An Investigation of Quantitative Measures of Sleep-Apnea-Induced Nocturnal Cardiac Stress

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ABSTRACT

Obstructive Sleep Apnea (OSA) affects an estimated 18 million individuals in the U.S. adult population. Numerous research findings indicate that OSA has significant adverse effects on the cardiac health. Current method of assessing the severity of OSA using apnea hypopnea index (AHI) which is the average count of apneic events per hour of sleep does not reflect how OSA affects the cardiovascular system health. In this study, we investigate the possibility of analyzing the nocturnal Electrocardiography (ECG) signal to assess the adverse impact of sleep apnea events on the heart. Our approach focuses on determining whether nocturnal cardiac arrhythmia is different depending on whether they occur during apneic events or during periods of normal breathing. We utilized the ECG recordings that are routinely made during full-night (6-8 hr) polysomnography to compute two metrics that are inspired by standard measures of heart rate turbulence (HRT): turbulence onset (TO), and turbulence slope (TS). Eleven volunteers (9M, 2F, 52±8 yrs., BMI 34.07±7.25 kg/m^2) who were either previously diagnosed as having obstructive sleep apnea or were suspected of having OSA and referred to our accredited sleep laboratory for diagnosis participated in the study. The volunteers exhibited AHI with 60.80±26.84 range of 18.3 to 105.4. The TS values obtained from averaged tachograms of premature ventricular contractions (PVCs) that occurred during apneic events and normal breathing were 16.11±10.36 ms/RR and 8.77±7.96 ms/RR, respectively and had no significant different means (p>0.08). The corresponding averaged TO were 13.41%±20.87% for PVCs during apneic events and 12.06%±21.02% for PVCs during normal breathing intervals did not significantly different mean either (p>0.8). However, the TO values computed for each PVC during apnea events had a different mean (21.75%±33.00%) compared with TO mean (31.96%±33.24%) for PVCs during normal breathing (p<0.0008). Similar analysis for TS values (72.01±97.84 ms/RR for apneic events and 52.29±73.02 ms/RR for normal breathing) showed that they also have significantly different means (p<0.007). The results of this study suggest that nocturnal PVCs appear to mediate quantifiably different disruptions in the heart sinus depending on whether they occur during normal breathing or during apneic events.

CCS CONCEPTS

• **APPLIED COMPUTING**; • **Life and Medical Sciences**; • **Physical Science and Engineering**;

KEYWORDS

Sleep apnea, Heart rate turbulence, Cardiac stress

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1 INTRODUCTION

It is estimated that as many as 18 million adults in the U.S. suffer from obstructive sleep apnea (OSA) [1]. This approximately equates to as many as of 9% of women and 24% of men in the U.S. adult population who are affected by OSA [2]. OSA is defined by repetitive cessation of breathing during sleep where each episode lasting at least 10s. Current understanding is that the cessation of breathing is due to loss of muscle tone in the upper airway during sleep and rolling back of the tongue. Definitive diagnosis of OSA is accomplished by nocturnal polysomnography (PSG) where patient's breathing and a number of other physiological parameters are concurrently measured and analyzed [3]. A universally used index of measuring the severity of OSA is the average count of number complete airway occlusion (i.e., apnea) and partial airway occlusion, called hypopnea, per hour of sleep. It is labeled as apnea-hypopnea index or AHI.

OSA is an insidious disease that is associated with serious cardiovascular morbidities including hypertension, atrial fibrillation and increases in cardiac-wall stress [4]. It is also associated with neurological adverse conditions such as memory loss, cognitive function deficits, and loss of brain matter [5].

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Of particular interest is the study of OSA-induced cardiac stress that may contribute to the development of the cardiac disease. Since electrocardiograms (ECG) are included in full polysomnography studies for the diagnosis of sleep apnea, it is possible to consider the effect of OSA on the heart using the nocturnal ECG recordings. Among possible analysis of ECG for determination of the effects of apnea on the heart, one can consider ventricular arrhythmias. Ventricular arrhythmias broadly categorized as ventricular tachycardia (VT), ventricular fibrillation (VF), accelerated idioventricular rhythm, and premature ventricular contraction (PVC). PVC refers to a heartbeat that occurs at earlier time point than the expected beat of the normal sinus rhythm. This premature heartbeat then is followed with prolongation of the temporal distance between the succeeding QRS complexes [6]. A method for quantifying this short-term fluctuation in the heartbeats is the computation of heart rate turbulence (HRT) [7]. It quantifies the short-term fluctuation in sinus cycle length that follows a ventricular premature complex (VPC) [8, 9].

The association of sleep apnea with occurrence of nocturnal PVC has long been established [10]. Recently researchers did a cross-sectional study that has analyzed the data from a large study of more than 1800 patients who participated in a study titled Determining Risk of vascular Events by Apnea Monitoring (DREAM) to determine the association of sleep-disordered breathing and nocturnal cardiac arrhythmias [11]. The cross-sectional study evaluated 982 of the patients. After excluding those patients who had some treatment for their OSA, less than 2 hours for their PSG diagnostic study, their PSG test was not available, or other indications, the record of remaining 697 patients were analyzed. The have shown that 57.1% of patients with mild OSA (i.e., $5 < \text{AHI} \leq 15$) had 5 or more isolated PVCs per hour. This percentage jumped to 61.5% in moderate to severe OSA patients (i.e., AHI > 15) while the percentage for without apnea (i.e., $\text{AHI} \leq 5$) was only 44.4%.

Although the association of PVC with apnea has been well studied, the impact of nocturnal PVCs on the heart rhythm and possible cardiac health consequences of them have not been fully investigated. One possible method of investigating the effect of nocturnal PVCs on cardiac health in apnea patients is by quantifying the impact using heart rate fluctuations that PVCs induces. Specifically, computation of heart rate turbulence is a promising method. Heart rate turbulence has been shown to be a good predictor of cardiac risk in various patient populations [12].

In this paper, we present preliminary findings regarding an investigation into whether the PVCs and temporal locations of apnea are related and report on the distribution of the heart rate turbulence parameters resulting from these PVCs. We further investigate the association of the heart rate turbulence parameters with the duration of apnea events as well as the temporal distance between the apnea events and PVCs in a sample population of sleep apnea patients.

2 MATERIALS AND METHODS

2.1 Determination of heart rate from PSG recording using RR intervals

To study the effect of apnea on cardiac function during the sleep, PSG data which includes ECG recording can be used to determine the variations in the heart rate. Considering that full-night PSG is collected over a period of 6 to 8 hours, a large number of QRS complexes (estimated to be between 21,600 to 28,800 complexes; assuming an average of 60 beats per minute) in the ECG recording of each patient has to be screened to identify the occurrence of nocturnal PVCs. To achieve this, we developed a custom-made program that detects the R peaks of the QRS complexes of the nocturnal ECG recordings from the PSG records. The program marks the detected R peaks with an asterisk on the plot of the ECG for the entire night. This allows a rapid visual validation that all R peaks are properly detected; a sample is shown in Figure 1. To detect anomalous heartbeats, as explained in the next section, the program generates a plot of RR values over the entire night. To achieve this, since heartbeats do not occur at regular intervals, it is helpful to interpolate between the heartbeats and resample the interpolated peaks with a fixed sample rate.

2.2 Detection of premature ventricular contraction

Once the interpolated RR interval data is obtained, it can be used to detect the PVCs. The detection algorithm is based on the recognition that isolated PVCs result in shorter RR interval (COUPL) followed by prolonged RR interval (COMP) (Figure 1). A search algorithm was implemented that allowed detecting the sequence of short and long intervals from the interpolated RR interval data. The detected location of PVCs were visually verified. This change in RR interval manifests itself on the averaged RR interval data as shown in Figure 2

2.3 Heart rate turbulence calculation

When a PVC occurs the heart sinus rate accelerates and then in the following beat(s) a deceleration of the rate occurs. HRT computations aims to capture the short-term fluctuations in sinus rhythm that reflect spontaneous the premature ventricular contraction. Two phases of heart rate fluctuations following a PVC, the early sinus rate acceleration and late deceleration, are quantified by computation of turbulence onset (TO) and turbulence slope (TS) parameters [13].

TO is expressed as a percentage and computed using the following formula

$$TO = \frac{(RR_1 + RR_2) - (RR_{-2} + RR_{-1})}{(RR_{-2} + RR_{-1})} \times 100$$

where RR_{-2} and RR_{-1} denote the elapsed time between two consecutive heartbeats that immediately precede the PVC and RR_1 and RR_2 signify the elapsed time intervals between the two consecutive heartbeats immediately following the PVC.

To compute TS, 15 RR-Intervals following the PVC are considered, denoting them as $RR_1, RR_2, \ldots, RR_{15}$. A linear regression line is fitted to the first five (5) of these values (i.e., $RR_1, RR_2, \ldots, RR_5$) and the slope of the resulting line is recorded. Next, a linear regression line is fitted to $RR_2, RR_3, \ldots, RR_6$, and the slope of the resulting regression line is recorded. This process is repeated for the remaining sets of 5 successive RR intervals of the heartbeats that succeed the PVC which can be obtained from RR_3 through RR_{15}.

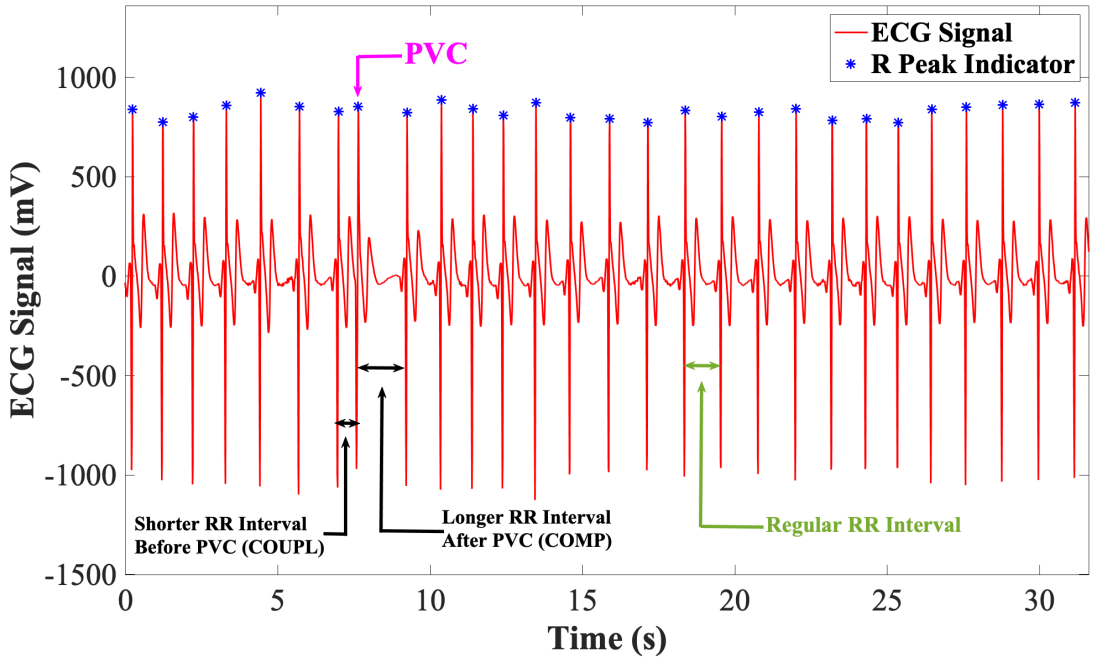

Figure 1: An illustration of Premature Ventricular Contraction (PVC) and RR-Interval on the ECG recording from one of the subjects retrieved from Sleep Apnea patient from Sleep Lab Database.

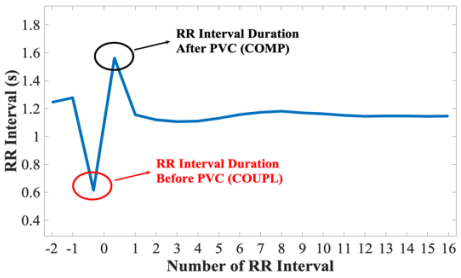

Figure 2: An illustration of averaged RR-Interval of the ECG recording from a subject retrieved from Sleep Apnea patient from Sleep Lab Database with a representation of average RR-Interval before and after occurrence of PVC.

These computations result in a total of 11 slope values per each occurrence of PVC. The highest slope value from this set of 11 slopes is selected as TS associate with each occurrence of PVC [13]. It is noted that TS values are usually computed by first aggregating the RR_{-2} through RR_{15} intervals – including the shortest and longest RR interval – associated with all PVCs that a subject presents during the ECG recording period. This aggregation is attained by aligning RR_1, RR_2, ..., RR_{15}. Generally, $TO \geq 0\%$ and TS ≤ 2.5 ms/RR were considered abnormal [14].

The computation of TO and TS were validated by using a test signal with known TO and TS values. After validation, TO and TS values for each occurrence of PVC in the all-night recorded ECG data as well the TS values using the aggregated tachograms were computed.

2.4 Experimental setup

The protocol and written subject consent form for testing subjects were approved by our Human Subject Institutional Review Board. Subjects were volunteer patients who were referred to our collaborating accredited sleep laboratory (Sleep Consultants Inc., Fort Worth Texas) for diagnosis of sleep apnea. Eleven volunteer subjects (52±8 yrs., BMI 34.07±7.25 kg/m^2) including nine Male (52±9 yrs., BMI 32.22±6.06 kg/m^2) and two Female (51±4 yrs., BMI 42.40±7.92 kg/m^2) signed the informed consent form. The AHI index values for each subject are as followed: 73.5, 42.3, 44.9, 18.3, 63.6, 42.8, 105.4, 31.1, 77.4, 87.3, and 82.2, respectively for subjects 1-11 (60.80±26.84). The subjects were instrumented with the standard clinical polysomnography sensors which included electroencephalogram (EEG), electrocardiogram (ECG), electrooculogram (EOG), and electromyogram for the chin and legs (EMG), chest and abdomen respiratory plethysmography bands, oximeter, and nasal pressure sensing canula. The subjects slept between 6 to 8 hours during the night and while the PSG data were recorded for the entire time. The data was scored by a certified sleep laboratory specialist who was blind to the objectives of this study to identify the episodes of central and obstructive apnea as well as hypopnea. The results of the scoring were used to identify the occurrence of apnea event.

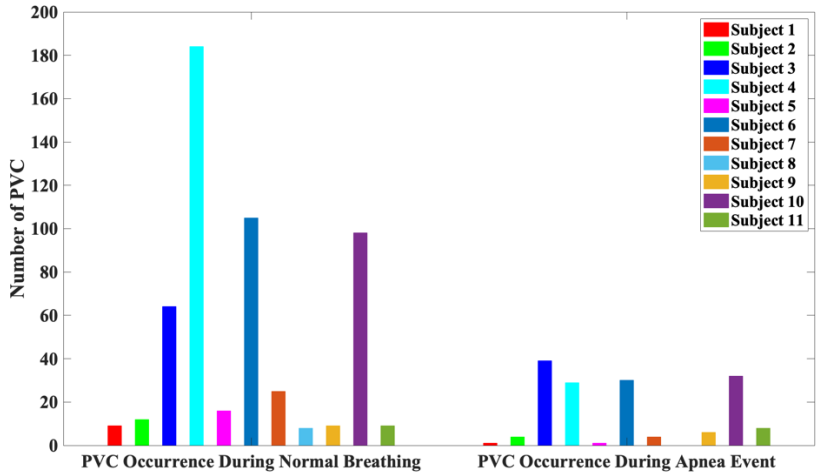

Figure 3: An illustration of the number of PVC occurred during the apnea event vs. the number of PVC occurred during normal breathing for 11 subjects with PVC.

2.5 Analysis of experimental data

Examination of the scored PSG data revealed that there are occurrences of PVC that are concurrent with apnea events as well as PVCs that occur during normal breathing. The PVCs that occurred concurrent with apnea events throughout the night as well as those that were outside the apnea events were identified using the PVC detection program described in experimental setup above. The mean of the count of these occurrences were statistically compared.

To investigate the effect of apnea events on the heart rate turbulence, TS and TO values were computed for individual PVCs as well as TS values over the averaged RR tachogram and averaged TO values that occurred concurrent with apnea events. Then, for these PVCs, we examined the duration of the apnea events versus the TO and TS values. Upon identifying the PVCs that occur during apnea episodes, we examined the associated TO and TS values for individual PVCs as well as TS values over the averaged RR tachogram and averaged TO. Similar analyses were caried out for the PVCs that were not concurrent with an apnea event (i.e., occurred during normal breathing). Additionally, the values of TO and TS were examined against the temporal length of the normal breathing interval during which PVCs occurred.

3 RESULTS AND DISCUSSION

Figure 3 displays the count of occurrences of PVC during apnea events and the number of PVC occurrences during normal breathing intervals throughout the night for each subject. These preliminary results show that in each of the tested subjects, the number of PVCs concurrent with normal breathing far exceeds the number of PVCs concurrent with apnea.

The distribution of TS values computed after each PVC versus duration of the apnea episode during which the PVC had occurred is shown in Figure 4A. Likewise, a plot of the TS values versus the duration of normal breathing intervals during which the PVC had occurred are shown in Figure 4B.

The distribution of TS values computed from averaged RR tachogram versus average duration of episodes apnea during which the PVCs had occurred is shown in Figure 5A. Likewise, the distribution of the TS values computed from averaged RR tachogram versus average duration of normal breathing interval during which the PVCs had occurred is shown in Figure 5B.

The statistical test of the mean count of the PVCs during apnea and normal breathing (Figure 3) showed that there is marginally significant difference in the means ($p = 0.07$), indicating that on the average similar number of PVCs may occur during normal breathing periods to the number of PVCs that occur during apnea episodes. The results shown in Figure 4A provides a visual illustration of the range of individual TS values that are computed for the PVCs that occur during apneic events. These results reveal that with the exception of subject number 10 the vast majority of individual TS values resulting from PVCs during apneic events fall below 150 ms/RR. Additionally, from Figure 4A it can be observed that most of the apneic events that were concurrent with PVCs lasted less than 40s. The results in Figure 4B illustrates that TS values for PVCs that were concurrent with periods of normal breathing are also vastly below 150 ms/RR. However, the mean of the TS values for apneic events proved to be statistically different from the mean of TS values during normal breathing ($p = 0.007$). It is important to note that when the tachograms of the PVCs during apneic events were averaged and the corresponding single value of TS for each subject was obtained (Figure 5A), the mean of the resulting TS values was not statistically different from the mean of their counterpart TS values during normal breathing shown in Figure 5B ($p = 0.083$). Additionally, from Figures 5A and 5B, it can be observed for TS values derived from that averaged tachograms the similarity of the patterns that was observed for TS derived from individual PVCs does not emerge. These findings suggest that averaging the

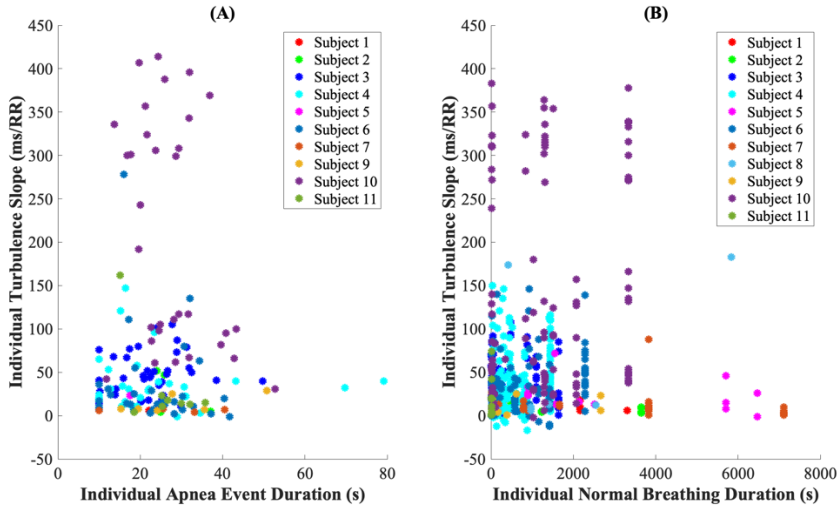

Figure 4: An illustration of the individual TS values vs. apnea (A) and normal breathing (B) duration.

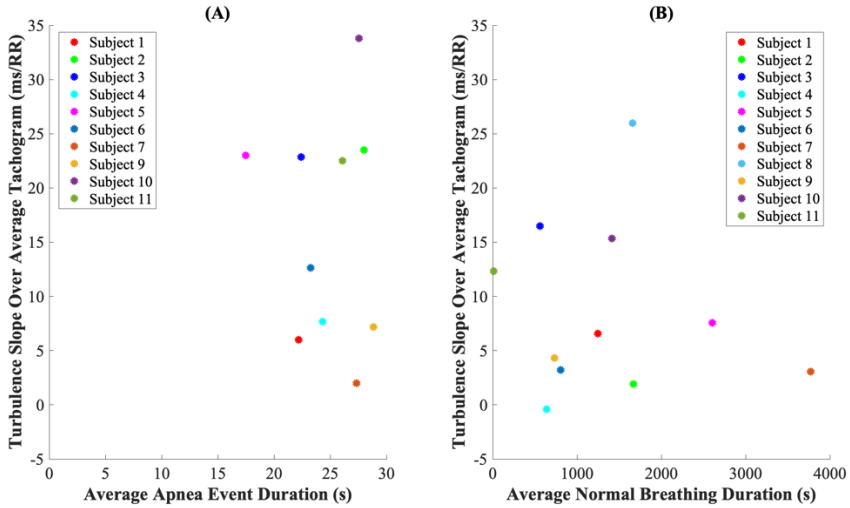

Figure 5: An illustration of the TS values obtained from averaged RR tachogram for PVCs that occurred during apnea episodes vs. the average duration of the corresponding apnea event (A), and the TS values obtained from averaged RR tachogram for PVCs that occurred during normal breathing vs. the of the average duration of the corresponding normal breathing (B).

tachograms may disguise some of the differences that exists in the heart rate oscillations that occur after each PVC. Indeed, a fruitful future investigation is quantifying the dispersion of the TS values obtained during apneic events and normal breathing.

Similarly, the distribution of TO values computed for each PVC versus duration of apnea episode during which the PVC occurred is shown in Figure 6A. The distribution of TO values computed for each PVC versus the duration of the normal breathing during which the PVC occurred is shown in Figure 6B. These plots provide a visualization of the distribution of the individual TO values for each PVC occurring during apneic event and normal breathing periods, respectively. The patterns of TO values in Figures 6A and 6B are somewhat similar to the observed patterns for individual TS shown in Figures 4A and 4B. That is, the subjects with larger TO values for their PVCs during apneic events also exhibit larger TO values for PVCs occurring during normal breathing (e.g., subject number 4 and 10). Further, the mean of the individual TO values during apneic events was statistically compared with the mean of the individual TO during normal breathing. The test shows that the mean values are different ($p = 0.0008$); as was the case for TS values discussed above.

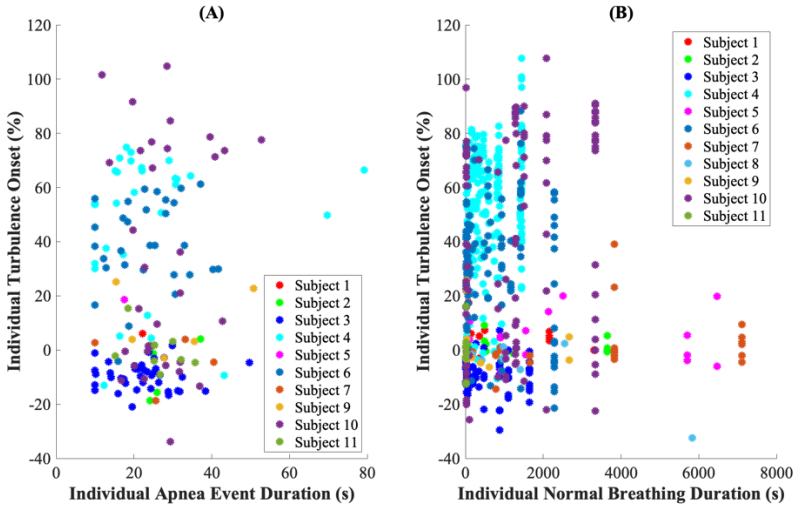

Figure 6: An illustration of the individual TO values vs. apnea (A) and normal breathing (B) duration.

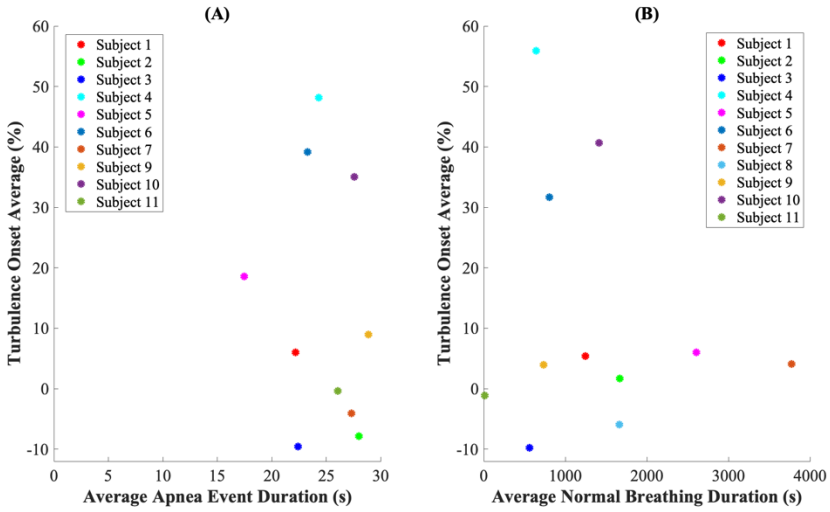

Figure 7: An illustration of the averaged TO values for PVCs that occurred during apnea episodes vs. the average duration of the corresponding apnea event (A), and the averaged TO values for PVCs that occurred during normal breathing vs. the of the average duration of the corresponding normal breathing (B).

The distribution of TO values computed from averaged TO versus average duration of episodes apnea during which the PVCs had occurred is shown in Figure 7A. Likewise, the distribution of the TO values computed from averaged TO versus average duration of normal breathing interval during which the PVCs had occurred is shown in Figure 7B.

When the results for TS and TO computations are considered together, several observations can be made from these plots. First, the PVCs have greater cooccurrence with apnea episodes that have shorter duration, as the breadth range of the data points in the Figures 4A and 6A show. Second, regardless of whether the PVC is concurrent with apnea or is during normal breathing, the individual values computed TS and TO have similar distribution (Figures 4A and 4B and Figures 6A and 6B). Third, vast majority of PVCs – regardless of whether they were concurrent with apnea events result in TS values that are between 0 to 100 ms/RR and TO values that are between -20 to 80%. Lastly, most of the computed values of individual TS and TO associated with the PVCs indeed fall in the normal range of TO and TS.

The distribution of TS values obtained from averaged RR tachogram of the PVCs that occurred during apnea episodes versus AHI is shown in Figure 8A. In the same way, the distribution of

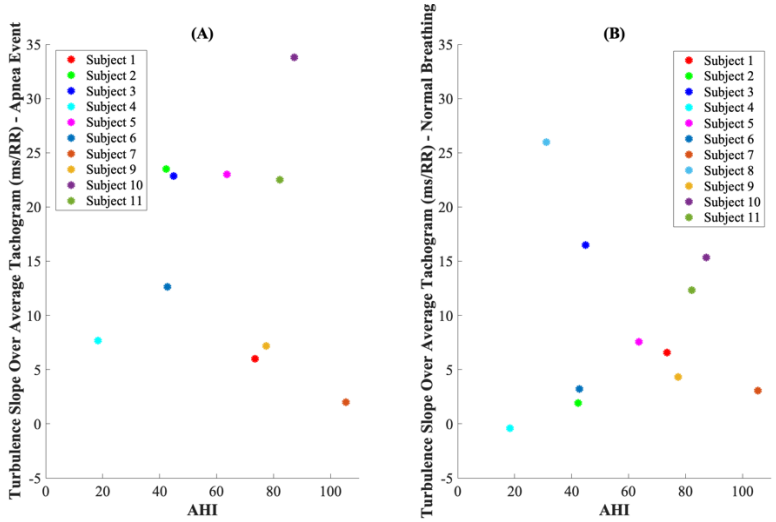

Figure 8: An illustration of the TS values over averaged RR tachogram during apnea (A) and normal breathing (B) vs. AHI.

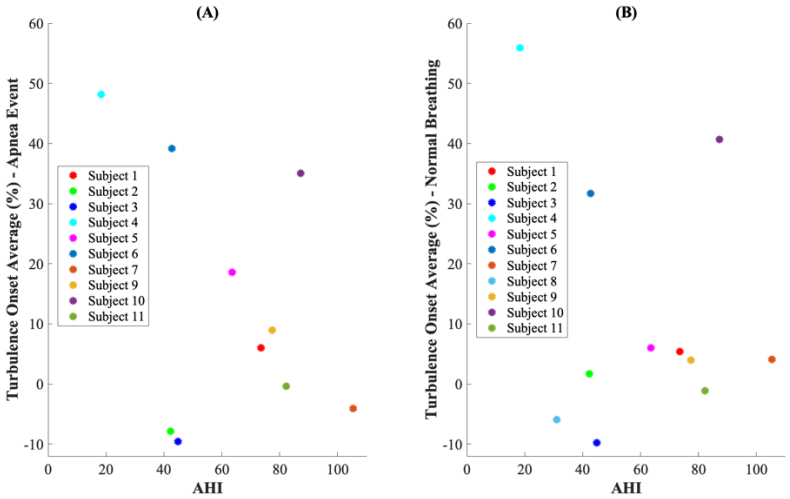

Figure 9: An illustration of the averaged TO values during apnea (A) and normal breathing (B) vs. AHI.

TS values obtained from averaged RR tachogram of the PVCs that occurred during normal breathing intervals versus AHI is shown in Figure 8B. The averaged TO values versus AHI for apnea concurrent with PVCs and normal breathing concurrent with PVCs are shown in Figure 9A and 9B, respectively. While no particular pattern emerged for the relationship between AHI and TO or TS values, this finding is congruent with results reported in a recent publication where only a weak correlation between AHI and TO ($r = 0.19$, $p = 0.02$) and moderate negative correlation ($r = -0.33$, $p = 1x10^{-4}$) between AHI and TS was reported [15].

4 CONCLUSION

This paper investigated quantitative means of assessing apnea-induced cardiac stress during sleep. The quantitative measures were inspired by the methodology of computing heart rate turbulence metrics of turbulence slope and turbulence onset. A program to process nocturnal ECG signal to detect PVCs was developed and validated in a sample of sleep apnea patients. By grouping the PVCs according to whether they occurred during normal respiration or during apnea, it was demonstrated that the resulting heart rate turbulence metrics reflecting the effects of the two PVC groups differ from one another. This research provides a tool for analyzing nocturnal ECG which is obtained routinely during PSG studies to

quantify the level of apnea-induced cardiac stress. Future investigation for this continuation of this preliminary study includes development of measures of dispersion of the proposed measure and evaluation of the measures based on data collection during per- and post-treatment of sleep apnea patients.

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