

Differentiating between light and deep sleep stages using an Ambulatory Device Based on Peripheral Arterial Tonometry

Ma'ayan Bresler¹, Koby Sheffy², Giora Pillar³, Meir Preiszler², Sarah Herscovici²

¹University of California Berkeley

²Itamar-Medical R&D department, Caesarea, ISRAEL

³Sleep Laboratory, Technion-Israel Institute of Technology Haifa, ISRAEL

Running title: Sleep staging using PAT

Disclosure: M Preiszler, K Sheffy and S. Herscovici are employees of Itamar Medical, the developer of the Watch_PAT100 device. G Pillar is a consultant to Itamar Medical, and has received research grants from Cephalon Ltd and from Actelion Ltd. M Bresler has nothing to disclose. Itamar Medical Ltd. provided the research support necessary to conduct this study.

Address correspondence to:

Sarah Herscovici

Itamar Medical

Caesarea 38900

Israel

e-mail: sarah@itamar-medical.com

Abstract

Objective: To develop and assess an automatic algorithm based on the peripheral arterial tone (PAT) signal to differentiate between light and deep sleep stages. The PAT signal is a measure of the pulsatile arterial volume changes at the finger tip reflecting sympathetic tone variations and is recorded by an ambulatory unattended device, the Watch-PAT100, which has been shown to be capable of detecting wake, NREM and REM sleep.

Methods: An algorithm to differentiate light from deep sleep was developed using a training set of 49 patients and was validated using a separate set of 44 patients. In both patient sets, Watch-PAT100 data were recorded simultaneously with polysomnography during a full night sleep study. The algorithm is based on fourteen features extracted from two time series of PAT amplitudes and inters pulse periods (IPP). Those features were then further processed to yield a prediction function that determines the likelihood of detecting a deep sleep stage epoch during NREM sleep periods.

Findings: Overall sensitivity, specificity and agreement of the automatic algorithm to identify standard 30sec epochs of light and deep sleep stages were 66%, 89%, 82% % and 65%, 87%, 80% for the training and validation sets respectively.

Conclusions: Together with the already existing algorithms for REM and wake detection we propose a close to full stage detection method based solely on the PAT and Actigraphy signals.

The automatic sleep stages detecting algorithm could be very useful for unattended ambulatory sleep monitoring assessing sleep stages when EEG recordings are not available.

Key Words: Peripheral arterial tone, deep sleep stages, light sleep stages, REM sleep, sleep apnea. Minimum Least-Square Optimization,

INTRODUCTION

Non-Rapid Eye Movement (NREM) sleep was traditionally classified into 4 stages, where stage 1 was defined as drowsiness (just falling asleep), stage 2 as light sleep, and stages 3 and 4 as deep sleep, which is considered the more refreshing sleep. Both Stages 1 and 2 NREM sleep, classified as light sleep, are characterized by theta EEG activity. In stage 1 NREM there may be slow vertical eye rolling while stage 2 of NREM is characterized by sleep spindles and/or K complexes, no eye movements and reduced EMG activity. Stages 3 and 4 NREM sleep, classified as deep sleep, are characterized by delta EEG activity (which is the reason for the common term describing these stages as slow-wave sleep), no eye movements (although the EOG channels commonly show EEG artifacts), and even further diminished EMG activity (Lavie et al., 2002; Rechtschaffen and Kales, 1968). Given the more restorative nature of deep sleep, and the common findings of increased deep sleep following sleep deprivation or treatment for sleep disorders, it may be of substantial clinical importance to distinguish between light and deep sleep stages.

Recently, the AASM Visual Scoring Task Force re-examined these rules and came up with a new terminology for sleep stages. Since no evidence was found to justify dividing slow wave sleep into two stages, i.e. stages 3 and 4 of NREM sleep, it was proposed to combine these into a single stage of deep sleep (Silber et al., 2007) However, despite coming up with new scoring criteria, as with its predecessor (Rechtschaffen & Kales, 1968) the activity of the autonomic nervous system (ANS) still does not play a major role in scoring sleep stages, despite increasing evidence for substantial and differential activities of this system in the various sleep stages. In other words, regardless of the EEG changes measured via surface electrodes, light and deep sleep seem to differ by autonomic activations manifested predominantly as higher and more

stable parasympathetic activity in deep sleep than light NREM sleep (Dvir et al., 2002; Herscovici et al., 2007; Lavie et al., 2000; Narkiewicz et al., 1998; Penzel et al., 2000; Penzel et al., 2003; Penzel et al., 2004; Pressman and Fry, 1989; Villa et al., 2000; Virtanen et al., 2007). Thus, ANS such as heart rate, heart rate variability or peripheral arterial tone may be of significant importance in evaluating the quality of NREM sleep.

The Watch_PAT100 (WP100) is an ambulatory sleep recorder, which is based predominantly on recordings of the peripheral arterial tone (PAT) signal and pulse rate, (two important outputs of the autonomic nervous system), actigraphy and pulse oximetry (Bar et al, 2004, Penzel et al, 2004, Pillar et al 2003). It has been shown to accurately detect sleep vs. wakefulness (Hedner et al., 2004), as well as to detect REM sleep (Dvir et al., 2002; Herscovici et al., 2007; Lavie et al., 2000). Given the well established changes of the autonomic nervous system characteristics in patients with obstructive sleep apnea (Aydin et al., 2004; Brooks et al., 1999; Jo et al., 2005; Narkiewicz et al., 1998; Narkiewicz and Somers, 1997; Penzel et al., 2000; Penzel et al., 2003; Pepin et al., 1994), the WP100 has been tested on both normal subjects and patients with OSA (Bar et al., 2003; Dvir et al., 2002; Hedner et al., 2004; Herscovici et al., 2007; Lavie et al., 2000; Penzel et al., 2004; Pillar et al., 2003). However, the ability to distinguish between light sleep and deep sleep based on autonomic nervous system outputs monitored by the WP100 has not been examined. Since deep sleep has been shown to be associated with increased parasympathetic activity (such as heart rate and heart rate variability), and more regular and stable heart rate (Berlad et al., 1993; Bonnet and Arand, 1997; Brandenberger et al., 2005; Burgess et al., 1999; Busek et al., 2005; Elsenbruch et al., 1999; Ferri et al., 2000; Kirby and Verrier, 1989; Kodama et al., 1998; Liguori et al., 2000; Monti et al.,

2002; Negoescu and Csiki, 1989; Noll et al., 1994; Okada et al., 1991; Penzel et al., 2003; Pressman and Fry, 1989; Somers et al., 1993; Takeuchi et al., 1994; Trinder et al., 2001; Villa et al., 2000), we sought to develop an algorithm which will allow detecting and distinguishing light from deep sleep solely based on the PAT signal. (i.e. the vascular tone and the pulse rate both are channels of the WP100). This allowed us to test the hypothesis that autonomic nervous system output changes are sleep-stage dependent.

MATERIALS AND METHODS

Subjects

The study group consisted of two separate sets: A training set, used to develop the algorithm, and a separate validation set, used to validate the algorithms. The training set consisted of 49 adult patients (27 males) referred to the Technion Sleep Disorders Center for evaluation of presumed obstructive sleep apnea syndrome (OSAS), and an additional 6 young healthy volunteers (3 males) without any complaints of sleep disruption, daytime sleepiness, or snoring, recruited via advertisements in the Faculty of Medicine of the Technion, Haifa. The healthy volunteers were free of any disease and were on no medications. The exclusion criteria for the suspected OSAS patients were: permanent pacemaker, non-sinus cardiac arrhythmias, peripheral vasculopathy or neuropathy, severe lung disease, S/P Bilateral cervical or thoracic sympathectomy, finger deformity that precluded adequate sensor application, use of alpha-adrenergic receptor blockers (24 hours washout period required), alcohol or drug abuse during the last 3 years.

The validation set consisted of 44 adult OSAS patients (30 males), and 10 young healthy volunteers (8 males) recruited in the same manner as the training set and according to the same inclusion and exclusion criteria. The study was approved by the Rambam Medical Center committee for studies in human subjects, and patients signed an informed consent form prior to participation.

The training and validation groups did not differ statistically in RDI, age, BMI Desaturation index, mean SAO₂ values, arousal index percent of Deep Sleep percent of REM sleep and total sleep time (see table 1).

Protocol

All participants underwent a whole night polysomnography (PSG, Embla system, Flaga HF, Iceland) with simultaneous recordings of the Watch-PAT100 (WP100) device (Itamar- Medical LTD, Caesarea, Israel). The PSG and the WP100 were synchronized using a continuous synchronization bi-level signal generated by the WP100 and recorded on both devices. The 2 sets of signals (the one from the PSG and the one from the WP100) were then synchronized to compensate differences in internal clock of the 2 systems. The final error in synchronization time does not exceed 20 sec, By the end of the recording, the two data files (in PSG and in Watch-PAT) included the same synchronization signal and could thus be aligned exactly off line for head to head comparisons.

Prior to the study, patients completed a sleep questionnaire including physical data (e.g. weight and height), general health condition and medical history, medication usage, and sleep habits. Lights off were no later than midnight, and lights on at 06:00 AM. The mean start time of the test was 11 PM \pm 30min and the end of the test was 6:00 \pm 45min and the mean duration was 7.99 \pm 42 min

The WP100 was attached to the forearm of the dominant hand of the patient. The PAT probe was mounted on the index finger and the oximetry probe on the adjacent finger. Recording started with lights off and continued in a synchronized mode till lights on. The data quality of both the WP100 and the PSG were quite good and the signals recorded were valid for about 90% of the study.

The PSG files were scored for Apnea-Hypopnea index using Chicago criteria .Data was blindly double scored for stages to assess inter-scorer variability. The kappa coefficient for the

stages double scoring was .0.83 _which is considered “Almost perfect agreement” according to Landis and Koch (1977).

In-Laboratory WP100 recording

The WP100 device has been previously described, (Bar et al., 2003; Hedner et al., 2004; Margel et al., 2003; Penzel et al., 2004; Penzel et al., 2004; Pillar et al., 2003). Briefly, it consists of a battery-powered, wrist-mounted recording device and software for post-acquisition viewing and analysis of the recorded PAT data, which are derived from a specialized finger probe which records the arterial pulse. It records 4 signals: PAT signal (arterial pulse wave amplitude), pulse rate derived from the PAT signal, oxyhemoglobin saturation, and wrist activity (derived from an accelerometer). The WP100 device contains a rechargeable power supply, preliminary signal conditioning hardware, 100 Hz data acquisition, and data storage on a removable compact flash disk.

In-Laboratory Polysomnography

All subjects underwent a standard in-laboratory overnight PSG. Recorded signals included: EEG (C4-A1, C3-A2, O2-A1 and O1-A2), EOG, sub-mental and bilateral tibial EMG, ECG, airflow (nasal pressure and thermistor), chest and abdominal motion (piezo bands), oxyhemoglobin saturation, positive airway pressure, and body position. All physiological data were collected and stored on the digital polysomnography system (Embla, Flaga, Reykjavik, Iceland). PSG recordings were scored manually, with the scorer being blinded to the PAT signals. Sleep was blindly staged on the PSG according to standard R&K criteria and applying the updated AASM

Visual Scoring Task Force criterion to combine the stages 3 and 4 into one deep sleep stage (Rechtschaffen and Kales, 1968; Silber et al., 2007).

PAT Algorithms Description

The WP100 system is already equipped with a set of algorithms, well described in the literature, detecting Sleep, Wake, and REM stages using actigraphy and PAT signal, with an epoch by epoch high resolution performance (Hedner et al., 2004, Herscovici et al. 2007). The newly developed algorithm described in the current study is intended to further separate the non-REM epochs, and classify them into deep or light sleep epochs. . The actigraph is used to differentiate between sleep and wake periods only and not used for differentiation within the sleep periods between REM, deep and light sleep stages and neither is the oximeter.

A set of 14 normalized features in both the frequency and time domains were derived from the PAT signal amplitude (AMP) time series and the Heart Rate i.e. inter-pulse period (IPP) time series. All the variables were scaled to their mean value so that they could be interpreted as a conditional probability. From each of the time series, a set of 7 similar type of variables were derived, making it a total of 14 variables. Each such set of 7 variables included scaling coefficients of a detrended fractal analysis (DFA) , the mean value (mean Amp and mean heart rate) and 4 spectral components, as well as the ratio between high and low frequency . . All the variables and their conditional probabilities were computed within a 5 minute sliding window advanced by 30 seconds epochs.

DFA is the scaling DFA exponent of the amplitude (in the Amp time series) and heart rate (in the IPP time series), LF is peak low frequency spectral density, ULF is the peak ultra low frequency spectral density, VLF is the peak very low frequency spectral density, HF is the peak high frequency spectral density, and SpectRatio is the ratio of the peak low frequency density to the peak high frequency density. As said before, each such type of variable is derived from each of the two time series. The frequency ranges, corresponding to the respiratory, baro-receptor, thermoregulation and hormonal ranges, are 0.4 -- 0.15 Hz (HF), 0.15 -- 0.04 Hz (LF), 0.04 -- 0.015 Hz (VLF) and 0.015 -- 0.005 Hz (ULF) (Burgess et al 2004).

To combine and weigh each of the features we performed a 2 steps algorithm. The first step was to filter each of the features by defining a ± 5 minutes window around each epoch, allowing for smoothing around the epoch under consideration. This filter is defined as a Neighboring Filter (NF). The second step was done by choosing weightings that minimize the differences between the PSG staging and the PAT derived staging. Each feature was examined for the degree to which it differentiates between light and deep sleep, prior and after the filtering. The total probability equation can be written as follows:

$$Y_{est}(n) = \sum_{j=1}^{14} \sum_{k \neq 0}^{10} W_{jk} * X_j(n+k)$$

Equation 1 PAT stages probability computation equation

Where

$Y_{est}(n)$ is the Probability of an epoch n to be a deep sleep epoch

$X_j(n)$ is the value of each one of the 14 features at epoch n

And W_{jk} is the 21 filter coefficient of each k features

The weights are computed analytically to minimize the error in the identification process

Equation 2 minimization criteria and weights computation method

Where Y_{actual} is "1" if the n epoch is deep and "0" otherwise

$$W_{jk} = \text{Min} \left(\sum_{n=1}^N Y_{est_n} - Y_{actual_n} \right)^2$$

The least squares error between the stage estimates Y_{est} and the PSG stages Y_{actual} (a vector of length N corresponding to the PSG sleep stage of each epoch),

Optimization was performed on a training set of 49 sleep studies. Rather than optimizing each estimator (W_{jk}) separately, the algorithm uses a single level of optimization wherein a linear classifier acts on an enlarged feature set composed of 20 epochs for every variable.

Analysis method

The algorithm accuracy was assessed by applying the weighted coefficient computed from the training set to the validation set.

. The PAT studies were analyzed using the Actigraph algorithm to separate the sleep and wake periods using previously described algorithms (Hedner et al, 2004) . The REM periods were detected using the previously described REM algorithm (Herscovici et al., 2007). The Non-REM periods were then separated into deep and light sleep periods using the newly developed algorithm. The oximetry measurement is not used to differentiate between deep and light neither

the actigraph.. The comparison was done based on a 30sec epoch by epoch comparison. Comparisons of performance in different OSA severity groups were made to show that the algorithm is not impaired by OSA severity effects on the PAT signal. The Algorithm performance was evaluated for each RDI group stratified by mild (0-20), moderate (20-40), and severe (more than 40) .

The total sensitivity specificity and agreement were measured using the whole 27,597 (20,555 Light Sleep and 7,042 Deep sleep) from the PSG epochs for training and 24,383(18,320 Light sleep and 6063 Deep Sleep) epochs for validation. Mean values of sensitivity specificity and agreement based on per subject value were also computed as well as Kappa Cohen agreement

RESULTS

Training data set

Figure 1 shows the normalized histogram of the 8 major contributive variables with the relative separation of each .

Figure 2 shows the combined histogram of all the variables (14 variables) for the combined data of all the patients for deep and light sleep, and illustrates the separation without filtration, and figure 3 shows the separation including the NF. The filtered data improves the separation between stages by 2% in sensitivity and 8% in specificity. Without filters the sensitivity/specificity is 72% and 77 % respectively (threshold -0.325). By adding the filter, the sensitivity and specificity increase to 74 % and 85% when choosing the threshold at the intersection point (threshold -.2).

The last step is to choose a threshold for the clinical application. The threshold was chosen in order to bring up the total specificity on an ROC curve to approximately 90%.

(Threshold 0.1) The one chosen yields in the training set sensitivity, specificity and agreement values of 66%, 89 % and 82% respectively for the whole training set. The per subject mean values of the sensitivity specificity and agreement were (63%± 89% ± 0.83±) respectively for the whole training set the Kappa Cohen coefficient was 0.52 (moderate agreement). mean value of Kappa averaging patients in each group is (0.52± 0.17 ,0.56±0.20 and 0.55± 0.28) for light, moderate and severe RDI groups respectively.

. Figure 4 shows the total agreement of all the training set stratified to RDI categories. It can be seen that there is no substantial difference between the severe, mild and moderate OSA patient groups.

The Bland Altman in figure 5 shows no offset and no systemic error in the results.

Validation data set

In order to assess the accuracy of the algorithm it was tested on a separate validation set of 44 studies, reflecting a broad range of sleep apnea severity. The whole validation set shows 65%, 87 % and 80% sensitivity specificity and agreement values respectively. The mean value of sensitivity specificity and agreement of all the patients is 56% 87% and 81 respectively. The total sensitivity, specificity, and agreement values for the validation set were very similar at 66%, 89% and 82% respectively. The correlation of percent of deep sleep over the night with the PSG was $R=0.51$ ($P<0.05$) for the whole validation set. The per subject mean values of the sensitivity specificity and agreement were (56%± 87% ± 0.81±) respectively for the whole training set the Kappa Cohen coefficient was 0.57 (moderate agreement). Mean value of Kappa averaging patients in each group is (0.46± 0.19 ,0.42±0.1 and 0.54± 0.3) for light, moderate and severe RDI groups respectively.

. Figure 7 shows the Bland Altman of the percent deep sleep for the validation set. There is no systemic error in percent deep sleep.

Discussion

The major contribution of the current study is the development of a novel algorithm that can reasonably distinguish between light and deep sleep stages based solely on the PAT signal without depending on EEG monitoring. The agreement of this algorithm with PSG to identify standard 30sec epochs of light and deep sleep stages was validated to be 80%. Together with the previously described algorithms for wake and REM detection, the ambulatory WP100 is now capable of providing sleep stages without recording EEG, EOG and/or EMG channels. Thus, although WP100 cannot be utilized as a substitution for polysomnography, it can provide good assessment of sleep structure in the home setting.

The autonomic nervous system consists broadly of sympathetic and parasympathetic arms, the activities of which are generally elicited during different somatic states. While the sympathetic system is active during stress, the parasympathetic arm dominates during relaxed periods. These systems have been very well studied during wakefulness, but to a much lesser extent during sleep. Spectral analysis of heart rate variability demonstrated that NREM is associated with high parasympathetic activity while REM is characterized by attenuated vagal tone and augmented sympathetic activity. The overall pattern during wakefulness showed an intermediate position between NREM and REM patterns; parasympathetic activity was lower than in NREM and higher than in REM, with an opposite trend for sympathetic activity (Berlad et al., 1993; Futuro-Neto and Coote, 1982; Levy and Pepin, 2003; Liguori et al., 2000). In an

attempt to distinguish the circadian from the sleep effects on the autonomic nervous system it has been reported that there is a primarily circadian, but not sleep, influence on the parasympathetic nervous system activity, and primarily a sleep, but not circadian, influence on the sympathetic nervous system activity. While several studies demonstrated the differences of the autonomic nervous system activities between wakefulness, REM sleep and non-REM sleep (Berlad et al., 1993; Futuro-Neto and Coote, 1982; Levy and Pepin, 2003; Liguori et al., 2000; Somers et al., 1993), the differences between light and deep non-REM sleep stages was only marginally studied. It was reported that stage 2 sleep shows some duality activity with a quiet period preceding slow wave stage and an active period preceding REM sleep (Brandenberger et al., 2005). Studying muscle sympathetic activity, it has been shown that light sleep (stage 2) is associated with around a 10% reduction of sympathetic activity (of wakefulness values) while deep sleep (stages 3-4) resulted in greater sympathetic activity decrement of 29% of the awake value (Hornyak et al., 1991). Our current study, by showing that it is possible to accurately differentiate light sleep from deep sleep based on autonomic signals, further supports the presence of substantial changes in the output of the autonomic system during these two non-REM sleep stages. It should be kept in mind, however, that the sample in this study consisted of 93 adult patients with suspected OSA and 16 healthy adult volunteers. Thus, the findings may not be applicable for children or patients with other disorders for example insomnia

OSA has a substantial influence on both autonomic nervous system and sleep staging. While generally OSA is associated with increased sympathetic activation (Aydin et al., 2004; Brooks et al., 1999; Jo et al., 2005; Narkiewicz et al., 1998; Narkiewicz and Somers, 1997; Penzel et al., 2000; Penzel et al., 2003; Pepin et al., 1994), the breathing disorder is also known to result in decreased proportions of deep sleep stages (Malhotra and White, 2002; Pillar et al.,

2000). The accuracy of the current algorithm in detecting light and deep sleep across a large variety of apnea severity, suggests that sleep staging and autonomic nervous system changes may result from a similar patho-physiologic mechanism. The somewhat higher accuracy of the algorithm to distinguish between light and deep sleep in more severe OSA (Fig 4, Fig 6) suggests that the strong effect of the sleep disordered breathing on the autonomic nervous system makes it easier to stage sleep in these patients.

In the era of emerging need for simple easy fast and accessible home diagnosis of OSA, the current study is of considerable importance. The WP100 is a simple device located solely on the hand and recording autonomic signals from a finger, with actigraphy and oximetry. Its ability to accurately detect wakefulness, REM sleep and non-REM sleep (Dvir et al., 2002; Hedner et al., 2004; Herscovici et al., 2007; Lavie et al., 2000), as well as light/deep sleep (current findings), opens new horizons for the home diagnosis of OSA.

Until now the ability to stage sleep in the home was only possible using home PSG (Chesson et al., 2003; Flemons et al., 2003), however, the current results show for the first time the ability of a very simple device, based on 4 channels of information, that sleep can be staged not only by PSG. Thus, we show that the PAT signal, which was previously used to separate REM from the non REM sleep, is rich in information regarding the further stratification of sleep stages, specifically the separation between deep and light sleep stages. In this respect, it could be argued that the 80-82% agreement reported here is insufficient for clinical usage. However, these results, are within the range of variability between registered PSG scorers, as was reported by Nancy Collop (Collop, 2002). Norman et al. (Norman et al., 2000) reported even worse results. The mean epoch by epoch agreement between scorers was 73% (range 67-82%). Agreements were higher in the normal subset (mean 76%, range 65-85%) than in the OSA subset

(mean 71%, range 65-78%). Since our cohort consists of patients with OSA, we believe our results of 80-82% agreement exceeds those of the inter observer variability in scoring PSG by the traditional way. Furthermore, in a recent paper which evaluated the standard scoring to several combinations of automated scoring with partial review by a technologist (Morpheus and Somnolyzer24X7 systems) the results were substantially lower (agreements of 70%-72%, and were considered acceptable (Svetnik et al., 2007). Thus, again, we believe the current results are within the acceptable range for clinical usage.

Limitations

The current study has several limitations. First, the cohort size used is not large enough to ensure accuracy of the system. The algorithm has been developed on 49 records and validated on 44 ones. Although by looking at epoch-by-epoch based comparisons, the sample size is in the order of thousands, still further studies to test this algorithm on large population are required. Second, the cohort did not include other sleep disorders such as insomnia or parasomnia, some of which are known to affect the autonomic nervous system. Thus, the results of the current study should be at this time limited to patients with suspected OSA. Finally, the system is supposed to be utilized in the home, while in the current study it was tested in the lab. Thus, again, further studies are required to validate this system in the home settings.

Conclusions

Despite the above mentioned limitations, we believe our study convincingly shows that algorithm which is based on the PAT signal is capable of detecting light and deep sleep stages. It is not suggested that the WP100 can substitute the polysomnography, but together with the

previously described algorithms to detect wake non-REM and REM sleep, we believe that the current study shows a useful method to comprehensively stage sleep when EEG recording is not available, based on actigraphy and autonomic nervous system signals derived from the PAT signal.

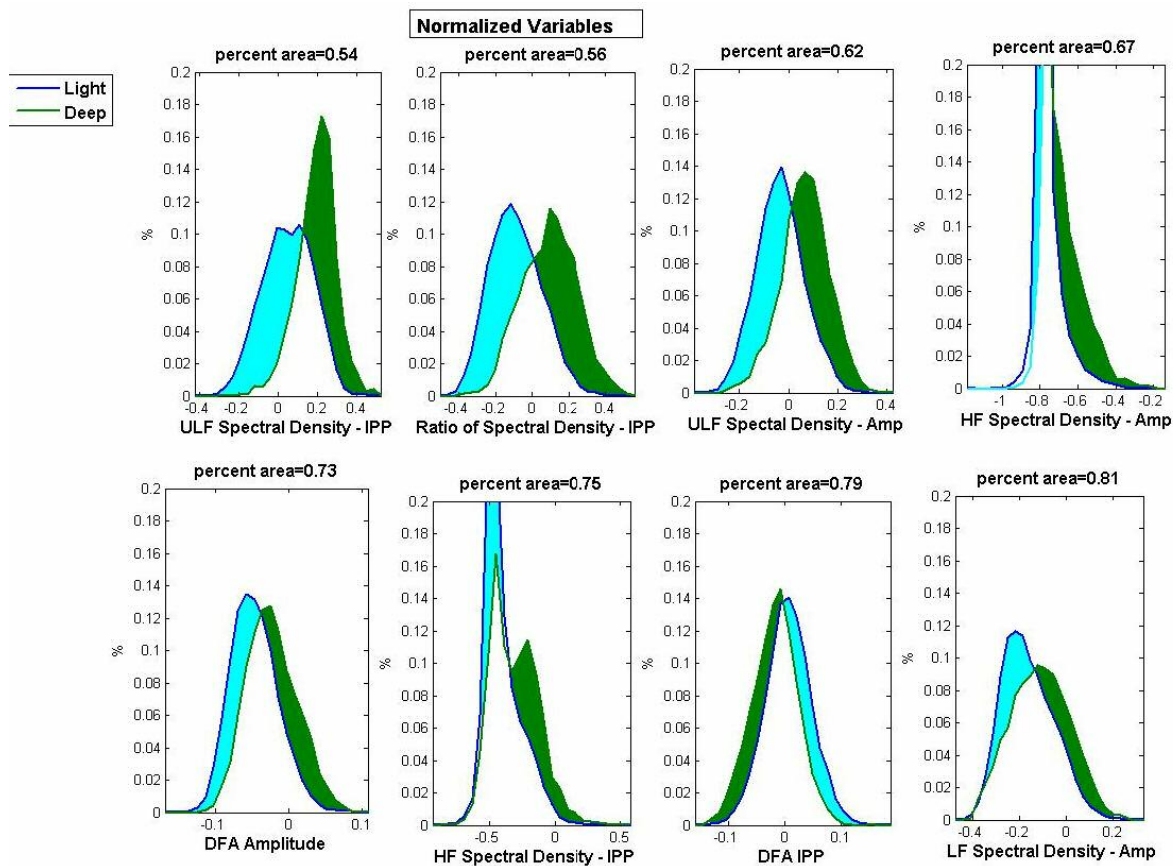


Figure 1: Histograms of separations for the variables that demonstrate the best separations (after NF). The best separation is given in the upper left panel and decreases clockwise. The dark green shaded region represents complete separation of deep sleep. The lighter blue shaded region represents complete separation of light sleep and the un-shaded area in between represents un-separation (overlap of the two). The value on top of the graph represent the un-separated area relative to deep sleep complete separation area (a lower ratio means better separation) .

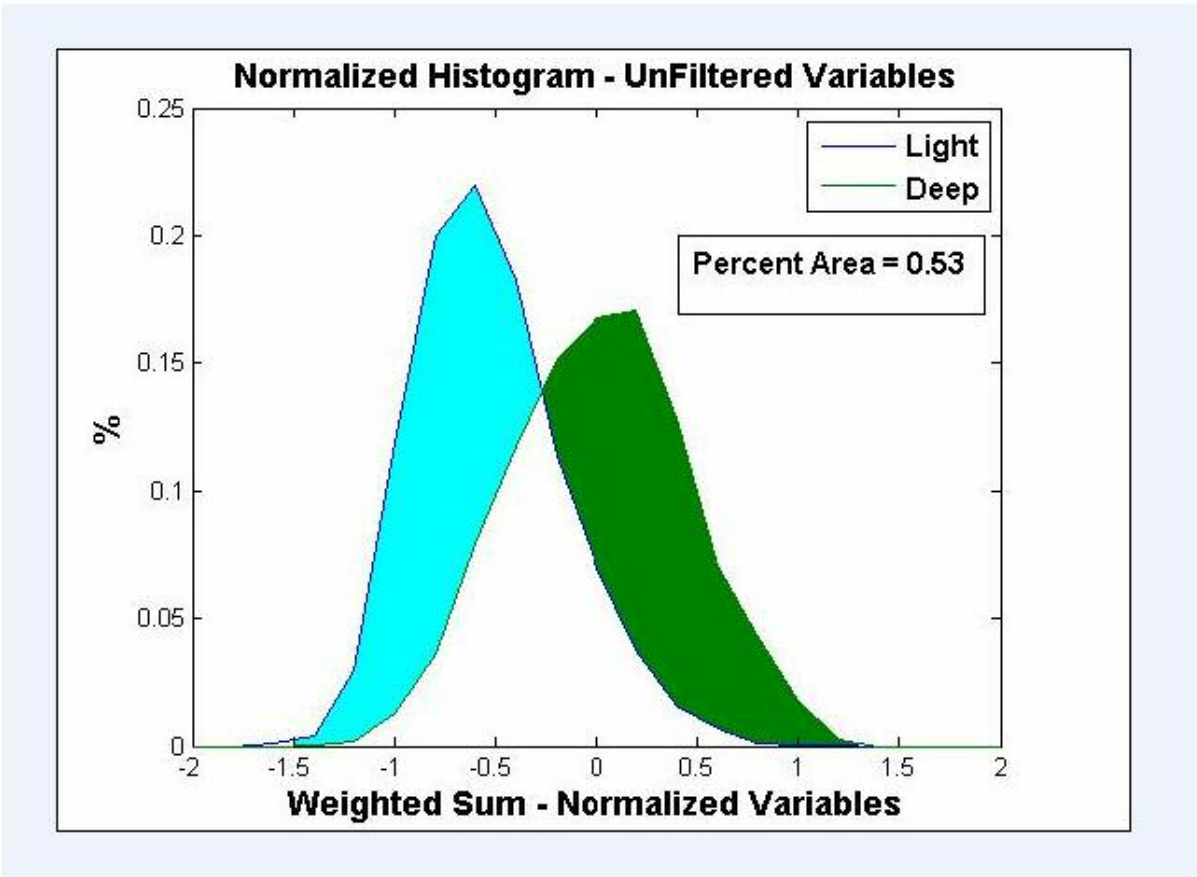


Figure 2: Weighted sum distribution Without NF. Shaded and un-shaded areas as in figures 1 & 2

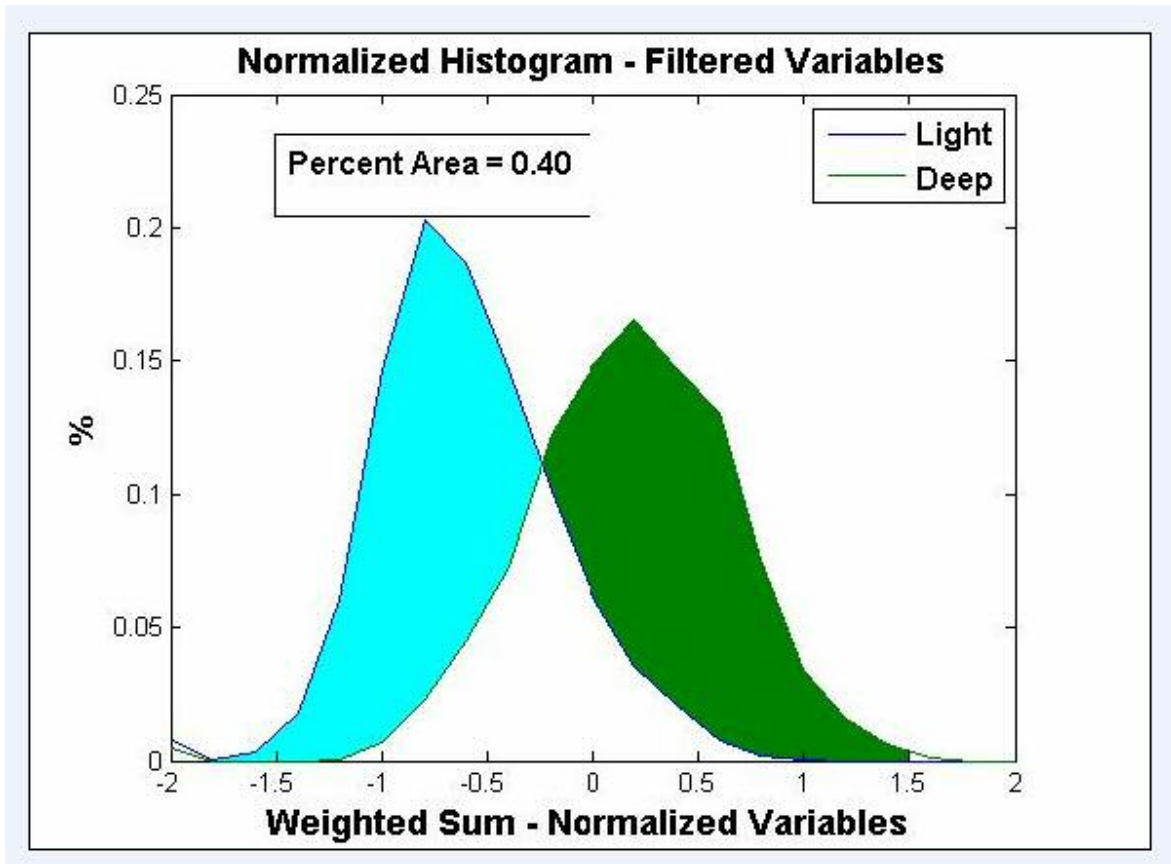


Figure 3: Weighted sum distribution with NF. Shaded and un-shaded areas as in figures 1 & 2

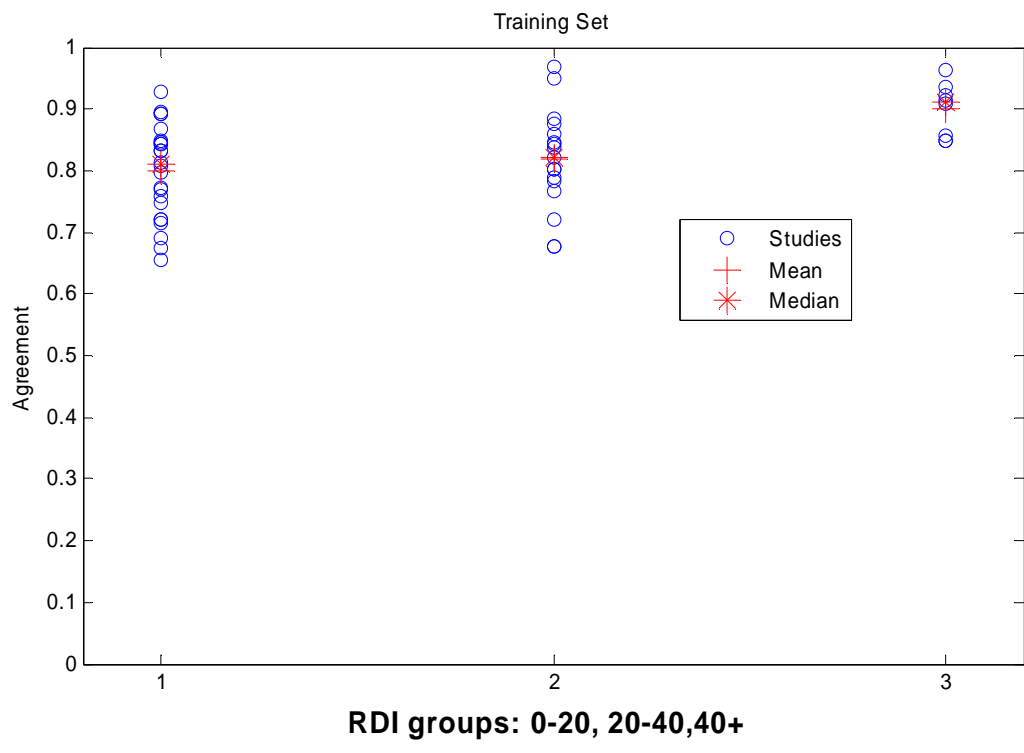


Figure 4: Agreement for mild (1), moderate (2), and severe (3) OSA training set

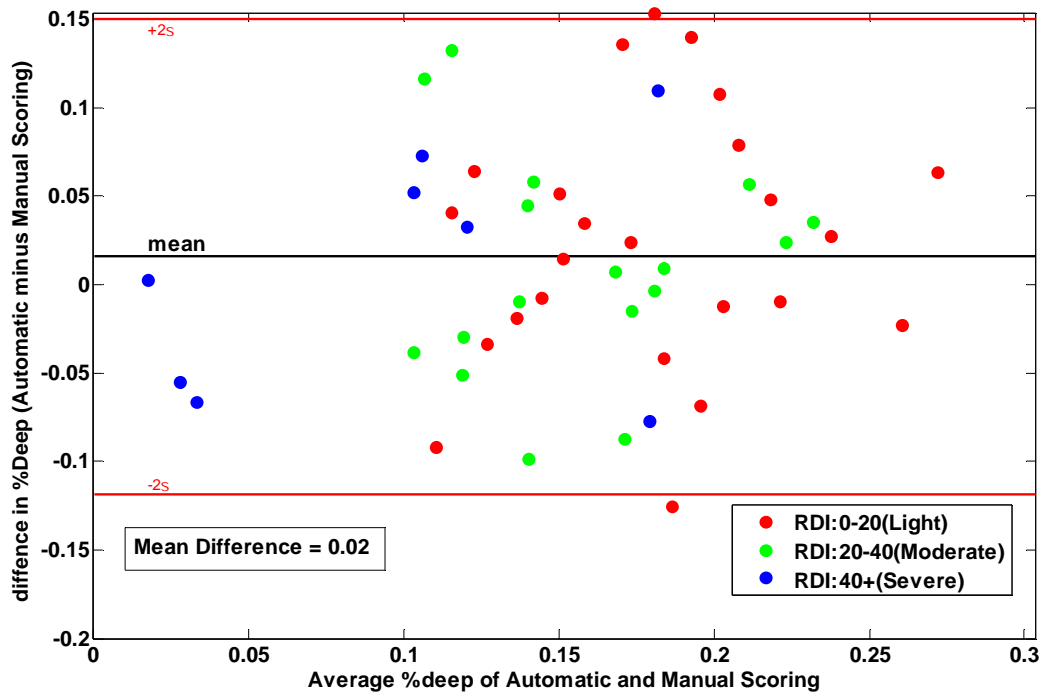


Figure 5 Bland Altman of error in % deep sleep stage detection (PSG vs. algorithm) for the training set

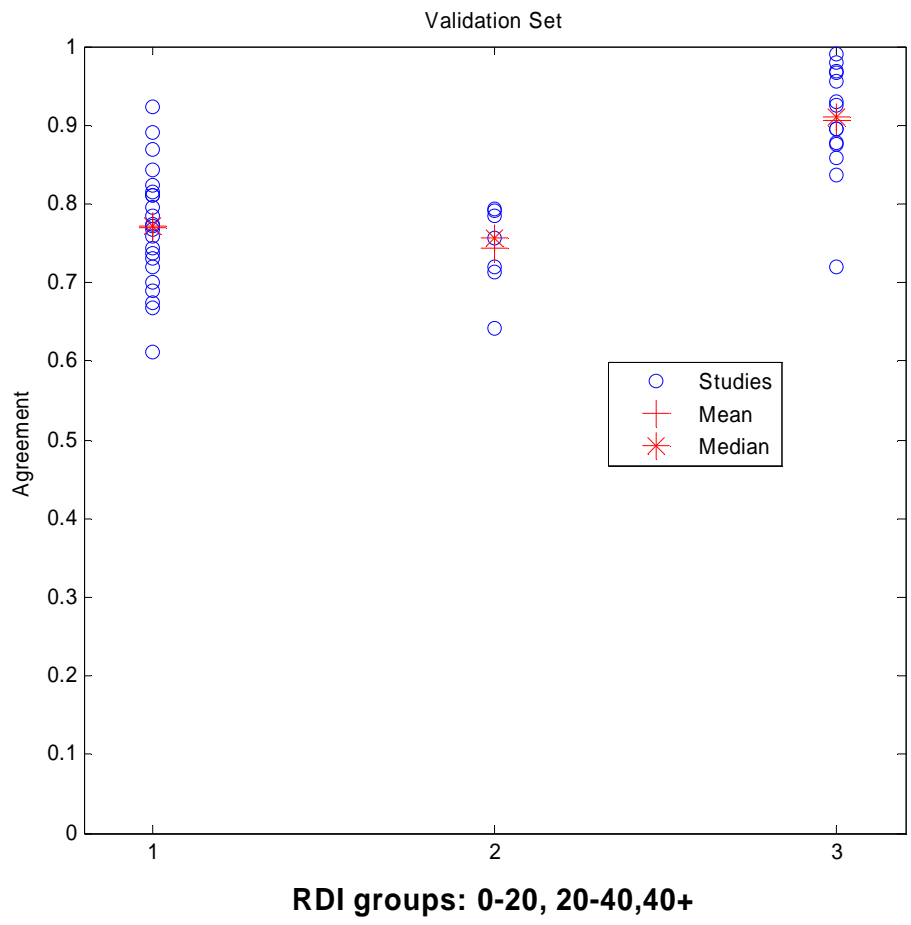


Figure 6: Agreement for mild (1), moderate (2) and severe (3) OSA Validation set

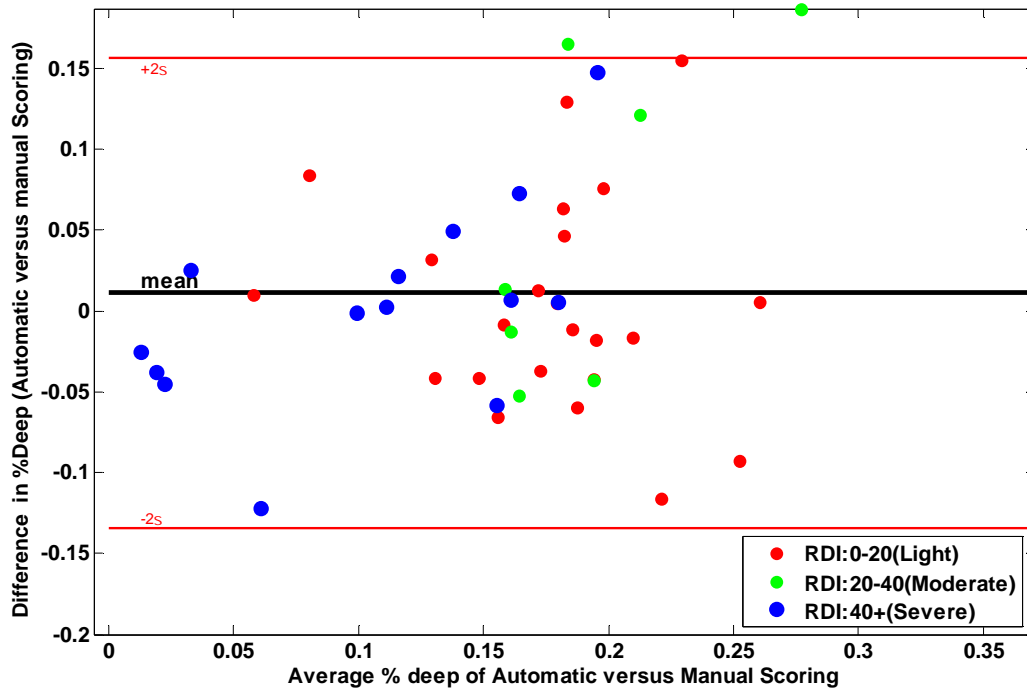


Figure 7 Bland Altman of error in % deep sleep stage detection (PSG vs. algorithm) for the validation set

	Training Set (N=49)	Validation Set (N=44)	P Value
Mean RDI	26.9 ±19.09	34.0 ± 30.28	NS
Mean Age	44.7 ±13.58	43.5 ± 14.67	NS
Mean BMI	27.4 ±5.31	28.7 ± 6.23	NS
Mean arousal index	33. ± 22	26.6 ± 14.	NS
Mean deep %	21 ±9	20.9 ± 10	NS
Mean REM %	21 ±7	19.4 ± 6	NS
Total Sleep time [min.]	351 ± 49	357 ± 61	NS
mean SaO2	86 ±19	84 ± 21	NS
De-saturation index	22 ±23	21 ± 23	NS
Sleep efficiency	0.83 ±11	0.84 ± 15	NS

Table 1: Demographic and Sleep Data for the Training and Validation Sets:

	Group 1 RDI<20	Group2 20<RDI<40	Group 3 RDI>40
Sensitivity[%]	61±26	55±23	72±32
Specificity[%]	89±10	87±13	87±6
Agreement[%]	82±7	78±13	85±6

Table 2 sensitivity specificity and agreement mean values by subject for the 3 groups

REFERENCES

- Aydin, M., Altin, R., Ozeren, A., Kart, L., Bilge, M., and Unalacak, M. (2004). Cardiac autonomic activity in obstructive sleep apnea: time-dependent and spectral analysis of heart rate variability using 24-hour Holter electrocardiograms. *Tex Heart Inst J* **31**, 132-6.
- Bar, A., Pillar, G., Dvir, I., Sheffy, J., Schnall, R. P., and Lavie, P. (2003). Evaluation of a portable device based on peripheral arterial tone for unattended home sleep studies. *Chest* **123**, 695-703.
- Berlad, I. I., Shlitner, A., Ben-Haim, S., and Lavie, P. (1993). Power spectrum analysis and heart rate variability in Stage 4 and REM sleep: evidence for state-specific changes in autonomic dominance. *J Sleep Res* **2**, 88-90.
- Bonnet, M. H., and Arand, D. L. (1997). Heart rate variability: sleep stage, time of night, and arousal influences. *Electroencephalogr Clin Neurophysiol* **102**, 390-6.
- Brandenberger, G., Ehrhart, J., and Buchheit, M. (2005). Sleep stage 2: an electroencephalographic, autonomic, and hormonal duality. *Sleep* **28**, 1535-40.
- Brooks, D., Horner, R. L., Floras, J. S., Kozar, L. F., Render-Teixeira, C. L., and Phillipson, E. A. (1999). Baroreflex control of heart rate in a canine model of obstructive sleep apnea. *Am J Respir Crit Care Med* **159**, 1293-7.
- Burgess, H. J., Trinder, J., and Kim, Y. (1999). Cardiac autonomic nervous system activity during presleep wakefulness and stage 2 NREM sleep. *J Sleep Res* **8**, 113-22.
- Burgess HJ, Penev PD, Schneider R, Van Cauter E. Estimating cardiac autonomic activity during sleep: impedance cardiography, spectral analysis, and Poincare plots. *Clin Neurophysiol* 2004;115:19-28.
- Busek, P., Vankova, J., Opavsky, J., Salinger, J., and Nevsimalova, S. (2005). Spectral analysis of the heart rate variability in sleep. *Physiol Res* **54**, 369-76.
- Chesson, A. L. J., Berry, R. B., and Pack, A. (2003). American Academy of Sleep Medicine; American Thoracic Society; American College of Chest Physicians. Practice parameters for the use of portable monitoring devices in the investigation of suspected obstructive sleep apnea in adults. *Sleep* **23**, 907-13.
- Collop, N. A. (2002). Scoring variability between polysomnography technologists in different sleep laboratories. *Sleep Med* **3**, 43-7.
- Dvir, I., Adler, Y., Freimark, D., and Lavie, P. (2002). Evidence for fractal correlation properties in variations of peripheral arterial tone during REM sleep. *Am J Physiol Heart Circ Physiol* **283**, H434-9.
- Elsenbruch, S., Harnish, M. J., and Orr, W. C. (1999). Heart rate variability during waking and sleep in healthy males and females. *Sleep* **22**, 1067-71.
- Ferri, R., Parrino, L., Smerieri, A., Terzano, M. G., Elia, M., Musumeci, S. A., and Pettinato, S. (2000). Cyclic alternating pattern and spectral analysis of heart rate variability during normal sleep. *J Sleep Res* **9**, 13-8.
- Flemons, W. W., Littner, M. R., Rowley, J. A., Gay, P., Anderson, W. M., Hudgel, D. W., McEvoy, R. D., and Loube, D. I. (2003). Home diagnosis of sleep apnea: a systematic review of the literature. An evidence review cosponsored by the American Academy of Sleep Medicine, the American College of Chest Physicians, and the American Thoracic Society. *Chest* **124**, 1543-79.

- Futuro-Neto, H. A., and Coote, J. H. (1982). Changes in sympathetic activity to heart and blood vessels during desynchronized sleep. *Brain Res* **252**, 259-68.
- Hedner, J., Pillar, G., Pittman, S. D., Zou, D., Grote, L., and White, D. P. (2004). A novel adaptive wrist actigraphy algorithm for sleep-wake assessment in sleep apnea patients. *Sleep* **27**, 1560-6.
- Herscovici, S., Pe'er, A., Pappan, S., and Lavie, P. (2007). Detecting REM sleep from the finger: an automatic REM sleep algorithm based on peripheral arterial tone (PAT) and actigraphy. *Physiol Meas* **28**, 129-40.
- Hornyak, M., Cejnar, M., Elam, M., Matousek, M., and Wallin, B. G. (1991). Sympathetic muscle nerve activity during sleep in man. *Brain* **114 (Pt 3)**, 1281-95.
- Jo, J. A., Blasi, A., Valladares, E., Juarez, R., Baydur, A., and Khoo, M. C. (2005). Determinants of heart rate variability in obstructive sleep apnea syndrome during wakefulness and sleep. *Am J Physiol Heart Circ Physiol* **288**, H1103-12.
- Kirby, D. A., and Verrier, R. L. (1989). Differential effects of sleep stage on coronary hemodynamic function. *Am J Physiol* **256**, H1378-83.
- Kodama, Y., Iwase, S., Mano, T., Cui, J., Kitazawa, H., Okada, H., Takeuchi, S., and Sobue, G. (1998). Attenuation of regional differentiation of sympathetic nerve activity during sleep in humans. *J Auton Nerv Syst* **74**, 126-33.
- Lavie, P., Pillar, G., and Malhotra, A. (2002). Sleep Disorders: Diagnosis and Treatment. A handbook for the clinician **Martin Dunitz L.T.D., London.**
- Lavie, P., Schnall, R. P., Sheffy, J., and Shlitner, A. (2000). Peripheral vasoconstriction during REM sleep detected by a new plethysmographic method. *Nat Med* **6**, 606.
- Levy, P., and Pepin, J. L. (2003). Sleep fragmentation: clinical usefulness of autonomic markers. *Sleep Med* **4**, 489-91.
- Liguori, R., Donadio, V., Foschini, E., Di Stasi, V., Plazzi, G., Lugaresi, E., and Montagna, P. (2000). Sleep stage-related changes in sympathetic sudomotor and vasomotor skin responses in man. *Clin Neurophysiol* **111**, 434-9.
- Malhotra, A., and White, D. P. (2002). Obstructive sleep apnoea. *Lancet* **360**, 237-45.
- Margel, D., White, D. P., and Pillar, G. (2003). Long-term intermittent exposure to high ambient CO₂ causes respiratory disturbances during sleep in submariners. *Chest* **124**, 1716-23.
- Monti, A., Medigue, C., Nedelcoux, H., and Escourrou, P. (2002). Autonomic control of the cardiovascular system during sleep in normal subjects. *Eur J Appl Physiol* **87**, 174-81.
- Narkiewicz, K., Montano, N., Cogliati, C., van de Borne, P. J., Dyken, M. E., and Somers, V. K. (1998). Altered cardiovascular variability in obstructive sleep apnea. *Circulation* **98**, 1071-7.
- Narkiewicz, K., and Somers, V. K. (1997). The sympathetic nervous system and obstructive sleep apnea: implications for hypertension. *J Hypertens* **15**, 1613-9.
- Narkiewicz, K., van de Borne, P. J., Cooley, R. L., Dyken, M. E., and Somers, V. K. (1998). Sympathetic activity in obese subjects with and without obstructive sleep apnea. *Circulation* **98**, 772-6.
- Negoescu, R. M., and Csiki, I. E. (1989). Autonomic control of the heart in some vagal maneuvers and normal sleep. *Physiologie* **26**, 39-49.
- Noll, G., Elam, M., Kunimoto, M., Karlsson, T., and Wallin, B. G. (1994). Skin sympathetic nerve activity and effector function during sleep in humans. *Acta Physiol Scand* **151**, 319-29.
- Norman, R. G., Pal, I., Stewart, C., Walsleben, J. A., and Rapoport, D. M. (2000). Interobserver agreement among sleep scorers from different centers in a large dataset. *Sleep* **23**, 901-8.

- Okada, H., Iwase, S., Mano, T., Sugiyama, Y., and Watanabe, T. (1991). Changes in muscle sympathetic nerve activity during sleep in humans. *Neurology* **41**, 1961-6.
- Penzel, T., Bunde, A., Grote, L., Kantelhardt, J. W., Peter, J. H., and Voigt, K. (2000). Heart rate variability during sleep stages in normals and in patients with sleep apnea. *Stud Health Technol Inform* **77**, 1256-60.
- Penzel, T., Kantelhardt, J. W., Grote, L., Peter, J. H., and Bunde, A. (2003). Comparison of detrended fluctuation analysis and spectral analysis for heart rate variability in sleep and sleep apnea. *IEEE Trans Biomed Eng* **50**, 1143-51.
- Penzel, T., Kesper, K., Pinnow, I., Becker, H. F., and Vogelmeier, C. (2004). Peripheral arterial tonometry, oximetry and actigraphy for ambulatory recording of sleep apnea. *Physiol Meas* **25**, 1025-36.
- Penzel, T., Kesper, K., Ploch, T., Becker, H. F., and Vogelmeier, C. (2004). Ambulatory recording of sleep apnea using peripheral arterial tonometry. *Conf Proc IEEE Eng Med Biol Soc* **5**, 3856-9.
- Pepin, J. L., Veale, D., and Levy, P. A. (1994). Heart rate variability during sleep in snorers with and without obstructive sleep apnea. *Chest* **105**, 1300-1.
- Pillar, G., Bar, A., Betito, M., Schnall, R. P., Dvir, I., Sheffy, J., and Lavie, P. (2003). An automatic ambulatory device for detection of AASM defined arousals from sleep: the WP100. *Sleep Med* **4**, 207-12.
- Pillar, G., Malhotra, A., Fogel, R. B., Beauregard, J., Slamowitz, D. I., Shea, S. A., and White, D. P. (2000). Upper airway muscle responsiveness to rising PCO₂ during NREM sleep. *J Appl Physiol* **89**, 1275-82.
- Pressman, M. R., and Fry, J. M. (1989). Relationship of autonomic nervous system activity to daytime sleepiness and prior sleep. *Sleep* **12**, 239-45.
- Rechtschaffen, A., and Kales, A. (1968). A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. *Los Angeles: Brain Information Service/Brain Research Institute*.
- Silber, M. H., Ancoli-Israel, S., Bonnet, M. H., Chokroverty, S., Grigg-Damberger, M. M., Hirshkowitz, M., Kapen, S., Keenan, S. A., Kryger, M. H., Penzel, T., Pressman, M. R., and Iber, C. (2007). The visual scoring of sleep in adults. *J Clin Sleep Med* **3**, 121-31.
- Somers, V. K., Dyken, M. E., Mark, A. L., and Abboud, F. M. (1993). Sympathetic-nerve activity during sleep in normal subjects. *N Engl J Med* **328**, 303-7.
- Svetnik, V., Ma, J., Soper, K. A., Doran, S., Renger, J. J., Deacon, S., and Koblan, K. S. (2007). Evaluation of automated and semi-automated scoring of polysomnographic recordings from a clinical trial using zolpidem in the treatment of insomnia. *Sleep* **30**, 1562-74.
- Takeuchi, S., Iwase, S., Mano, T., Okada, H., Sugiyama, Y., and Watanabe, T. (1994). Sleep-related changes in human muscle and skin sympathetic nerve activities. *J Auton Nerv Syst* **47**, 121-9.
- Trinder, J., Kleiman, J., Carrington, M., Smith, S., Breen, S., Tan, N., and Kim, Y. (2001). Autonomic activity during human sleep as a function of time and sleep stage. *J Sleep Res* **10**, 253-64.
- Villa, M. P., Calcagnini, G., Pagani, J., Paggi, B., Massa, F., and Ronchetti, R. (2000). Effects of sleep stage and age on short-term heart rate variability during sleep in healthy infants and children. *Chest* **117**, 460-6.

Virtanen, I., Ekholm, E., Polo-Kantola, P., and Huikuri, H. (2007). Sleep stage dependent patterns of nonlinear heart rate dynamics in postmenopausal women. *Auton Neurosci* **134**, 74-80.