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Heart Rate Variability Assessment by the Entropy Parameters during Sleep

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Abstract*: The nonlinear heart rate variability (HRV) parameter quantifies autonomic nervous system (ANS) activity based on the complexity or irregularity of an HRV dataset. At present, among various entropy-related parameters during sleep, approximate entropy (ApEn) and sample entropy (SampEn) are not as well understood as other entropy parameters such as Shannon entropy (SE) and conditional entropy (CE). Therefore, in this study, we investigated the characteristics of ApEn and SampEn to differentiate a rapid eye movement (REM) and nonrapid eye movement (NREM) for sleep stages. For nonlinear sleep HRV analysis, two target 10-minute, long-term HRV segments were obtained from each REM and NREM for 16 individual subjects. The target HRV segment was analyzed by moving the 2-minute window forward by 2 s, resulting in 240 results of each ApEn and SampEn. The ApEn and SampEn were averaged to obtain the mean value and standard deviation (SD) of all the results. SampEn provides excellent discrimination performance between REM and NREM in terms of the mean and SD ($p<0.0001$ and $p=0.1989$, respectively; 95% CI), but ApEn was inferior to SampEn ($p=0.1980$ and $p=0.9931$). The results indicate that SampEn, but not ApEn could be used to discriminate REM from NREM and detect various sleep-related incidents.

Keywords*: Heart rate variability, approximate entropy, sample entropy, autonomic nervous system, sleep.

I. INTRODUCTION

Heart rate variability (HRV) is a useful measure to investigate autonomic nervous system (ANS) activity, which comprises the parasympathetic nervous system (PNS) and sympathetic nervous system (SNS). During sleep, a rapid change in ANS activity is marked by complex physiological and cardiac autonomic activities [1, 2, 3]. In sleep HRV analysis, the logarithmic values of frequency-domain HRV parameters have been widely used relative to nonlinear HRV parameters: very low frequency (Ln VLF), low frequency (Ln LF) and high frequency (Ln HF) in the frequency domain and approximate entropy (ApEn) and sample entropy (SampEn) in the nonlinear domain [4, 5, 6].

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Most sleep studies include the discrimination ability between rapid eye movement (REM) and nonrapid eye movement (NREM), as well as the transition from REM to NREM or from NREM to REM, because sleep stages are continuously switched during the entire sleep course [7, 8, 9]. Some studies have reported that, among frequency-domain HRV parameters, the Ln LF/Ln HF ratio is increased in REM similar to the wakeful state and decreased in NREM [7, 10, 11]. The Ln LF/Ln HF ratio has become a good marker for differentiating REM and NREM, with ratios above 1.0 corresponding to increased sympathetic and decreased parasympathetic tones, and ratios less than 1.0 corresponding to increased parasympathetic and decreased sympathetic tones. Meanwhile, Ln VLF is not well defined to quantify ANS activity because Ln VLF includes relatively shared PNS and SNS activities. For nonlinear HRV analysis, nonlinear parameters have been reported to be better measures for long-term cardiac patients than frequency-domain HRV parameters [12]. Among nonlinear parameters, an entropy-derived feature has been recently used to assess ANS complexity or irregularity throughout the nighttime period [13, 14]. During sleep, the sympathovagal balance and reflex circuits, such as baroreflex and chemoreflex control, influence the normal-to-normal (NN) interval between two successive heartbeats in milliseconds, resulting in HRV irregularity [7, 15]. For instance, a decrease in HRV complexity comes from impaired cardiovascular control and the pathological state in a patient: the better is a patient, the greater is the irregularity [15]. Entropy parameters, such as Shannon entropy (SE) and conditional entropy (CE), which represent a degree of HRV complexity, have been investigated to obtain information on autonomic complexity during sleep [16]. However, ApEn and SampEn are not fully understood when determining the HRV pattern distribution of the NN intervals to discriminate REM and NREM in sleep stages. Therefore, in this study, we investigated the characteristics of ApEn and SampEn to verify the discrimination performance between REM and NREM as well as the ability to detect dynamic ANS activity. To calculate ApEn and SampEn parameters, two target 10-minute HRV datasets were collected from the respective REM and NREM of the recorded HRV dataset over 6 hours during sleep for 16 individual subjects.

A target long-term HRV segment was divided into many 2-minute windows (n=240) after the time shifting of every 2 s, leading to 240 results of ApEn and SampEn. Comparison parameters were introduced as the mean and standard deviation (SD) of 240 results for both ApEn and SampEn, and spectral profiles. A significant difference was found between REM and NREM regarding the mean and SD (p<0.0001 and p=0.0229; 95% CI) for SampEn, whereas no significant difference was found for ApEn (p=0.1980 and p=0.9931, 95% CI). The results demonstrate that nonlinear HRV parameters are not better measures than frequency-domain HRV parameters to differentiate REM and NREM; however, SampEn could be used as a better predictor than ApEn.

II. SUBJECTS

In this study, 16 patients in good health were enrolled and had the following characteristics: all males; age, 41.13±14.39 years; height, 169.87±9.74 cm; weight, 73.60±13.80 kg; BMI, 25.37±3.51; heart rate (REM), 66.33±6.63 bpm; and heart rate (NREM), 65.33±7.67 bpm. Electrocardiography (ECG) signals were measured at a sampling frequency of 200 Hz using a computerized polysomnographic (PSG) device (Nox-A1; Nox Medical Inc., Reykjavik, Iceland). All the subjects had no history of any medical condition to influence ANS function, such as obstructive sleep apnea (OSA) and symptoms of sleep deprivation.

III. PROCESSING SCHEME

ApEn and SampEn parameters were calculated by moving the 2-minute window forward by 2 s for a target 10-minute HRV segment. Sleep HRV analysis was carried out in the research mode of the pulse analyzer TAS9VIEW (CANOPY9 RSA; IEMBIO Co., Ltd, Chuncheon-si, Republic of Korea). The HRV research software application has been developed by the authors. Fig. 1 shows that, based on the overlapping segments, the 2-minute window is slid forward to calculate the result of each segment and obtain the mean and SD of the 240 results.

IV. APEN AND SAMPEN PARAMETERS

ApEn provides random signal information that quantifies complexity or irregularity in the NN intervals in the time series. An advantage of ApEn is that it requires a relatively short time series such as < 5-minute length to evaluate the randomness of a signal. To investigate dynamic ANS activity, a degree of HRV complexity is calculated through sequential comparison of predetermined vector arrays that are selected segments of NN intervals in the HRV dataset. These vector arrays are defined as the embedding dimension, m, which corresponds to the vector size. Additionally, a predetermined tolerance value, r, which compares the magnitude between two consecutive elements and consists of m vector arrays, is employed. In a given HRV dataset that comprises the total data points (N), an array vector of N-m+1 is created as follows:

$$M(N-m+1) = \{NN(N-m+1), NN(N-m+2,\ldots,NNN \quad (1)$$

In equation (1), m discrete data points in the time series are prepared. The distance between two consecutive vectors M(i) and M(j) represents the maximum difference in their respective corresponding elements, as in equation (2),

$$d[M(i), M(j)] = \max_{k=1,2,\ldots,m}(|NN(i+k-1) - NN(j+k-1) \quad (2)$$

where i=1, 2, …, N-m+1, and j=1, 2, …, N-m+1. Two embedding vectors, M(i) and M(j), are similar if $d[M(i), M(j)]$ is less than r, which is defined as 20% of the standard deviation of the NN intervals (SDNN),

$$r = 20\% * SDNN \quad (3)$$

$$\alpha = \sum_{i \neq j} \Delta\{r - d[M(i), M(j)]\} \quad (4)$$

where

$$\Delta\{x\} = \begin{cases} 1, x \geq 0, \\ 0, x < 0. \end{cases} \quad (5)$$

The probability of finding m vector similar to the sequence M(i):

$$C_i^m(r) = \frac{1}{N-(m-1)}\alpha \quad (6)$$

Consequently, the ApEn value of an infinite time series can be calculated as

$$ApEn(r, m) = \lim_{N\to\infty}\left[ln\frac{C_i^m(r)}{C_i^{m+1}(r)}\right]. \quad (7)$$

For practical applications, a finite time series should be defined as:

$$ApEn(r, m, N) = ln\frac{C_i^m(r)}{C_i^{m+1}(r)}. \quad (8)$$

Using equation (8), ApEn reaches zero when a time series data has a periodic waveform and no random signal. Thus, the greater the similarity is, the lower the ApEn value is. The reliability of the ApEn estimation depends on total HRV data length N, embedding dimension m and tolerance value r. Considering the ApEn mathematical equation, ApEn is influenced by the bias caused by self-matching of the M(i) vector. To reduce the bias by eliminating this self-matching, the equations (4) and (6) are redefined as:

$$\alpha = \sum_{i \neq j} j\ such\ that\{r \geq d[M(i), M(j)]\} \quad (9)$$

$$C_i^m(r) = \frac{1}{N-(m-1)}\alpha \quad (10)$$

Then, SampEn is finally defined in the following equation:

$$SampEn(r, m, N) = ln\frac{C_i^m(r)}{C_i^{m+1}(r)}. \quad (11)$$

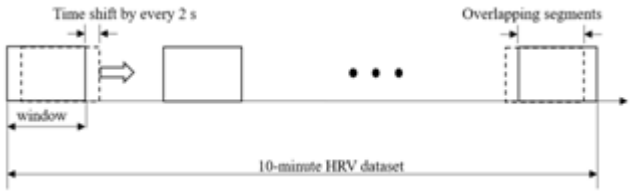


Fig. 1. Processing scheme to calculate ApEn and SampEn with 240 results after moving the 2-minute window forward by 2 s for a 10-minute HRV dataset.

V. RESULTS AND DISCUSSION

The discrimination ability between REM and NREM in terms of ApEn and SampEn was evaluated for 16 subjects. SampEn was found to become a more excellent predictor to discriminate REM from NREM than ApEn in the mean value as shown in **Table- I**. A statistically significant difference was found between REM and NREM for SampEn (p<0.0001; 95% CI), whereas no difference was found for ApEn (p=0.1980). The mean (SD) changes in REM and NREM were -0.66 (0.13) and 0.05 (0) for SampEn and ApEn, respectively. The SD value, which reflects how much the entropy parameter fluctuates in each sleep stage, did not differ (**Fig. 2**). The mean ApEn was lower in REM than in NREM, while that of SampEn was larger in NREM than in REM. ApEn and SampEn were calculated using a fixed value of m = 2 and r = 0.2*SDNN because they are largely affected by m and r. **Fig. 3** shows that the nonlinear ApEn parameter is characterized by fewer fluctuations between REM and NREM, a feature that contributes to self-comparison of the embedding vectors, m. In the NREM sleep stage in which parasympathetic activity dominates, ApEn resulted in a lower value than that in REM. In the future, the extent to which ApEn reflects a parasympathetic predominance state during sleep should be investigated relative to the sympathetic state. In a Box-and-Whisker plot, a central box ranges from the 25th to 75th percentiles, with middle line corresponding to the median and vertical line extending from the minimum to the maximum value. Outlier values are displayed as separate points.

Table- I: Results of paired t-test statistics to differentiate REM and NREM.

n=16	REM		NREM		*p*-value	
	Mean	SD	Mean	SD	Mean	SD
ApEn	0.71	0.10	0.66	0.10	0.1980	0.9931
SampEn	1.27	0.37	1.94	0.24	<0.0001	0.0229

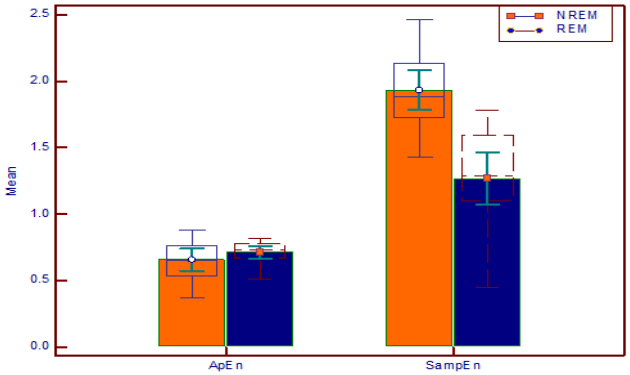


Fig. 2. Mean values between REM and NREM according to ApEn and SampEn.

Considering sleep stages, **Fig. 4** shows how much entropy parameters differ between REM and NREM. The value of SampEn during NREM increased by approximately 200% relative to that of ApEn. Consequently, an increase in SampEn during NREM reflects parasympathetic predominance because NREM sleep shows random behavior of the NN intervals compared with REM sleep, while ApEn does not differ. Values near 1.8 - 2.2 in nonlinear analysis using the 2-minute window during NREM were found to be characteristic of SampEn and were associated with the dynamic change in ANS activity. However, during REM, a large reduction in SampEn was found with a range of 0.5 to 1.0.

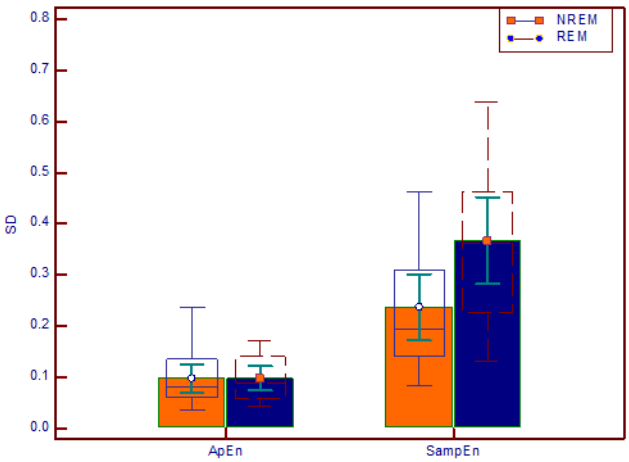


Fig. 3. SD between REM and NREM according to ApEn and SampEn.

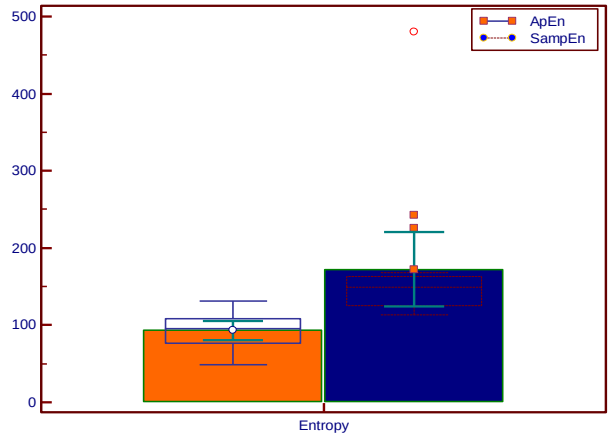


Fig. 4. Influence of ApEn and SampEn on REM and NREM.

The profiles of all 240 results for SampEn were plotted to differentiate REM and NREM for two different subjects as shown in **Fig. 5**. A SampEn profile plotted in the top panel of **Fig. 5** clearly differentiated REM from NREM in real time, but not the profile plotted in the bottom panel of **Fig.5**. Although the mean value of NREM was larger than that of REM, continuous monitoring of a single SampEn during sleep stages still has problems in evaluating the complexity of HRV.

For another subject, a sudden rise in the profiles of SampEn was observed, returning to an initial level in no less than 1-minute in the bottom panel. This SampEn feature depending largely on the subject should be investigated for clinical sleep interpretation in association with sleep HRV analysis. Additionally, most of the SampEn in NREM showed higher values than those in REM, representing parasympathetic activity over sympathetic activity; but several reversals were observed. The number of reversals in SampEn profiles between REM and NREM was expected to be linked to sleep efficiency but was not confirmed. However, the number of reversals for a target HRV segment may provide clinical information on dynamic ANS functioning. **Fig. 6** shows the ApEn profiles of 240 results using the 2-minute window for two different subjects. No significant differences were found between REM and NREM for the ApEn profiles. Therefore, the ApEn profile including its mean and SD showed no discrimination performance between REM and NREM.

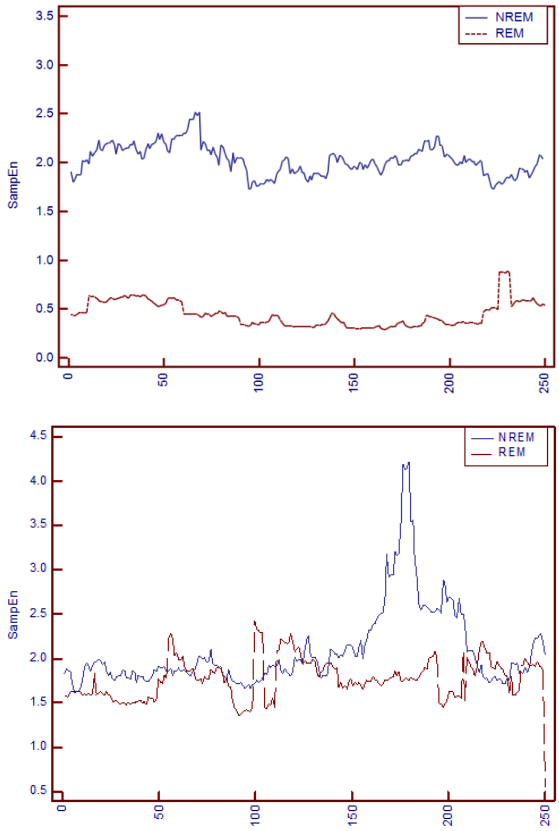
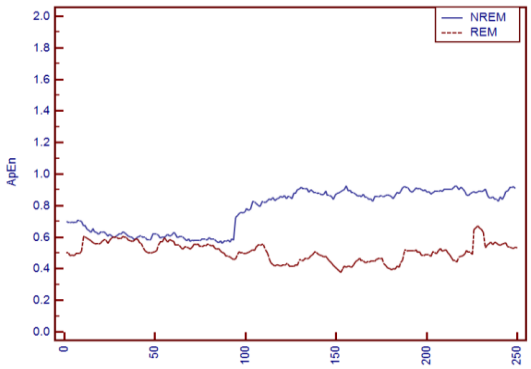


Fig. 5. SampEn profiles of 240 results using 2-minute window for two different subjects.



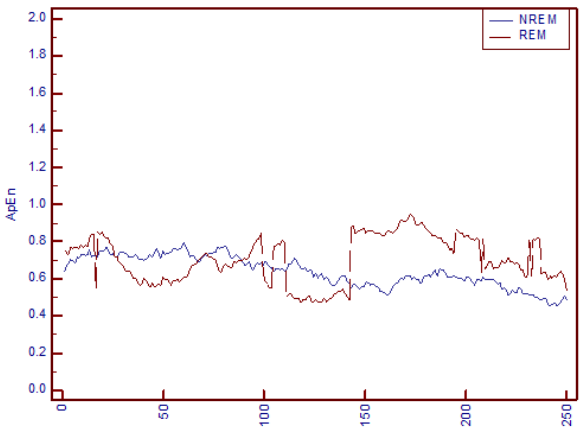


Fig. 6. ApEn profiles of 240 results using the 2-minute window for two different subjects.

VI. CONCLUSION

HRV analysis during sleep was performed to differentiate REM and NREM using the nonlinear HRV parameters ApEn and SampEn. Increased SampEn during NREM was observed compared with that during REM regarding the mean value of 16 subjects using the 2-minute window. However, regarding the ApEn parameter, no significant difference was found between REM and NREM. The relationship between ApEn and SampEn during sleep stages was not statistically significant. Like SampEn, ApEn can quantify the complexity of HRV, which is decreased or increased. However, ApEn is different from SampEn in the characteristics for distinguishing REM from NREM for sleep HRV analysis. This finding indicates that because the ApEn value depends on self-matching between consecutive embedding vectors relative to SampEn and the length of the NN intervals in the time series, an optimal size of m and tolerance value, r, should be determined to use the ApEn index for sleep HRV analysis. Theoretically, to overcome these shortcomings of ApEn statistics, SampEn was proposed to measure the complexity in the NN intervals. In conclusion, we suggest that the SampEn index during sleep could be used as a useful predictor to distinguish sleep stages and identify sleep-related events.

SampEn showed excellent characteristics reflecting increased parasympathetic activity during NREM as well as large change in both REM and NREM.

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