Entropy-based Measures of EEG Arousals as Biomarkers for Sleep Dynamics: Applications to Hypertension

Reza Jamasebi, MS; Susan Redline, MD, MPH; Sanjay R Patel, MD, MS; Kenneth A. Loparo, PhD

1Department of Electrical Engineering & Computer Science; 2Center for Clinical Investigation; 3Division of Pulmonary, Critical Care and Sleep Medicine, Case Western Reserve University, Cleveland, OH

Study Objectives: We propose a generation of PSG-derived measures that using entropy can quantify temporal patterns of sleep, and investigate the role of these measures as predictors of hypertension. We also investigate the influence of age on these entropy-based measures as compared to traditional indices.

Design and Setting: Cross-sectional analyses of the association between hypertension status with traditional PSG and novel measures using adjusted and unadjusted logistic regression models. The novel measures were developed to quantify variability of the arousal event process.

Patients or Participants: Analyses were based on a subsample of subjects from the Cleveland Family Study with clearly disparate hypertension status.

Measurements and Results: Among traditional PSG indices, the apnea hypopnea index (AHI) has the highest Odds Ratio (unadjusted and adjusted for age, gender, race, BMI: OR = 2.36 (95% CI: 1.48, 3.75, P = 0.0003) and 1.18, (95% CI: 0.76, 1.84, P = 0.46), respectively). The best predictor among the entropy-based measures is derived from analysis of the temporal patterns of arousal duration with unadjusted and adjusted ORs of 1.36 (95% CI: 1.08, 1.71, P = 0.0085) and 2.08 (95% CI: 1.19, 3.64, P = 0.01), respectively.

Conclusions: Our findings suggest that when adjusted for common confounders such as age, gender, race, and BMI, the entropy-based features that quantify the variability of the arousal event process are more strongly associated with hypertension as compared to traditional PSG indices; they are not as strongly influenced by age as are the traditional indices. The result implies that the regularity of arousals may be an important feature associated with hypertension. These measures may provide a powerful tool for discriminating individuals at risk for comorbidities, such as hypertension, associated with sleep disturbances.

Keywords: Arousal, sleep architecture, entropy, polysomnography, hypertension

Citation: Jamasebi R; Redline S; Patel SR; Loparo KA. Entropy-based measures of EEG arousals as biomarkers for sleep dynamics: applications to hypertension. SLEEP 2008;31(7):935-943.

Disclosure Statement
This was not an industry supported study. The authors have indicated no financial conflicts of interest.

Submitted for publication January, 2008
Accepted for publication February, 2008
Address correspondence to: Reza Jamasebi, Case Western Reserve University, 10800 Euclid Ave, 603 Olin Building, Cleveland, OH 44106; Tel: (216) 526-4246; Fax: (216) 368-6888; E-mail: rezaj@case.edu

biomarker of underlying disease processes. We focus on EEG arousals because the frequency of arousals has been identified as a marker of sympathetic nervous system activation that may be associated with propensity for hypertension, as well as a marker for sleep discontinuity predisposing to daytime sleepiness. The data relating arousal frequency to health outcomes have been inconsistent, however. In part this may relate to difficulties in reliably scoring arousals or because the arousal index (Arl) measures the total number of arousals per hour of sleep and does not capture the dynamic behavior of the arousal events and their distribution in both time and intensity (duration). Given other systems in which additional information was derived by quantifying temporal patterns and regularity of events, we propose to treat the arousal events as a dynamic process (time series data) by characterizing the temporal patterns of this time series to determine if such an approach provides alternative information compared to the Arl. Accordingly, the strength of association of hypertension, a condition associated with increased arousal frequency, with traditional PSG measures is compared to the association with temporally derived PSG measures.

MATERIAL AND METHODS

Study Sample

The analytic sample is derived from participants in the Cleveland Family Study, an ongoing genetic epidemiologic cohort study beginning in 1990 examining the natural history and outcomes of SDB. Recruitment and data collection methods have been previously described. From a sample of 380 studies from participants older than 16 years participating in the last exam (July 2001 to June 2005), not using CPAP therapy, without scored alpha intrusion, and with complete covariate data, we performed a nested case control sample to identify 2 groups with disparate hypertension status. Subjects were included as hypertensive cases (HTN) if the average of 9 readings obtained during the clinical exam, explained below) diastolic blood pressure (DBP) was greater than 90 mm Hg or the average systolic blood pressure (SBP) was greater than 140 mm Hg. An equal number of non-hypertensive (non-HTN) controls were identified on the basis of a DBP less than 70 mm Hg and SBP less than 110 mm Hg and not on antihypertensive medication.

Protocol

Participants were studied in a dedicated clinical research facility and underwent overnight 14-channel PSG, blood pressure (BP) measurements, venipuncture, anthropometry, and glucose tolerance testing. Prior to the PSG, each participant completed the Cleveland Health and Sleep Questionnaire, a standardized and validated questionnaire assessing sleep habits and symptoms, medical history, health habits, and medication use, including diabetic and antihypertensive medications. Current smokers were identified as answering affirmatively to smoking at least 1 cigarette per day over the prior one month; caffeine use was quantified as the number of caffeine containing drinks consumed on average per day. Height was measured to the nearest centimeter, with the subject in stocking feet, using a wall-mounted stadiometer; weight (to the nearest 0.1 kg) was measured with a calibrated scale (Healthometer). Body mass index (BMI) was computed as the ratio of weight to the square of the height (kg/m²). Neck circumference was directly measured using a non-stretchable tape with the subject’s head in the Frankfort horizontal plane.

Sleep Data Measurements

The PSG data were collected using Compumedics E Series System (Abbotsford, AU). The recording montage consisted of C/A2 and C/A2 electroencephalograms; right and left electrooculograms; a bipolar submental electromyogram; thoracic and abdominal respiratory inductance plethysmography; “airflow” (by nasal-oral thermocouple); nasal pressure (via a nasal cannula); finger pulse oximetry (Nonin, MN), electrocardiogram; body position (by a mercury gauge sensor); and bilateral leg movements (by peizolectric sensors). Each study was scored by one dedicated certified research technologist. Sleep staging and arousals were scored using Rechtschaffen and Kales criteria and recommended criteria from the American Academy of Sleep Medicine (formerly known as the American Sleep Disorders Association, ASDA), respectively. Apneas and hypopneas were defined using Sleep Heart Health Study (SHHS) criteria modified to include nasal pressure. An apnea was defined as a complete or almost complete reduction in the thermocouple signal, lasting >10 sec. Hypopneas were scored when the amplitude of the sum of the abdominal and thoracic inductance signals or the nasal pressure flow signal were clearly reduced for >10 sec, with reductions at least 30% below “baseline” breathing amplitude. We used a hypopnea definition that required a minimum of a 3% desaturation to be observed with each event. The arousal index was defined as the number of arousals per hour of sleep. Intra-rater reliability for the arousal index for the scorer who analyzed all studies was formally assessed in a scoring reliability assessment, showing an intraclass correlation coefficient of 0.96.

Blood Pressure Measurement

Participants had 3 supine blood pressure measurements each performed after lying quietly for 10 min: before bed (22:00) and upon awakening (07:00), and another 3 sitting at 11:00, following standardized guidelines using a calibrated sphygmomanometer. Cuff size was determined by the circumference of the upper arm and the appropriate bladder size from a standard chart. BP was determined as the average of the 9 measurements.

Entropy-Based PSG Features

Details of this method are provided as an Appendix. The arousal start time and arousal duration, based on manually scored arousals, were used to create an arousal event time series. We quantified the temporal and statistical regularity of the arousal events by computing entropy measures derived from the arousal time series. There are various forms of entropy, with the most common being Shannon Entropy (SE). In general, entropy is a measure of information content (alternatively, uncertainty) in a signal or time series and was originally introduced by Shannon in the context of estimating channel.
capacity in a communication system. In this paper, we use conditional entropy (CE)\textsuperscript{14} to quantify the pattern of regularity or variability in a short time series. CE measures the amount of information contained in one random variable about another random variable. When comparing the conditional entropy of 2 time series, the one with the lower value is referred to as being more predictable than the one with the higher. In our approach, we combine different characteristics of the arousal event time series to quantify the dynamics of the arousal process using these combined features. One approach was to construct a new time series with the arousal start time as the time points and the arousal duration as the magnitude of each data point. The new time series includes the 2 major characteristics of an arousal (arousal start time and arousal duration), and by analyzing this new time series we can obtain more detailed information about the dynamics of the arousal event process. The PSG measures that are derived from the arousal events include:

1) Arousal Duration Entropy (ADE)

The ADE was derived to address the hypothesis that the regularity of the arousal duration is different between individuals with different clinical characteristics. As a result, this feature is derived from the conditional entropy of the arousal duration time series that would be a unique measure for each subject. In this context, the conditional entropy is a measure that quantifies predicting an arousal duration pattern of length $L$ given the occurrence of an arousal duration pattern of length $L-1$.

2) Cross Correlation Function Entropy (CCE)

Here we consider the arousal duration and arousal start time simultaneously by analyzing the linear correlation between the arousal start time and the arousal duration. Conditional Entropy is used to quantify the regularity or variability in the arousal event process. Figure 1 depicts the process for calculating this feature.

3) Randomly Sampled Discrete Fourier Transform Driven Entropy (RSE)

Another technique for the combined analysis of the arousal start time and arousal duration uses a randomly sampled time series that consists of impulses at the arousal start time points with the intensity of each signal equal to the duration of the corresponding arousal. Because this is not a uniformly sampled time series, standard times series analysis techniques such as the Fourier transform cannot be directly applied. However, we can analyze this type of time series using the discrete Fourier transform of randomly sampled time series.\textsuperscript{24} Note this is similar to the problem that occurs in the spectral analysis of beat-to-beat variations in heart rate variability. To the best of our knowledge, this is the first time such an analysis method has been applied to arousals. An example of a randomly sampled time series is shown in Figure 2, and Figure 3 depicts the process for computing the RSE.

**Statistical Analysis**

Subject characteristics and sleep indices are summarized using means, standard deviations and medians for continuous variables, and frequencies and proportions for categorical variables. Generalized estimating equations (GEE)\textsuperscript{25} with an exchangeable within-family correlation structure and robust variance estimates were used to estimate the odds of each outcome without covariate adjustment as well as with adjustments for different covariates. Results are summarized using odds ratios (OR) and 95% confidence intervals. Mutual Information is used to capture linear or nonlinear dependency between covariates that cannot be captured by linear models.\textsuperscript{26} Fully adjusted models included age, age–square, age–square root, gender, race, BMI, neck circumference, current smoking status, and average daily caffeine consumption. However, final estimates in models that included current smoking status and average daily caffeine consumption and quadratic terms for age did not substantially influence final estimates and were therefore not included in the final adjusted models. The generalized additive model is used to find the relationship between predictors and response variables that cannot be described by generalized linear models.\textsuperscript{27}

**RESULTS**

**Sample Characteristics**

Characteristics of the sample population from which cases and controls were selected, as well as the characteristics of each
univariate associations among age and BMI with ADE (arousal duration entropy, the index most strongly associated with HTN compared to the other entropy measures; data shown later). We assessed this in the overall sample from which cases and controls were selected to provide a broad range of age and BMI levels (Table 3). Age was correlated with both the AHI and ArI ($r = 0.28$ and $0.26$, respectively, $P < 0.01$). In contrast, the magnitude of interrelationships among traditional PSG indices and temporally Based Arousal indices

Table 2 shows the Spearman correlation coefficients relating the strength of the linear associations among the temporally derived arousal measures and the traditional arousal and apnea-hypopnea indices. As seen, the highest linear correlation was between ADE with CCE ($r = 0.55$). ADE also had a strong correlation with ArI ($r = 0.77$) that indicated a linear dependence between these 2 measures. However, as shown later, the ADE measure also captured some nonlinear features associated with arousal events that were not captured in ArI.

Relationships among ADE, ArI, AHI, Age, and BMI

Because age is one of the strongest predictors of HTN and BMI is one of the strongest correlates of SDB, we present the subsample, are shown in Table 1. The average age for the overall sample was 43.2 years; 44.7% of the participants were male and 47% were African American. The mean systolic blood pressure and mean diastolic blood pressure for the sample were 123 and 74 mm Hg respectively. On average, participants with HTN were significantly older (54.18 vs. 35.03 years), heavier (BMI 34.77 vs. 28.69 kg/m$^2$), and more likely to be African American (58.69% vs. 32.61%). Those with HTN had a significantly higher average AHI (26.15 vs. 6.30) and ArI (22.61 vs. 13.19).

Figure 3—The computation of RSE (randomly sampled discrete Fourier transform entropy) measure that quantifies the temporal pattern of arousal time series.

Figure 4—The boxplot comparing the values of ADE (arousal duration entropy) values between Hypertensive and Non-Hypertensive group; $P < 0.01$.

Figure 5—The boxplot comparing the values of CCE (cross correlation function entropy) between Hypertensive and Non-Hypertensive group; $P < 0.01$.

Figure 6—The boxplot comparing the values of RSE (randomly sampled discrete Fourier transform entropy) between Hypertensive and Non-Hypertensive group; $P < 0.01$.
The arousal event time series as a sequence of impulses at the arousal start time points with the intensity of each signal equal to the duration of the corresponding arousal event for 2 subjects from hypertensive and non-hypertensive groups.

**Figure 7**

**Table 1**—Characteristics of Overall Sample; HTN Subsample; Non-HTN Subsample*

<table>
<thead>
<tr>
<th></th>
<th>Overall Sample (n = 380)</th>
<th>HTN Subsample (n = 46)</th>
<th>Non-HTN Subsample§ (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.2 ± 17.0 (44.6)</td>
<td>54.18 ± 14.32 (51.81)</td>
<td>35.03 ± 14.21 (35.63)</td>
</tr>
<tr>
<td>Male</td>
<td>170 (44.7%)</td>
<td>21 (45.65%)</td>
<td>9 (19.56%)</td>
</tr>
<tr>
<td>African American</td>
<td>179 (47%)</td>
<td>27 (58.69%)</td>
<td>15 (32.61%)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>32.3 ± 8.2 (30.8)</td>
<td>34.77 ± 7.94 (32.93)</td>
<td>28.69 ± 6.86 (27.04)</td>
</tr>
<tr>
<td>AHI</td>
<td>14.5 ± 20.9 (5.5)</td>
<td>26.15 ± 25.53 (17.28)</td>
<td>6.30 ± 10.62 (1.61)</td>
</tr>
<tr>
<td>ArI</td>
<td>15.8 ± 10.0 (13.7)</td>
<td>22.61 ± 14.91 (16.53)</td>
<td>13.19 ± 8.07 (10.97)</td>
</tr>
<tr>
<td>Average systolic blood pressure</td>
<td>123.3 ± 15.27 (120.94)</td>
<td>152.70 ± 13.96 (149.67)</td>
<td>104.28 ± 5.12 (106.33)</td>
</tr>
<tr>
<td>Average diastolic blood pressure</td>
<td>74.1 ± 9.25 (73.78)</td>
<td>88.05 ± 9.99 (88.94)</td>
<td>64.07 ± 5.62 (64.33)</td>
</tr>
</tbody>
</table>

*Mean ± standard deviation and median for continuous variables, N and % for categorical variables.
§ all P values comparing HTN and non-HTN subsamples < 0.01.
BMI, body mass index; AHI, apnea hypopnea index; ArI, arousal index.

**DISCUSSION**

Studying the associations among sleep physiology, sleep disorders, and other physiological processes has been the interest of researchers for many years. An area of growing research has been the study of the association between sleep apnea, as measured by simple frequency counts of apneas, hypopneas, and arousals, with HTN, cardiovascular disease, and metabolic outcomes.\(^{28,29}\) In this type of investigation, as well as in clinical studies, the appropriateness of using summary metrics such as the AHI and ArI, has been questioned, as there has been increasing recognition of the need to more fully utilize the dynamic properties of PSG data to better understand sleep physiology and the consequences of abnormal sleep on health. Nonetheless, there has been little work that has tested the abilities of temporally derived indices of sleep fragmentation to discriminate subgroups of the population. In this paper, we introduced a family of entropy-based PSG-derived features as potential predictors of hypertension, a key outcome associated with both sleep apnea\(^{10}\) and sleep deprivation.\(^{31}\) A major finding is that

non-hypertensive group. The ADE for the hypertensive subject was 0.28 versus 0.43 for the non-hypertensive subject (lower numbers are indicative of more regular or predictable temporal patterns). The mean and standard deviation of arousal duration for the subject with hypertension were 11.78 and 5.88, respectively, and 9.49 and 5.62 for the subject without hypertension. To quantify the relationship with each PSG index and HTN, a log-linear model was used to compute the odds between each PSG index and HTN in both unadjusted and adjusted models (Table 4). In unadjusted models, of all PSG indices considered, the AHI had the highest Odds Ratio (OR = 2.36 per 0.5 SD change, 95% CI: 1.48, 3.75, P = 0.0003). However, the Odds Ratio (OR) dropped by a factor of almost 2 after adjusting for potential confounders (OR = 1.18, 95% CI: 0.76, 1.84, P = 0.46). ArI and CCE also behaved similarly to AHI, and the association with HTN was attenuated after covariate adjustment. In contrast, the OR for ADE was significantly associated with HTN in both unadjusted and adjusted models (adjusted OR = 2.08 per 0.5 SD change, 95% CI: 1.19, 3.64, P = 0.008) indicating that the odds of HTN increased with the increased regularity of arousal duration.
characterization of the temporal pattern of EEG arousals based on measures of entropy, in particular the regularity of arousal duration, may provide a better prediction of HTN than a simple count of arousal number (as shown in the example of 2 subjects with the same arousal index but different arousal duration patterns).

Traditional measurement of arousals during PSG adds complexity and burden to the processing and scoring of PSGs. Despite the challenges in reliably scoring arousals, the measurement of arousals has often been deemed important because arousals may serve as surrogate markers for sympathetic nervous system activity, which is one physiological pathway important in HTN pathogenesis. A prior study from the Cleveland Family Study that assessed the relationship of traditional PSG measures with HTN identified, in covariate adjusted analyses, found the AHI to be more strongly associated with HTN than either the AHI or measures of nocturnal desaturation. The current study extends these findings in a sample of the original cohort selected to represent individuals with clearly disparate HTN status. The current analyses suggest that it is not only arousal number, but arousal event pattern, that can discriminate HTN from non-HTN individuals. Our analyses suggest that individuals with HTN not only have a higher frequency of arousals but also have an arousal duration pattern that is more regular across the sleep period. The regularity of arousal duration may be more tightly linked to HTN than arousals that have a more irregular or variable duration pattern if the increased regularity causes a more sustained increase in sympathetic tone than the irregular arousal duration patterns. It is also possible that more regular arousal duration patterns are a reflection of more continuous sleep and/or breathing interruptions than would arousals with more irregular or sporadic duration, which may be less tightly linked to other physiological behaviors, such as respiratory disturbances. In addition, consistent with analyses of entropy in other physiological systems, it is possible that more regular arousal duration patterns occur in individuals with less variability in their intrinsic homeostatic mechanisms, and it is these individuals who are at greatest risk for disturbed cardiovascular responses that lead to HTN. However, because the data were based on cross-sectional analyses, the direction of the causal association between any of the PSG indices and HTN cannot be determined. Thus, it is also possible that HTN per se may influence the pattern of arousals via effects on brainstem-mediated or other reflexes.

An unexpected finding was that the ADE was less strongly correlated with age than was the ArI. We speculate that this may be because age-related phenomena may generally increase arousal number without greatly influencing arousal pattern, while disease-specific exposures influence pattern as well as number of arousals. It is well known that many sleep processes change with aging, including increased Stage 1 and 2 sleep and reduced slow wave sleep. Indices of sleep architecture have been postulated to serve as biomarkers for aging and various disease processes. With the growing availability of digital analysis of PSG records, further research should consider how temporally derived data extracted from the PSG EEG signals can be used to understand both aging and disease states.

The weaker association between age and arousal pattern likely explains the differences in the strength of the ORs for the ADE and AHI in unadjusted and adjusted models; i.e., adjustment attenuated the association for the ADE and increased it for the AHI. One challenge in understanding the impact of sleep disorders on health outcomes is that most exposures, such as the AHI, are strongly associated with correlates of disease (e.g., BMI, age). Accordingly, in most adjusted models, the strength of associations is attenuated after adjusting for potential confounders. Identifying measures of sleep physiology that are relatively independent of such confounders may help in quantifying events that are associated with sleep disorders.

A study limitation includes the cross-sectional design, which limits inferences about causality. Future studies may better identify the role of arousal pattern in disease by evaluating their association to incident hypertension and responsiveness to therapeutic interventions. Another study limitation is the relatively small sample chosen for detailed physiological analysis. It is possible that arousal patterns do not as well discriminate blood pressure levels across the continuum as well as discriminate between 2 groups with markedly disparate HTN status. The HTN and non-HTN groups also differed by demographic and anthropometric factors well known to be associated with HTN. Because data were derived from an existing cohort, it was not possible to match on these factors. However, we believe this may be a strength and not a weakness of the analysis, which is aimed at identifying measures that discriminate HTN status in populations where age, BMI, and race differences are correlated with HTN status. Furthermore, the most interesting entropy-

---

**Table 2**—Spearman Correlations Relating the Strength of the Linear Associations Among the Entropy Derived Features and ArI and AHI (Overall Cohort Sample; n = 380)*

<table>
<thead>
<tr>
<th></th>
<th>ArI</th>
<th>AHI</th>
<th>ADE</th>
<th>CCE</th>
<th>RSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ArI</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI</td>
<td>0.68</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADE</td>
<td>0.77</td>
<td>0.50</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCE</td>
<td>0.42</td>
<td>0.26</td>
<td>0.55</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>RSE</td>
<td>-0.24</td>
<td>-0.23</td>
<td>-0.01**</td>
<td>0.25</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*All P-values < 0.01
**P-value > 0.05
ArI, arousal index; AHI, apnea hypopnea index; ADE, arousal duration entropy; CCE, cross correlation function entropy; RSE, randomly sampled discrete Fourier transform entropy.

**Table 3**—Spearman Correlations Relating the Strength of the Linear Associations Among ADE, ArI, and Demographic Factors (Overall Cohort Sample; n = 380)*

<table>
<thead>
<tr>
<th></th>
<th>ADE</th>
<th>ArI</th>
<th>AHI</th>
<th>AGE</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADE</td>
<td>1.00</td>
<td>0.77</td>
<td>0.50</td>
<td>0.11</td>
<td>0.15</td>
</tr>
<tr>
<td>ArI</td>
<td>1.00</td>
<td>0.68</td>
<td>0.28</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>AHI</td>
<td>1.00</td>
<td>0.26</td>
<td>0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGE</td>
<td>1.00</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All the P-values <0.05
ADE, arousal duration entropy; ArI, arousal index; AHI, apnea hypopnea index; BMI, body mass index.
Table 4—Unadjusted & Adjusted Odds Ratios of HTN

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>P-value</th>
<th>Adjusted</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ArI</td>
<td>1.72* (1.22, 2.43)</td>
<td>0.0019</td>
<td>1.35 (0.84, 2.16)</td>
<td>0.21</td>
</tr>
<tr>
<td>ADE</td>
<td>1.36 (1.08, 1.71)</td>
<td>0.0085</td>
<td>2.08 (1.19, 3.64)</td>
<td>0.01</td>
</tr>
<tr>
<td>CCE</td>
<td>1.60 (1.23, 2.08)</td>
<td>0.0005</td>
<td>1.55 (1.03, 2.33)</td>
<td>0.03</td>
</tr>
<tr>
<td>RSE</td>
<td>1.61 (1.17, 2.23)</td>
<td>0.0037</td>
<td>1.74 (0.98, 3.08)</td>
<td>0.0564</td>
</tr>
<tr>
<td>AHI</td>
<td>2.36 (1.48, 3.75)</td>
<td>0.0003</td>
<td>1.18 (0.76, 1.84)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

*Generalized estimating equations, with each adjusted model including age, gender, race, and BMI.
†Odds ratio shown for 0.5 standard deviation change.
††ADE decreases with an increase in regularity (the coefficient for ADE is reversed to indicate a higher value is associated with increased regularity).

Table 4 shows that the strong association between the ArI and hypertension was likely attributable to arousals associated with respiratory events rather than to arousals occurring spontaneously. In our sample there was a relatively strong correlation between the AHI and ArI, which may be partly due to the relatively high AHI in the sample and high proportion of respiratory events associated with arousals (about 50%). Thus, the strong observed association between the ADE and hypertension may reflect underlying differences in respiratory disturbances and airflow obstruction that cause distinct arousal patterns in hypertensive and non-hypertensive individuals. Further, the increased regularity of arousal duration patterns in the HTN group may also be attributable to arousals associated with respiratory events rather than to arousals occurring more spontaneously in the non-HTN group. Future work will be needed to both extend the analyses (using additional signals and algorithms, and testing alternative outcomes such as OSA status) as well as assess how the analysis generalizes across population groups, including those with lower levels of AHI.

In summary, temporally derived measures of arousal pattern appear to have the potential to explain variability that is observed in the population that is not currently captured by demographic data and traditional PSG-derived measures. We also observe that all the entropy-based measures derived from the arousal events are associated with HTN status including measures that describe the regularity of arousal duration across the sleep period (ADE) and measures that quantify the regularity of the interaction between arousal start time and arousal duration (CCE and RSE), suggesting that the dynamic characteristics of the arousal event process in the HTN group are different than those in the non-HTN group. These measures thus provide a unique opportunity to improve risk stratification and more precisely describe phenotypic variability in sleep than do traditional measures. Because traditional indices are influenced by age, our data also suggests the potential for identifying measures that are not strongly associated with age and thus may provide more specific indices of disease rather than the aging associated processes.

The search for biomarkers for a given disease phenotype is a creative endeavor that requires determining not only what data to use, but also which features need to be extracted from a given data source and how these features should be combined to yield the level of statistical significance required for clinical applications and utility. The approach in this paper represents a step in this direction.

ACKNOWLEDGMENTS

Support: NIH HL 46380, M01RR00080, U01HL63463, and HL081385

REFERENCES

APPENDIX

In this section, we introduce two entropy measures (Shannon and conditional entropy) as means to quantify the temporal patterns of a time series. Shannon entropy was initially developed to describe the capacity of a communication channel and is the foundation for other entropy measures introduced later. We present the derivation of conditional entropy that is used in this paper beginning from the concept of Shannon entropy.

a. Shannon Entropy

Shannon defined the entropy of a continuous random variable with density function \( p(x) \) as:

\[
H = -\int_{-\infty}^{\infty} p(x) \log p(x) \, dx
\]

Similarly, the entropy of a discrete random variable with probabilities \( p_1, \ldots, p_n \) is defined as:

\[
H = -\sum p_i \log p_i
\]

The Shannon entropy can be interpreted as a measure of randomness, so lower values of Shannon entropy are associated with reduced uncertainty or increased predictability.

b. Conditional Entropy

Conditional entropy as implied by its name is used to quantify the uncertainty of a random variable \( X \) given random variable \( Y \). This measure can be derived from the concept of Shannon entropy as follows. If \( X \) and \( Y \) are two random variables, the conditional entropy of \( X \) given a realization of the random variable \( Y \) is:

\[
H(X \mid Y = y) = -\sum_x P(x \mid Y = y) \log p(x \mid Y = y)
\]

The conditional entropy of the random variable \( X \) given the random variable \( Y \) is then defined as the weighted average of \( H(X \mid Y = y) \) over all realizations of \( Y \):

\[
H(X \mid Y) = \sum_y P(y) H(x \mid Y = y)
\]

\[
H(X \mid Y) = -\sum_{y} P(y) \sum_{x} P(x \mid Y = y) \log p(x \mid Y = y)
\]

One application of conditional entropy is to quantify the periodicity or regularity of a short data sequence through an analysis of the regularity or repetition of a given temporal pattern in the data. In this context, the conditional entropy will be a measure that quantifies predicting the Lth pattern given the occurrence of the L-1th pattern. The entropy of a sequence \(\{x(k)\}; \quad k = 1,2,\ldots,N\) is consequently defined as:

\[
En(L/L-1) = -\sum_{L-1} p_{L-1} \sum_{L/L-1} P_{L/L-1} \log P_{L/L-1}
\]

where \(p_{L-1}\) is the joint probability of the sequence \(x_{L-1}(k)\) and \(P_{L/L-1}\) is the conditional probability of the Lth sample of pattern \(x_L(k)\) given the L-1th pattern. Here, \(x_L(k)\) is a L-dimensional embedding vector constructed from the observable time series with a unity time delay as follows:

\[
x_L(k) = (x_N(k), x_N(k-1), \ldots, x_N(k-L+1))
\]

where \(x_N(k)\) is \(x(k)\) normalized. Conditional entropy provides a measure to discriminate between repetitive patterns in a sequence versus aperiodic dynamics and is well suited for many biological or physiological applications where increased regularity or predictability of a physiological rhythm is a trend toward an abnormal state. The strength of conditional entropy over other entropy related measures is in its ability to deal with time series data with a limited number of observations. Most entropy-based techniques cannot be used effectively to quantify the characteristics of short data sequences.