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ORIGINAL ARTICLE

Analysis of respiratory events in obstructive sleep apnea syndrome: Inter-relations and association to simple nocturnal features

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Abstract
Objective: This study carefully evaluates the association of different respiration-related events to each other and to simple nocturnal features in obstructive sleep apnea–hypopnea syndrome (OSAS). The events include apneas, hypopneas, respiratory event-related arousals and snores.
Methods: We conducted a statistical study on 158 adults who underwent polysomnography between July 2012 and May 2014. To monitor relevance, along with linear statistical strategies like analysis of variance and bootstrapping a correlation coefficient standard error, the non-linear method of mutual information is also applied to illuminate vague results of linear techniques.
Results: Based on normalized mutual information weights (NMIW), indices of apnea are 1.3 times more relevant to AHI values than those of hypopnea. NMIW for the number of blood oxygen desaturation below 95% is considerable (0.531). The next relevant feature is ''respiratory arousals index'' with NMIW of 0.501. Snore indices (0.314), and BMI (0.203) take the next place. Based on NMIW values, snoring events are nearly one-third (29.9%) more dependent to hypopneas than RERAs.
Conclusion: 1. The more sever the OSAS is, the more frequently the apneic events happen. 2. The association of snore with hypopnea/RERA revealed which is routinely ignored in regression-based OSAS modeling. 3. The statistical dependencies of oximetry features potentially can lead to home-based screening of OSAS. 4. Poor ESS-AHI relevance in the database under study indicates its disability for the OSA diagnosis compared to oximetry. 5. Based on poor RERA-snore/ESS relevance, detailed history of the symptoms plus polysomnography is suggested for accurate diagnosis of RERAs.

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Introduction

Obstructive sleep apnea–hypopnea syndrome (OSAS) is a sleep-related breathing disorder affecting 2–4% of the American adults in 1990s[1] with an internationally increasing prevalence with greater obesity and aging.[2,3] Frequent episodes of airway subsidence (apnea) or tapering (hypopnea) during sleep characterizes OSAS.[4]

Through abrupt changes in sympathetic neural activity, untreated OSAS may lead to severe cardiovascular side-effects.[5–8] OSAS can also lead to type 2 diabetes,[9] impaired cognition, and psychiatric symptoms.[10] Therefore the early detection and treatment of OSAS is essential.

The gold standard for the OSAS diagnosis is overnight polysomnography (PSG). The PSG-driven apnea–hypopnea index (AHI) is used to characterize OSAS severity.[11,12]

However the contribution of other polysomnographic features to OSAS severity and symptoms is investigated in the literature. In one study the association of standard PSG features to variables reflecting disease burden and treatment outcome was examined using Spearman correlations and linear regression. These statistical tools did not show a consistent association between features in mild–moderate OSAS patients.[13]

In another study, the relationship between PSG features and chronic intermittent hypoxia (CIH) of OSAS patients was examined using multiple linear regression and covariance analysis. The achieved results showed ''total sleep time'' was the strongest predictor and may be better than AHI for evaluating CIH among OSAS patients.[14]

There is also a large body of literature on the relationship of bio-chemical factors to OSAS severity.[14–18] In a multivariate linear regression model, AHI in rapid eye movement (REM) sleep was associated with increasing levels of hemoglobin A1c.[15] Another investigation assessed OSAS severity in relation to levels of fibrinogen using the Chi-square and Wilcoxon rank-sum tests.[16] In another research project the relevance of PSG-driven OSAS indices to serum thyroid hormones were examined by Mann–Whitney *U* test, the Pearson correlations and the regression models. These tools showed no significant difference in the level of hormones among OSAS patients. Only the mean apnea duration significantly correlated with thyroid-stimulating hormone (TSH).[17]

Simply acquired non-polysomnographic features are also studied. They can serve as predictors of OSAS severity before expensive and time-consuming PSG tests are requested for moderate to severe OSAS suspects. Obesity-related measures such as body fat distribution, neck circumference, and body mass index (BMI),[18–20] body and trunk position,[21,22] maxillary and mandibular study of oral cavity,[20] and age[23] are monitored.

The unpaired Student's *t*-test,[18,23] the Mann–Whitney *U* test[19] or the Wilcoxon signed-rank test[21] was used to compare groups' mean and the Pearson correlation plus multiple linear regression to examine relationships.[18–21,23]

Though most of the linear models were adjusted for multiple predictors, no association was found between sleep disordered breathing (SDB) and hypertension in those aged <60 years. Many of the calculated Pearson correlations were statistically significant, however, none had high values.[23]

In another attempt only the frequency of occurrence is reported for the defined position-dependent OSAS based on head and trunk position sensors and AHI.[22]

The observed controversy among the reported studies (i.e. some have reported a significant relationship in a very specific category of subjects under investigation[23] and some failed to find a consistent association[13]) is mainly because all these studies considered only linear statistics such as comparison of means, correlation and regression. In regression, it is assumed that the predictable mean of outcome is dependent on one or more statistically independent predictors.[24] The strong assumption of independency might not be true for many of the biological features.

To address this issue we have changed our statistical tool and compared the results with the conventional correlation method. Out of the previously researched factors we mentioned BMI which is an important risk factor and is included in STOP-BANG questionnaire as well. In other published papers the authors report on the relationship of OSA with the clinical symptoms.[10] The purpose of this study is to get and overview of the relationship of each respiratory event (apnea, hypopnea, RERA and snoring) on AHI and their mutual relations using the strong method of mutual information (MI). To the best of our knowledge, such a study has not been conducted. MI checks dependency of all orders (not just the linear dependency or correlation). Based on the results more accurate OSAS prediction is possible by weighting the non-PSG driven features with their degree of dependency to AHI. OSAS prediction means initial OSAS screening based on simple nocturnal measures to refer only the medium or severe OSAS suspects to sleep laboratories.

Materials and methods

We conducted this cross-sectional study at the sleep laboratory of Ibn-e-Sina Hospital, Mashhad, Iran, from July 2012 to May 2014. The study was approved by the ethics committee overseeing the research proposal (permission no. 92/620792, date 2014/03/07). We were allowed to use clinical data only, with no deviation from AASM protocol. The PSG (model: Alice LE, part no. 1002387, Philips Respironics) recordings were conducted in baseline montage with 16 channels on the 158 referred patients. Out of all participants, 134 subjects were diagnosed with OSAS and 24 ones were healthy according to International Classification of Sleep Disorders II (ICSD-II).[11] The information regarding age, gender, weight, height, and medical history of the patients was gathered. The Epworth Sleepiness Scale (ESS)[25] was calculated to assess daytime sleepiness and the BMI[26] to evaluate obesity. Detailed history of the presenting symptoms was also requested. We ascertained sleep apneas as $\geq$10 s of air flow pauses and hypopnea as a $\geq$3% of oxygen desaturation/or arousal proceeded by a 50% decrement in the amplitude of baseline airflow. We determined the severity of OSAS by AHI (AHI; mean number of apnea + hypopnea per hour of sleep). In this study, AHI was classified as mild (5–15), moderate (15–30), and severe (>30).[11]

The analyzed features are BMI, number of blood oxygen de-saturation levels below 95%, 90%, 80%, 75% in total sleep time, minimum and mean level of SpO2 (%) in total sleep