Detecting sleep apnea by volatility clustering of heart rate variability

Yuo-Hsien Shiau [a,b,*], Jia-Hong Sie [c], Sai-Ping Li [d]

[a] Graduate Institute of Applied Physics, National Chengchi University, Taipei 11605, Taiwan, ROC
[b] Research Center for Mind, Brain, and Learning, National Chengchi University, Taipei 11605, Taiwan, ROC
[c] Institute of Biomedical Engineering, National Yang-Ming University, Taipei 11605, Taiwan, ROC
[d] Institute of Physics, Academia Sinica, Nankang, Taipei 115, Taiwan, ROC

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It is well accepted that heart rate variability (HRV) is the result of complex cardiorespiratory dynamics including heart rate, blood pressure, and respiration rate. One well-known phenomenon of cardiorespiratory interaction is respiratory sinus arrhythmia (RSA) [1]. In particular, obstructive sleep apnea (SA), one of RSA-related disorders, is the repeated, temporary cessation of breathing during sleep caused by intermittent airway obstruction, and SA is considered an independent risk factor for hypertension, ischemic heart attacks, and stroke [2–4]. The physiological mechanisms leading to cardiovascular disease in SA are complex and not fully understood. However, it is believed that changes in the cardiac autonomic regulation should be involved in the development of cardiovascular disease for SA patients [5]. Previous studies indicated that changes in HRV are present in SA patients, and linear parameters of HRV in time domain have been proposed as a screening tool [6]. However, in the study of Yang et al. [7] no significant differences in time-related linear parameters of HRV were observed. Therefore, application of time-domain HRV parameters for SA patients is still debatable.

It is known that previous time-domain analysis requires stationary signals. This means that the mean value, standard deviation, and higher order moments of the analyzed signal must remain the same for the period investigated. However, SA with its highly dynamic pattern of HRV is nonstationary and therefore the application of linear time-domain analysis has been questioned before [8]. In this study, we report a novel nonlinear method in time domain that can recognize SA from HRV changes alone. Moreover, the underlying meaning of this proposed method can well reflect the nonstationary physiologic process for SA patients during sleep (see below).

Three groups of subjects were considered in this study. Apnea (class A), borderline apnea (class B), and normal (control, or class C) subjects were classified according to the total time duration of apnea and hypopnea that happened during sleep. In clinical applications, the apnea–hypopnea index (AHI) is often used to identify the severity of apnea patients. In addition, disordered breathing (DB) is also a quantity which counts the total time duration of apnea and hypopnea in overnight sleep. Our analyzed data including 40 recordings in class A, 10 recordings in class B, and 20 recordings in class C were obtained from the Apnea–ECG Database [9], which has been publicly released in PhysioNet [10].

In order to characterize heart rate fluctuations, the logarithmic return of heartbeat intervals $R(i)$ is considered.

$$R(i) = \ln\left[\frac{RR(i)}{RR(i-1)}\right], \tag{1}$$

where $RR(i)$ is the heartbeat interval at the beat number i. Moreover, the normalized return $R_{nor}(i)$ is defined as

$$R_{nor}(i) \equiv \frac{R(i)-\mu}{\sigma}. \tag{2}$$

where μ and σ are the mean and standard deviation of $R(i)$ series, respectively. Fig. 1 illustrates $RR(i)$ and $R_{nor}(i)$ of an SA patient as well as a normal subject. It is clear to find that the average heart rate of the normal subject is lower than that of the SA patient. In addition, the SA patient, compared to the normal subject, exhibited the dramatic volatility in $R(i)$ series. This dramatic volatility accompanied with cyclic variations is more pronounced for the SA patient [14]. Relatively, the normal subject displayed a uniform stochastic pattern in $R_{nor}(i)$ series, but the nonuniform dynamic pattern is obvious for the SA patient. This nonuniformity is strongly related to the clustering degree of large volatility in $R_{nor}(i)$ series. Therefore, the detection of the volatility clustering index R_l embedded in heart rate fluctuations would be an intuitive idea to differentiate between SA patients and normal subjects. The detailed mathematical procedure for the R_l index is shown in Appendix A.

The last row in Fig. 1 illustrates the number of events with largest 40% fluctuations within a 5-beat window for an SA patient (left) as well as for a normal subject (right) (see Appendix A). It is obvious that volatility clustering embedded in heart rate fluctuations is much more dominant for the SA patient. Thus the R_l index of SA patients should be larger than that of normal subjects. Fig. 2 demonstrates the statistical characteristics of R_l for apnea, borderline apnea, and control subjects. As expected, the apnea group has a higher R_l compared with that of the other two groups. Statistical differences between these three groups were assessed by Scheffe post hoc test. In Fig. 2 we can find that the R_l index provides significant differentiations for the apnea and control groups ($^{**}P<0.01$) as well as for the apnea and borderline apnea groups ($^{*}P<0.05$), however, no significant differences between the borderline apnea and control groups. In addition, based upon results shown in Fig. 2 the receiver operating characteristic (ROC) curve for the apnea and control groups reflects both high sensitivity and specificity (Fig. 3), where the AUC value can be up to 0.759.

In autonomic neuroscience, it is known that a series of changes in autonomic functions can be found during sleep via fast Fourier transform (FFT). For example, quiet sleep (QS) can be characterized by concurrent vagal activation and sympathetic withdrawal. This kind of autonomic alternations is totally different in the rapid eye movement stage [11,12]. Recently, Yang et al. used the short-term FFT to investigate the relationship between depth of QS and HRV indices for normal subjects and found that cardiac sympathetic regulation is negatively related to the depth of sleep, but vagal regulation is not [13]. In Fig. 2 the R_l index for normal subjects is larger than 1. It implies that normal sleep including a series of changes of sleep stages may induce the phenomenon of volatility clustering embedded in heart rate fluctuations. And the R_l index seems to provide a different point of view on changes in the cardiac autonomic regulation. In addition, it is also known that episodes of SA are accompanied by a characteristic heart rate pattern, which consists of

* Corresponding author at: Graduate Institute of Applied Physics, National Chengchi University, Taipei 11605, Taiwan, ROC. Tel.: +886 2 29393091x62987; fax: +886 2 29360360.
E-mail address: yhshiau@nccu.edu.tw (Y.-H. Shiau).

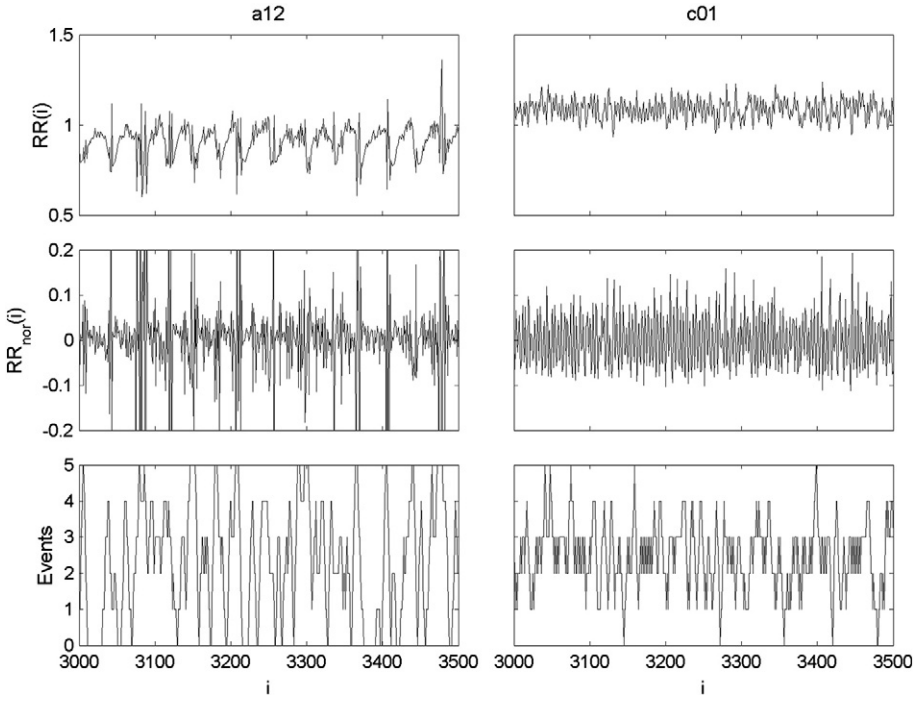

Fig. 1. Illustrations of $RR(i)$ (top), $R_{nor}(i)$ (middle), and the number of events with largest 40% fluctuations within a 5-beat window (bottom) for an SA patient (left) as well as for a normal subject (right).

bradycardia during apnea followed by abrupt tachycardia on its cessation [14]. Thus the dramatic volatility in heart rate can be expected for SA patients. Based upon results shown in Figs. 2–3, the number of apnea events has a significant influence on the clustering degree of large volatility embedded in heart rate fluctuations.

AHI and DB are well-accepted indices to identify the severity of apnea patients. Thus it can be expected that the high correlation (0.88, $P<0.01$) between AHI and DB can be observed in the analyzed database. The correlations for R_I vs. AHI and R_I vs. DB are, respectively, equal to 0.33 ($P<0.01$) and 0.36 ($P<0.01$). It is not surprising that R_I has a low correlation with DB as well as with AHI. As mentioned above, the R_I index is strongly related to a series of changes in sleep stages as well as the number of apnea events during overnight sleep. Although there is an intrinsic difference between R_I and AHI (or DB), the R_I index still provides significant differentiations for apnea and control groups as well as for apnea and borderline apnea groups (Fig. 2). However, it should be noted that periodic leg movements (PLMs) during sleep could be seriously related to the present study. The reason is PLM can make a similar heart rate pattern as that of SA [15,16]. In well-controlled clinical settings people found that the efficiency of automated SA detection will be strongly reduced for subjects with a higher PLM index [17]. The open-access database we used in this study did not provide the PLM information for all analyzed groups. Therefore, it would be interesting to test the efficiency of our apnea index R_I under controlled clinical settings for future studies.

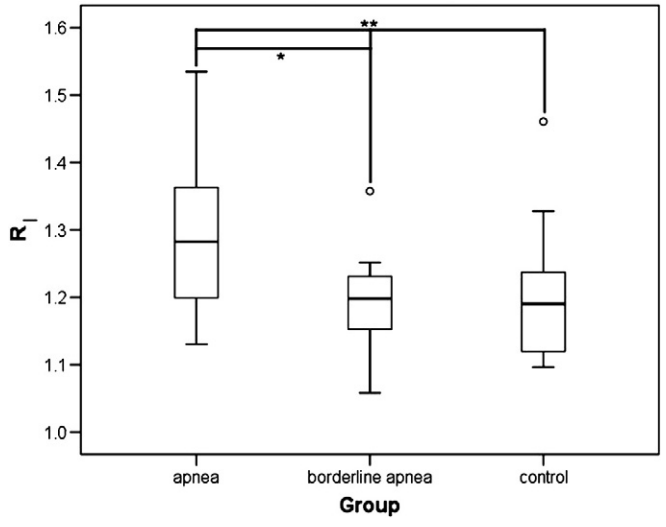

Fig. 2. Boxplot for comparisons of R_I in between apnea, borderline apnea, and control subjects. Boxes represent the 75th percentile, median, and 25th percentile. Whiskers show the largest and the smallest observed values. Difference was assessed by Scheffe post hoc test ($^{**}P<0.01$ and $^{*}P<0.05$).

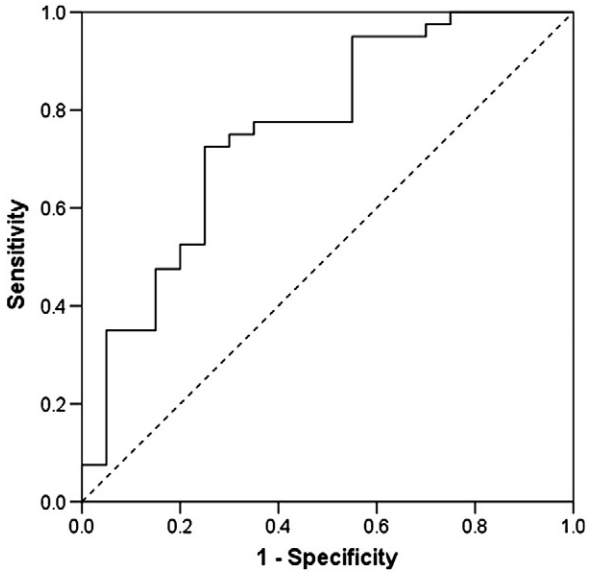

Fig. 3. The illustration of the ROC curve (solid) between the apnea and control groups, where the AUC value can be up to 0.759. The diagonal (dashed) is used as a reference line.

Finally, we shall explain why we chose the 5-beat window size as well as the largest 40% fluctuations in this study. In the rest status heart rate for normal subjects is 60–100 bpm, then one heartbeat needs 0.6–1.0 s and the time characteristic of a 5-beat window is 3.0–5.0 s. If the average breathing frequency for normal subjects is 0.2 Hz, then one breath needs 5.0 s. In addition, each single apnea must be longer than 10.0 s in order to be counted [9]. Therefore, the 5-beat window can measure the clustering degree of large volatility embedded in HRV during one breath and during a single apnea event. Concerning the largest 40% fluctuations, it is based upon the characteristic of the Apnea–ECG Database, where the average value of time spent in DB divided by the duration of the ECG recording is around 36.8%. Therefore, the present used parameters can detect apnea-induced volatility clustering embedded in heart rate fluctuations.

To conclude, in this study we propose an apnea index R_l from the time-domain HRV analysis. This index reflects the clustering degree of large volatility embedded in HRV. In addition, the underlying meaning of such an index should be strongly related to changes of the cardiac autonomic functions, where a series of changes in sleep stages and apnea events are the two main factors to influence this derived index. Although R_l cannot replace the target indices AHI and DB, our results suggest that this index provides significant differentiations for different groups. Thus clinical applications can be expected under the consideration of reduction of personal costs.

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Appendix A

Volatility clustering is a term that has been used to describe the clustering of large fluctuations in financial markets. It has been noticed for a long time that large fluctuations in financial time series tend to cluster together. In [18], an index is introduced to quantitatively measure the degree of clustering in a time series. This index has theoretical upper and lower bounds and is defined to be equal to 1 if the fluctuations cluster like a Gaussian noise sequence. This index can be used to measure clustering of fluctuations in any time series. In this analysis, we employ this index to measure the fluctuations in the normalized return sequence $R_{\mathrm{nor}}(i)$. The absolute returns $|R_{\mathrm{nor}}(i)|$ are first sorted and the largest p% fluctuations are identified. We would want to see if these large fluctuations will have clustering behavior. To do so, the simplest way is to replace the largest p% fluctuations of the $|R_{\mathrm{nor}}(i)|$ sequence by 1, and the rest of the sequence by 0. Therefore, the $|R_{\mathrm{nor}}(i)|$ sequence will be translated into a binary series, which contains only 0 and 1. We use the so called moving window method to measure the clustering behavior of the binary-type $|R_{\mathrm{nor}}(i)|$ series. A moving window with fixed size n-beat is first chosen. We put the window on the first event of the binary series and count the number of events with values equal to 1 within the window. We then move the window to the second event and again do the counting. We repeat the same procedure until we finish scanning through the whole binary sequence. We will then calculate the standard deviation σ_l of the number of events within the window and compare it with that of the Gaussian noise.

To obtain the clustering index of heart rate fluctuations, the statistic property of Gaussian noise should be reminded for the following process. In statistics, the mean value of Gaussian noise among the largest p% fluctuations with a window size n is equal to $p\times n/100 = Pn$, where P denotes $p/100$. The standard deviation of Gaussian noise also depends on p% fluctuations and window size. In mathematics, the probability of having m-beat largest p% fluctuations within an n-beat window can be expressed as

$$\frac{n!}{m!(n-m)!}P^m(1-P)^{n-m}. \tag{3}$$

The standard deviation is written as $\sigma = \sqrt{(x-\langle x\rangle)^2}$. Next, we can use Eq. (3) to rewrite the formula of standard deviation as

$$\sigma_G = \left[\sum_{m=0}^{n}(m-Pn)^2P^m(1-P)^{n-m}\right]^{1/2} = \sqrt{nP(1-P)}. \tag{4}$$

By comparing the result of counting the binary-type $|R_{nor}(i)|$ sequence with that of the Gaussian noise sequence, one can define a clustering index R_l of the largest p% fluctuations, which is the ratio of the standard deviation of the largest p% fluctuations within the n-beat window between the binary-type $|R_{nor}(i)|$ data and Gaussian noise,

$$R_l \equiv \frac{\sigma_l}{\sigma_G}. \tag{5}$$

A clustering index much larger than one denotes that the behavior of clustering is much stronger.

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