) aged 14-16 yrs (mean=15.19, $SD=.76$). Circadian preference, health-related quality of life (HRQoL), sleep disturbances, sleep-related dysfunctional cognitions, and general perceived self-efficacy were assessed online.

Morning-orientated adolescents reported significantly higher HRQoL and less insomnia symptoms compared with evening-oriented chronotypes. In the total sample, insomnia symptoms mediated the relationship of chronotype and HRQoL. The strongest predictor of HRQoL in evening types was the degree of sleep-related dysfunctional cognitions. HRQoL in morning types was most strongly predicted by general self-efficacy, i.e., the global confidence in coping abilities. The findings support a negative relationship of eveningness and HRQoL in adolescents.

Insomnia symptoms were identified to be mediating factors in this relationship. The influence of the mediating factors on HRQoL differed between morning and evening types. The model provides implications of how to enhance HRQoL in adolescents according to their circadian preference.

4. *Chronobiol Int.* 2012 Dec;29(10):1376-82.

Circadian typology and sensation seeking in adolescents.

Muro A, Gomà-i-Freixanet M, Adan A.

The relationship of circadian typology with personality has been largely studied in adults, but there are few studies exploring such relationship in adolescents. Adolescence has been associated with a greater tendency to eveningness preference, sleeping problems, poorer academic achievement, earlier substance use, or risky behaviors, and it is suggested that this association might be mediated by personality factors. Given the relevance of identifying the behavioral outcomes of young evening types to detect and prevent health problems, the present study aimed to explore, for the first time, the relationship between sensation seeking and circadian typology in an adolescent sample of 688 students

(51.45% boys) from 12 to 16 yrs old. They answered the Spanish versions of the Morningness-Eveningness Scale for Children (MESC) and the Junior Sensation Seeking Scale (J-SSS), which includes four subscales measuring Thrill and Adventure Seeking, Experience Seeking, Disinhibition, and Boredom Susceptibility. Analyses showed that boys obtained significantly higher scores than girls on J-SSS total score and all subscales except Boredom Susceptibility, whereas evening-type adolescents of both sexes scored significantly higher than neither types and than morning types on J-SSS total score. These results indicate that evening-type adolescents show a greater desire for varied, new, complex, and intense sensations, and they are ready for experiencing more risks than morning types. The implications of this study suggest the need of being aware of individual differences in the SS trait in evening-type adolescents, as well as taking into account the wide variety of behaviors associated with it, either prosocial or antisocial, to design better preventive health and academic programs.

5. *J Clin Sleep Med.* 2012 Oct 15;8(5):527-33.

Detection of sleep disordered breathing and its central/obstructive character using nasal cannula and finger pulse oximeter.

Sommermeier D, Zou D, Grote L, Hedner J.

STUDY OBJECTIVE: To assess the accuracy of novel algorithms using an oximeter-based finger plethysmographic signal in combination with a nasal cannula for the detection and differentiation of central and obstructive apneas. The validity of single pulse oximetry to detect respiratory disturbance events was also studied.

METHODS: Patients recruited from four sleep laboratories underwent an ambulatory overnight cardiorespiratory polygraphy recording. The nasal flow and photoplethysmographic signals of the recording were analyzed by automated algorithms. The apnea hypopnea index (AHI(auto)) was calculated using both signals, and a respiratory disturbance index (RDI(auto)) was calculated from photoplethysmography alone. Apnea events were classified into obstructive and central types using the oximeter derived pulse wave signal and compared with manual scoring.

RESULTS: Sixty-six subjects (42 males, age 54 ± 14 yrs, body mass index 28.5 ± 5.9 kg/m²) were included in the analysis. AHI(manual) (19.4 ± 18.5 events/h) correlated highly significantly with AHI(auto) (19.9 ± 16.5 events/h) and RDI(auto) (20.4 ± 17.2 events/h); the correlation coefficients were $r = 0.94$ and 0.95 , respectively ($p < 0.001$) with a mean difference of -0.5 ± 6.6 and -1.0 ± 6.1 events/h. The automatic analysis of AHI(auto) and RDI(auto) detected sleep apnea (cutoff AHI(manual) ≥ 15 events/h) with a sensitivity/specificity of 0.90/0.97 and 0.86/0.94, respectively. The automated obstructive/central apnea indices correlated closely with manually scoring ($r = 0.87$ and 0.95 , $p < 0.001$) with mean difference of -4.3 ± 7.9 and 0.3 ± 1.5 events/h, respectively.

CONCLUSIONS: Automatic analysis based on routine pulse oximetry alone may be used to detect sleep disordered breathing with accuracy. In addition, the combination of photoplethysmographic signals with a nasal flow signal provides an accurate distinction between obstructive and central apneic events during sleep.

6. *J Vis Exp.* 2012 Sep 27;(67). pii: 4234.

Monitoring cell-autonomous circadian clock rhythms of gene expression using luciferase bioluminescence reporters.

Ramanathan C, Khan SK, Kathale ND, Xu H Liu AC.

In mammals, many aspects of behavior and physiology such as sleep-wake cycles and liver metabolism are regulated by endogenous circadian clocks (reviewed). The circadian time-keeping system is a hierarchical multi-oscillator network, with the central clock located in the suprachiasmatic nucleus (SCN) synchronizing and coordinating extra-SCN and peripheral clocks elsewhere. Individual cells are the functional units for generation and maintenance of circadian rhythms, and these oscillators of different tissue types in the organism share a remarkably similar biochemical negative feedback mechanism. However, due to interactions at the neuronal network level in the SCN and through rhythmic, systemic cues at the organismal level, circadian rhythms at the organismal level are not necessarily cell-autonomous. Compared to traditional studies of locomotor activity *in vivo* and SCN explants *ex vivo*, cell-based *in vitro* assays allow for discovery of cell-autonomous circadian defects. Strategically, cell-based models are more experimentally tractable for phenotypic characterization and rapid discovery of basic clock mechanisms. Because circadian rhythms are dynamic, longitudinal measurements with high temporal resolution are needed to assess clock function. In recent years, real-time bioluminescence recording using firefly luciferase as a reporter has become a common technique for studying circadian rhythms in mammals, as it allows for examination of the persistence and dynamics of molecular rhythms. To monitor cell-autonomous circadian rhythms of gene expression, luciferase reporters can be introduced into cells via transient transfection or stable transduction. Here we describe a stable transduction protocol using lentivirus-mediated gene delivery. The lentiviral vector system is superior to traditional methods such as transient transfection and germline transmission because of its efficiency and versatility: it permits efficient delivery and stable integration into the host genome of both dividing and non-dividing cells. Once a reporter cell line is established, the dynamics of clock function can be

examined through bioluminescence recording. We first describe the generation of P(Per2)-dLuc reporter lines, and then present data from this and other circadian reporters. In these assays, 3T3 mouse fibroblasts and U2OS human osteosarcoma cells are used as cellular models. We also discuss various ways of using these clock models in circadian studies. Methods described here can be applied to a great variety of cell types to study the cellular and molecular basis of circadian clocks, and may prove useful in tackling problems in other biological systems.

7. *Chronobiol Int.* 2012 Oct;29(8):1078-97.

An improved method for estimating human circadian phase derived from multichannel ambulatory monitoring and artificial neural networks.

**Kolodyazhnyi V, Späti J, Frey S, Götz T
Wirz-Justice A, Kräuchi K, Cajochen C
Wilhelm FH.**

Recently, we developed a novel method for estimating human circadian phase with noninvasive ambulatory measurements combined with subject-independent multiple regression models and a curve-fitting approach. With this, we were able to estimate circadian phase under real-life conditions with low subject burden, i.e., without need of constant routine (CR) laboratory conditions, and without measuring standard circadian markers, such as core body temperature (CBT) or pineal hormone melatonin rhythms. The precision of ambulatory-derived estimated circadian phase was within an error of 12 ± 41 min (mean \pm SD) in comparison to melatonin phase during a CR protocol. The physiological measures could be reduced to a triple combination: skin temperatures, irradiance in the blue spectral band of ambient light, and motion acceleration. Here, we present a nonlinear regression model approach based on artificial neural networks for a larger data set (25 healthy young males), including both the original data and additional data collected in the same protocol and using the same equipment. Throughout our validation study, subjects wore multichannel ambulatory monitoring devices and went about their daily routine for 1 wk. The devices collected a large number of physiological, behavioral, and environmental variables, including CBT, skin

temperatures, cardiovascular and respiratory functions, movement/posture, ambient temperature, spectral composition and intensity of light perceived at eye level, and sleep logs. After the ambulatory phase, study volunteers underwent a 32-h CR protocol in the laboratory for measuring unmasked circadian phase (i.e., "midpoint" of the nighttime melatonin rhythm). To overcome the complex masking effects of many different confounding variables during ambulatory measurements, neural network-based nonlinear regression techniques were applied in combination with the cross-validation approach to subject-independent prediction of circadian phase. The most accurate estimate of circadian phase with a prediction error of -3 ± 23 min (mean \pm SD) was achieved using only two types of the measured variables: skin temperatures and irradiance for ambient light in the blue spectral band. Compared to our previous linear multiple regression modeling approach, motion acceleration data can be excluded and prediction accuracy, nevertheless, improved. Neural network regression showed statistically significant improvement of variance of prediction error over traditional approaches in determining circadian phase based on single predictors (CBT, motion acceleration, or sleep logs), even though none of these variables was included as predictor. We, therefore, have identified two sets of noninvasive measures that, combined with the prediction model, can provide researchers and clinicians with a precise measure of internal time, in spite of the masking effects of daily behavior. This method, here validated in healthy young men, requires testing in a clinical or shiftwork population suffering from circadian sleep-wake disorders.

8. *J Clin Sleep Med.* 2012 Jun 15;8(3):251-5.

Risk of obstructive sleep apnea lower in double reed wind musicians.

Ward CP, York KM, McCoy JG.

STUDY OBJECTIVES: Obstructive sleep apnea (OSA) is caused by a collapse of the upper airway. Respiratory muscle training with a wind instrument (didgeridoo) in patients with moderate OSA has been previously shown to improve OSA symptomology.

However, a survey of orchestra members did not indicate a difference in OSA risk between wind and non-wind

instrumentalist. The present study examines whether playing of different wind instrument types may affect the risk of OSA.

METHODS: A national sample of active musicians (n = 906) was surveyed through the internet. Participants' risk for OSA was determined by the Berlin Questionnaire.

Additional survey items included questions about general health and musical experience.

RESULTS: A binary logistic regression was conducted to determine if OSA risk was predicted by gender, age, number of years playing instrument, number of hours per week playing instrument, and instrument type. Musicians who played a double reed instrument had a lower risk of OSA ($p = 0.047$) than non-wind instrumentalists. Additionally, in double reed instrumentalists, the number of hours spent playing the instrument predicted lower OSA risk ($p = 0.020$). The risk for OSA in other wind instruments (i.e., single reed, high brass, and low brass) was not significantly different from non-wind musicians.

CONCLUSIONS: Playing a double reed musical instrument was associated with a lower risk of OSA.

9. *Biomed Eng Online. 2012 May 24;11:26.*

Sleep/wake estimation using only anterior tibialis electromyography data.

Hwang S, Chung G, Lee J, Shin J, Lee SJ Jeong DU, Park K.

BACKGROUND: In sleep efficiency monitoring system, actigraphy is the simplest and most commonly used device. However, low specificity to wakefulness of actigraphy was revealed in previous studies. In this study, we assumed that sleep/wake estimation using actigraphy and electromyography (EMG) signals would show different patterns. Furthermore, each EMG pattern in two states (sleep, wake during sleep) was analysed. Finally, we proposed two types of method for the estimation of sleep/wake patterns using only EMG signals from anterior tibialis muscles and the results were compared with PSG data.

METHODS: Seven healthy subjects and five patients (2 obstructive sleep apnea, 3 periodic limb movement

disorder) participated in this study. Night time polysomnography (PSG) recordings were conducted, and electrooculogram, EMG, electroencephalogram, electrocardiogram, and respiration data were collected. Time domain analysis and frequency domain analysis were applied to estimate the sleep/wake patterns. Each method was based on changes in amplitude or spectrum (total power) of anterior tibialis electromyography signals during the transition from the sleep state to the wake state. To obtain the results, leave-one-out-cross-validation technique was adopted.

RESULTS: Total sleep time of the each group was about 8 hours. For healthy subjects, the mean epoch-by-epoch results between time domain analysis and PSG data were 99%, 71%, 80% and 0.64 (sensitivity, specificity, accuracy and kappa value), respectively. For frequency domain analysis, the corresponding values were 99%, 73%, 81% and 0.67, respectively. Absolute and relative differences between sleep efficiency index from PSG and our methods were 0.8 and 0.8% (for frequency domain analysis). In patients with sleep-related disorder, our proposed methods revealed the substantial agreement ($\text{kappa} > 0.61$) for OSA patients and moderate or fair agreement for PLMD patients.

CONCLUSIONS: The results of our proposed methods were comparable to those of PSG. The time and frequency domain analyses showed the similar sleep/wake estimation performance.

10. *Cochrane Database Syst Rev. 2012 May 16;5:CD007834.*

Iron for restless legs syndrome.

Trotti LM(1), Bhadriraju S, Becker LA.

BACKGROUND: Restless legs syndrome (RLS) is a common neurologic syndrome and is associated with iron deficiency in many patients. It is unclear whether iron therapy is effective treatment for RLS.

OBJECTIVES: The objective of this review was to assess the effects of iron supplementation (oral or intravenous) for patients with RLS.

SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Jan 1995 to April 2011); EMBASE (Jan 1995 to April 2011); PsycINFO (Jan 1995 to April 2011); and CINAHL (Jan

1995 to April 2011). Corresponding authors of included trials and additional members of the International Restless Legs Syndrome Study Group were contacted to locate additional published or unpublished trials.

SELECTION CRITERIA: Controlled trials comparing any formulation of iron with placebo, other medications, or no treatment in adults diagnosed with RLS according to expert clinical interview or explicit diagnostic criteria.

DATA COLLECTION AND ANALYSIS: Two review authors extracted data and at least two authors assessed trial quality. We contacted trial authors for missing data.

MAIN RESULTS: Six studies (192 total subjects) were identified and included in this analysis. The quality of trials was variable. Our primary outcome was restlessness or uncomfortable leg sensations, which was quantified using the IRLS severity scale in four trials and another RLS symptom scale in a fifth trial.

Combining data from the four trials using the IRLS severity scale, there was no clear benefit from iron therapy (mean difference in IRLS severity scores of -3.79, 95% CI: -7.68 to 0.10, $p = 0.06$). However, the fifth trial did find iron therapy to be beneficial (median decrease of 3 points in the iron group and no change in the placebo group on a 10 point scale of RLS symptoms, $p = 0.01$). Quality of life was improved in the iron group relative to placebo in some studies but not others. Changes in periodic limb movements were not different between groups (measured in two studies). Objective sleep quality, subjective sleep quality and daytime functioning were not different between treatment groups in the studies that assessed them. The single study of subjects with end stage renal disease did show a benefit of therapy. Most trials did not require subjects to have co-morbid iron deficiency and several excluded patients with severe anemia. The single study that was limited to iron deficient subjects did not show clear benefit of iron supplementation on RLS symptoms. There was no clear superiority of oral or intravenous delivery of iron. Iron therapy did not result in significantly more side effects than placebo (RR 1.39, 95% CI 0.85 to 2.27).

AUTHORS' CONCLUSIONS: There is insufficient evidence to determine whether iron therapy is beneficial for the treatment of RLS. Further research to determine whether some or all types of RLS patients may benefit from iron therapy, as well as the best route of iron administration, is needed.

11. *Sleep*. 2012 Apr 1;35(4):483-90.

The extracellular matrix of the lateral pharyngeal wall in obstructive sleep apnea.

**Dantas DA, Mauad T, Silva LF
Lorenzi-Filho G, Formigoni GG, Cahali MB.**

STUDY OBJECTIVES: To compare the components of the extracellular matrix in the lateral pharyngeal muscular wall in patients with and without obstructive sleep apnea (OSA). This may help to explain the origin of the increased collapsibility of the pharynx in patients with OSA.

DESIGN: Specimens from the superior pharyngeal constrictor muscle, obtained during pharyngeal surgeries, were evaluated using histochemical and immunohistochemical analyses to determine the fractional area of collagen types I and III, elastic fibers, versican, fibronectin, and matrix metalloproteinases 1 and 2 in the endomysium.

SETTING: Academic tertiary center. **PATIENS:** A total of 51 nonobese adult patients, divided into 38 patients with OSA and 13 nonsnoring control subjects without OSA.

INTERVENTIONS: Postintervention study performed on tissues from patients after elective surgery.

MEASUREMENTS AND RESULTS: Pharyngeal muscles of patients with OSA had significantly more collagen type I than pharyngeal muscles in control subjects. Collagen type I was correlated positively and independently with age. The other tested components of the extracellular matrix did not differ significantly between groups. In a logistic regression, an additive effect of both the increase of collagen type I and the increase in age with the presence of OSA was observed (odds ratio (OR), 2.06; 95% confidence interval (CI), 1.17-3.63), when compared with the effect of increased age alone (OR, 1.11; 95% CI, 1.03-1.20).

CONCLUSION: Collagen type I in the superior pharyngeal constrictor muscle was more prevalent in patients with OSA and also increased with age. It was hypothesized that this increase could delay contractile-relaxant responses in the superior pharyngeal constrictor muscle at the expiratory-inspiratory phase transition, thus increasing pharyngeal collapsibility.