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Heart rate variability assessment during sleep derived from ultrashort-term and short-term windows

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Abstract

Objective: Heart rate variability (HRV) is a useful measure to quantify autonomic nervous system (ANS) function. A short-term window (5 min) for HRV analysis has been adopted in many sleep studies to differentiate between rapid eye movement (REM) and non-REM (NREM) sleep. In this study, an ultrashort-term window (2 min) was proposed to overcome the problem that the short-term window cannot investigate instantaneous ANS changes during REM or NREM.

Methods: We obtained a 10-minute HRV dataset from polysomnographic data for 21 individual patients in both REM and NREM (N3 stage). This target dataset was analyzed by shifting the ultrashort-term and short-term windows forward by 2 s to create multiple power spectral densities (n=250 and n=140, respectively) with the short time Fourier transform (STFT). Three main frequency bands were investigated: very low frequency (Ln VLF), low frequency (ln LF), and high frequency (Ln HF).

Results: The standard deviation (SD) of spectral profiles obtained by ultrashort-term windows was found to be a new potential indicator to differentiate REM and NREM ($p<0.0001$). How many times or whether the Ln LF/Ln HF ratio and Ln HF crossed the designated threshold line could be used to detect rapid ANS changes during both REM and NREM. Ln VLF and Ln LF were higher in REM than NREM, whereas Ln HF was lower.

Conclusion: The results suggested that an ultrashort-term window based on the STFT with a time resolution of 2 s would be more useful for tracking rapid changes in ANS activity than a short-term window.

Keywords: heart rate variability; rapid eye movement; power spectrum; autonomic nervous system; sleep

1. Introduction

Classification of sleep stages plays a critical role in the diagnosis of sleep diseases, such as obstructive sleep apnea, insomnia, and narcolepsy. Five sleep stages, in general, are categorized based on results of overnight standard polysomnography (PSG), which includes brainwave frequency bands and amplitudes from an electroencephalogram (EEG), an electrooculogram (EOG), and an electromyogram (EMG): rapid eye movement (REM), and N1, N2, N3, and N4, known as non-REM(NREM). The use of PSG for sleep-stage classification is cumbersome for patients. Therefore, recently, to overcome the shortcomings of PSG, heart rate variability (HRV) analysis using a single sensor has been introduced as an alternative. HRV represents the time intervals between two successive heartbeats, which are regulated by the activity of the autonomic nervous system (ANS) during sleep.

In this study, two types of sleep, REM and NREM (N3 stage), were identified from short time Fourier transform (STFT) with an optimal window and time resolution in terms of HRV frequency parameters. STFT with an ultrashort-term (2 min) window and a time resolution of 2 s showed the ability to differentiate between sleep stages. In addition, spectral profiles, in the form of the mean and standard deviation (SD) of the four frequency-domain HRV parameters derived from ultrashort-term windows, were evaluated to detect rapid ANS changes. We showed that the SD obtained from an

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ultrashort-term window was found to be a potential sleep stage indicator. The reliability of these HRV parameters was verified through a comparison with those from a short-term window. The results demonstrated that averaged trends of ultrashort-term HRV parameters with time shift of 2 s were significantly correlated with those of short-term HRV parameters that have been traditionally referenced ($p<0.0001$, 95% CI).

2. Literature reviews

HRV analysis is a noninvasive method for investigating changes in ANS activity, as it evaluates the dominance between the parasympathetic nervous system (PNS) and sympathetic nervous system (SNS) (Task Force, 1996; Evans et al., 2013; Scheff et al., 2014; Soares-Miranda et al., 2014). Most studies have reported that HRV analysis, specifically analysis using a short-term (5 min) window, predicted ANS function by evaluating the degree of fluctuation in time- and frequency-domain HRV parameters (Ori et al., 1992; Kemp and Quintana, 2013; Goldberger et al., 2019). However, sleep-related clinical applications using short-term HRV analysis are limited because the associated spectral estimates do not reflect rapid ANS fluctuations over time, which are enough to differentiate REM and NREM. Regarding the response time to ANS stimuli, some studies have reported that the response time to a parasympathetic stimulus ranged from 0.2 to 0.6 s, whereas the response time to a sympathetic stimulus ranged over 1 s (Zygmunt and Stanczyk, 2010; Colombo et al., 2015). These findings suggest that dynamic ANS activities can take place within seconds in various biological systems. To analyze these dynamic ANS activities, three main mathematical models have been proposed: the Fourier transform (FT), autoregressive (AR) spectral density, and wavelet transform (WT). The main drawback of FT and AR is that they lack time information, which is critical to detect sudden ANS changes for sleep studies. Therefore, the FT and AR methods recommended by HRV Task Force Guidelines (Task Force, 1996) show the disadvantage of only detecting relatively slow changes in autonomic status over minutes, depending on data length and model order, whereas both methods are widely applied in medical devices and research applications with numerous comparable results (Hyndman and Gregory, 1975; Chemla et al., 2005; Ziemssen et al., 2008). For this reason, short time Fourier transform (STFT)-based spectral analysis that provides time-frequency information has attracted many sleep researchers. For STFT for HRV analysis, it is important to set an optimal boundary between either high time resolution or high frequency resolution (Novak and Novak, 1993; Elsenbruch et al., 2000; Mainardi, 2009). Determining the frequency and time resolutions depends on which one is more important for the clinical application; the time resolution should be decided according to how fast ANS changes (Pola et al., 1996). For frequency resolution depending on HRV data length, some studies have reported the characteristics of frequency domain HRV parameters using different time windows (Malik et al., 1996; Li et al., 2019). WT, which provides good time-frequency information, has been increasingly applied, but it has a wide variety of wavelets that influence the time-frequency resolution, resulting in no generalized wavelet that is optimized for HRV analysis (Hossen et al., 2013; Ziemssen and Siepmann, 2019; Geng et al., 2020). WT-based HRV parameters using different wavelets must be more carefully considered than the STFT parameters, especially where the balance between PNS and SNS activities is assessed for HRV sleep studies. During sleep, a high frequency to low frequency ratio (Ln LF/Ln HF) among HRV parameters, which corresponds to the ANS balance, has been linked to various sleep-related disease states (Bonnet and Arand, 1997; Zhang et al., 2020). Additionally, it has been reported that decreased parasympathetic activity along with increased sympathetic activity during sleep is associated with an increased risk of cardiovascular disease in patients with obstructive sleep apnea (OSA) syndrome. OSA patients with coronary artery disease were also found to demonstrate SNS dominance over PNS (Burgess et al., 2004; Sessa et al., 2018; Nastałek et al., 2019). Regarding sleep stage, rapid eye movement (REM) and nonrapid eye movement (NREM) continuously alternate with sudden increases or decreases in vagal and sympathetic tones (Walsh et al., 1994; Dijk, 2008). To monitor this alternation, several studies have used an ultrashort-term window (1-2 min) for a target HRV dataset of 30 min to 1 h to calculate the HRV spectrogram, but a time shift of 20-30 s was determined to be the time resolution, resulting in no detection of rapid changes in spectral profiles (Kleiger et al., 2005; Pecchia et al., 2018).

3. Methods

3.1 Subjects

Twenty-one patients with clinical suspicion of OSA were qualified to participate in the study (age: 40.43 ± 13.26 years; BMI: 25.70 ± 4.12; heart rate

associated with REM: 65.43±8.29 bpm, and heart rate associated with NREM: 63.67±8.05 bpm). We randomly selected 21 patients' dataset from each stage to use in this study, after we excluded patients who have neurodegenerative diseases because they showed distorted sleep architecture. Standard overnight polysomnography (PSG) was performed for all subjects using a computerized polysomnographic device (Nox-A1, Nox Medical Inc. Reykjavik, Iceland). A 10 min segment from each REM and NREM period that was taken from stage 3 (N3) sleep was selected to secure enough quality frequency-domain HRV parameters. None of the subjects had a history of any medical condition that could influence sympathovagal activity. This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Hallym Medical University Chuncheon Sacred Hospital (IRB No. 2020-03-022). Additionally, the need for written informed consent was waived because this study was designed to be retrospective.

We applied the paired-sample t-test and Pearson correlation coefficient to evaluate the difference between REM and NREM and the relationship between ultrashort-term and short-term windows in terms of frequency-domain HRV parameters, respectively. The results were reported with correlation coefficient, p-value, and 95% confidence interval. The p-value lower than 5% ($p<0.05$) means that there are no statistically significant differences between ultrashort-term and short-term HRV parameters.

3.2 Processing Scheme

We used the commercial TAS9VIEW pulse analyzer (CANOPY9 RSA, IEMBIO Co., Ltd, Chuncheon, Republic of Korea) to obtain frequency-domain HRV parameters with the STFT. Four spectral powers were analyzed by shifting predetermined segments that were termed "windows" (2 min and 5 min) forward by 2 s during the 10 min HRV target dataset, which were collected from each REM and NREM sleep stage. These spectral powers were total power (Ln TP), very low frequency (Ln VLF), low frequency (Ln LF), and high frequency (Ln HF). The term "window" refers to the moving time window that was used for continuous analysis as depicted in Fig. 1. A short-term segment is traditionally defined to be 5 min in duration, and an ultrashort-term segment is defined to be 2 min. The number of results obtained from the ultrashort-term and short-term windows for each frequency-domain HRV parameter was 240 and 150, respectively for a 10 min due to a time shift of 2 s (the time resolution).

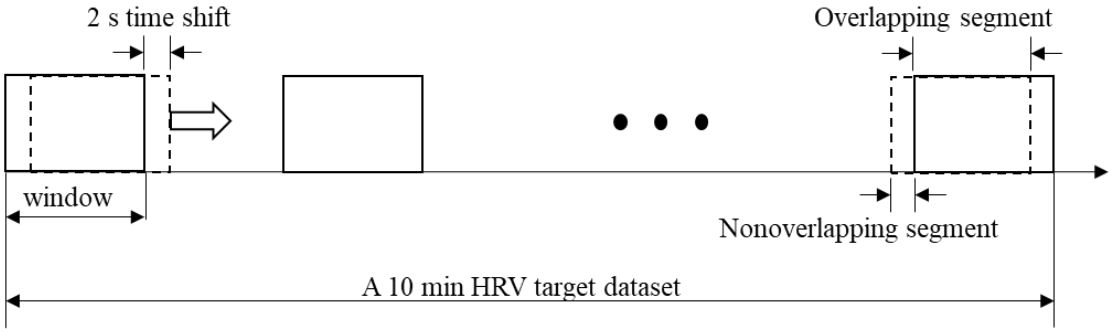

Fig. 1. **The processing scheme for calculating power-spectral estimates based on a minimal nonoverlapping segment (2 s).**

3.3 Power Spectral Analysis

The PSD measures the degree to which the energy of a normal-to-normal (NN) heartbeat interval signal in a time series is distributed in terms of frequency bands. The PSD was basically acquired by means of a discrete Fourier transform (DFT), which is similar to an analog fast Fourier transform (FFT) incorporating 1024 data points that were resampled by linear interpolation. HRV guidelines recommend that NN intervals be collected at a high (1 kHz) sampling frequency using either electrocardiogram (ECG) or photoplethysmogram (PPG) signals (Task Force, 1996). In our previous study, we found that there were no significant differences between HRV parameters at sampling frequencies of 1 kHz and 500 Hz, and that a sampling frequency lower than 500 Hz led to decreased Ln HF (Ahn and Kim, 2020). However, the current ECG embedded in the polysomnographic device measured NN intervals at a sampling frequency of 200 Hz with an interval of 333 ms, and a slight decrease in Ln HF was thus anticipated. The Fourier coefficient of the discrete time signal NN[n] is defined as follows:

$$X[m] = \sum_{n=0}^{N-1} NN[n] e^{-j\omega n} \quad (1)$$

Because $\omega=2\pi f/Fs$ and $f=mFs/N$, we have

$$X[m] = \sum_{n=0}^{N-1} NN[n]\, e^{-\frac{j2\pi mn}{N}} \quad (2)$$

Here, N is the number of sampled points, m is the discrete frequency number for the frequency domain which ranges from 0 to N-1, and Fs is the sampling frequency. Equation (2) consists of a real part and an imaginary part for every frequency number m. Before the DFT calculation, the Hanning window was applied to input discrete time signals, NN[n]*w[n], and thus avoid a spectral leakage via the following equation:

$$w[n] = 0.5\left[1 - \cos\left(2\pi \frac{n}{N-1}\right)\right],\ 0 \le n \le N - 1 \quad (3)$$

Next, the STFT was applied to obtain a sequence of DFT results of multiple windows along with time information, t, which moves forward by 2 in the following equation:

$$X[m,t] = \sum_{n=0}^{L-1} w[n] NN[t+n]\, e^{-\frac{j2\pi mn}{N}} \quad (4)$$

Finally, Ln HF, Ln LF, and Ln VLF were calculated in real time by integrating the spectral profiles with frequency bands as shown in the following equations:

$$\text{Ln HF} = \ln \int_a^b |X[m,t]^2| dm \quad (5)$$

$$\text{Ln LF} = \ln \int_c^d |X[m,t]^2| dm \quad (6)$$

$$\text{Ln VLF} = \ln \int_e^f |X[m,t]^2| dm \quad (7)$$

where the Ln HF bands range between a=0.15 and b=0.4 Hz, the Ln LF bands range between c=0.04 and d=0.15 Hz, and the Ln VLF bands range between e=0.0033 and f=0.04 Hz. Ln TP is defined as the summation of Ln VLF, Ln LF, and Ln HF. The power spectrum $X[m,t]$ was calculated as the squared magnitude of all Fourier coefficients.

Results

4.1 Characteristics of the mean and SD of the frequency-domain HRV parameters

A 10 min HRV target segment was divided into consecutive, individual, ultrashort-term (n=240) and short-term (n=150) 2 s windows. All frequency-domain HRV parameters were averaged to discriminate REM from NREM and obtain the mean and SD of all mean values for each subject. We attempted to confirm which HRV parameters are most influenced by sleep stage. All HRV parameters fluctuated more during REM than during NREM regardless of the window size, as shown in Fig. 2. The HRV fluctuations in ultrashort-term windows were large compared to those in short-term windows in terms of all the frequency-domain parameters. This observation suggested that ultrashort-term HRV analysis could provide fundamental insights allowing us to detect reactions in the form of instantaneous changes in both parasympathetic and sympathetic activities. Ln LF/Ln HF variations, which correspond to the balance between sympathetic and parasympathetic activities were greater in ultrashort-term windows than in short-term windows, while they remained relatively consistent during NREM sleep compared to during REM sleep.

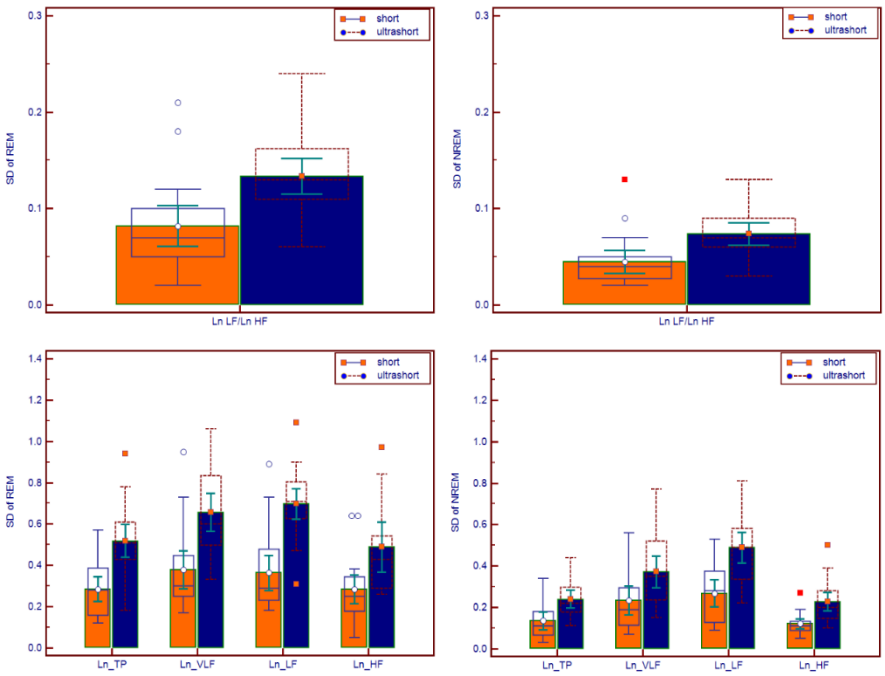

Fig. 2. **Comparison between ultrashort-term (n=240) and short-term (n=150) windows based on REM and NREM in terms of the SD of the mean values for 21 individual patients.**

For ultrashort-term windows, the SD showed that discrimination between REM and NREM could clearly be achieved (p<0.001; 95% CI), while the mean showed a significant difference between REM and NREM, except for that of Ln TP (p=0.1297), as shown in Table 1. Therefore, the SDs could be better potential ANS fluctuation indices for providing clinical judgment on various sleep states than the means. For short-term windows, the means of the individual HRV parameters (Ln LF/Ln HF, Ln VLF, and Ln LF) showed statistically significant differences between REM and NREM (p<0.001), while the SDs showed a statistical significance for Ln TP and Ln HF (Table 2). These comparison results indicated that the SDs of HRV parameters obtained with an ultrashort-term window may be of greater potential to produce various sleep interpretations.

Table 1. **Paired-sample t-test results verifying the difference between REM and NREM under an ultrashort-term window (95% CI).**

Ultrashort-term window (n = 21)	REM		NREM		p-value	
	Mean	SD	Mean	SD	Mean	SD
Ln LF/Ln HF	1.21	0.13	0.88	0.07	<0.0001	<0.0001
Ln TP	7.61	0.52	7.30	0.24	0.1297	<0.0001
Ln VLF	6.74	0.66	5.85	0.37	<0.0001	<0.0001
Ln LF	6.55	0.70	5.70	0.49	0.0007	0.0006
Ln HF	5.52	0.49	6.50	0.23	0.0007	0.0005

Table 2. **Paired-sample t-test results verifying the difference between REM and NREM under a short-term window (95% CI).**

Short-term window (n=21)	REM		NREM		p-value	
	Mean	SD	Mean	SD	Mean	SD
Ln LF/Ln HF	1.24	0.08	0.86	0.04	<0.0001	0.0039
Ln TP	7.13	0.29	6.44	0.14	0.0032	0.0005
Ln VLF	6.61	0.38	5.28	0.23	<0.0001	0.0112
Ln LF	5.73	0.36	4.83	0.27	0.0010	0.1333
Ln HF	4.72	0.28	5.61	0.12	0.0030	0.0003

Fig. 3 shows the scale of the difference between both the REM and NREM spectral HRV parameters and the two windows. The trend in HRV parameters remained unchanged between the two windows while changing from a REM to a NREM sleep stage. The difference in Ln VLF between REM and NREM was anticipated due to smaller bin numbers in an ultrashort-term window than in a short-term window, but there was no significant difference between the ultrashort-term and short-term windows. However, during NREM sleep, a slight difference in the mean of Ln VLF was found between the ultrashort-term and short-term windows. This result suggested that NREM sleep involved a possible long-term regulatory factor that cannot be found in the REM period. Three frequency-domain parameters (not Ln HF) were reduced as the sleep stage changed from REM sleep to NREM sleep. This finding showed the same trend as HRV parameters obtained by a WT-based HRV analysis (Hossen et al., 2013) as well as a FFT-based HRV analysis (Bonnet and Arand, 1997; Kuo et al., 2016).

4.2 Characteristics of Spectral Profiles in Ultrashort-term and Short-term Windows

Ultrashort-term windows may allow the detection of various sleep events, such as transitions between REM and NREM or vice versa, instant ANS changes during sleep stages, physical activity, respiration, and changes in cardiac autonomic activity. To confirm this ultrashort-term performance, spectral profiles for a subject are plotted in Fig. 4. Significantly more fluctuations were observed in spectral profiles from ultrashort-term windows than from short-term windows. However, the increased number of fluctuations in ultrashort-term windows may be unstable because ultrashort-term windows have no sufficient frequency resolution that corresponds to frequency information. To investigate the degree to which spectral HRV parameters in an ultrashort-term window differ relative to those in a short-term window, the correlation coefficients (r) between the two windows were calculated for REM and for NREM (Table 3). No significant differences were found between the two windows for either REM or NREM (all p<0.05 and r>0.9), indicating that the spectral profiles of an ultrashort-term window were as stable as those of a short-term window. Specifically, the degree of ANS activity derived from ultrashort-term windows between sleep stages was

expected to influence sleep efficiency, but no linear relationship was found. Among HRV parameters, the spectral profiles of the Ln LF/Ln HF ratio and Ln HF were significantly different between REM and NREM, while those of the Ln VLF and Ln LF did not differ. The threshold value that could differentiate between REM and NREM in terms of spectral profiles was found to be 1.0 for the Ln LF/Ln HF ratio (both windows) and 6.0 (ultrashort-term window) and 5.0 (short-term window) for Ln HF. The crossing points between the two REM and NREM spectral profiles for the Ln LF/Ln HF ratio obtained by ultrashort-term windows could reflect rapid dynamic changes in ANS activity during sleep stages. No crossing points for Ln HF spectral profiles were found regardless of the window during both REM and NREM sleep stages for individual patients. A strong increase in Ln HF during NREM relative to that during REM was found, meaning that parasympathetic activation dominated over sympathetic activation throughout the sleep period regardless of sleep stage. Taken together, these findings suggest that the Ln LF/Ln HF ratio, its crossing points, and the least fluctuations in Ln HF derived from an ultrashort-term window may be potential predictors of sleep status, such as deep (N3) or light sleep (N1 and N2), or sleep stage (REM or NREM).

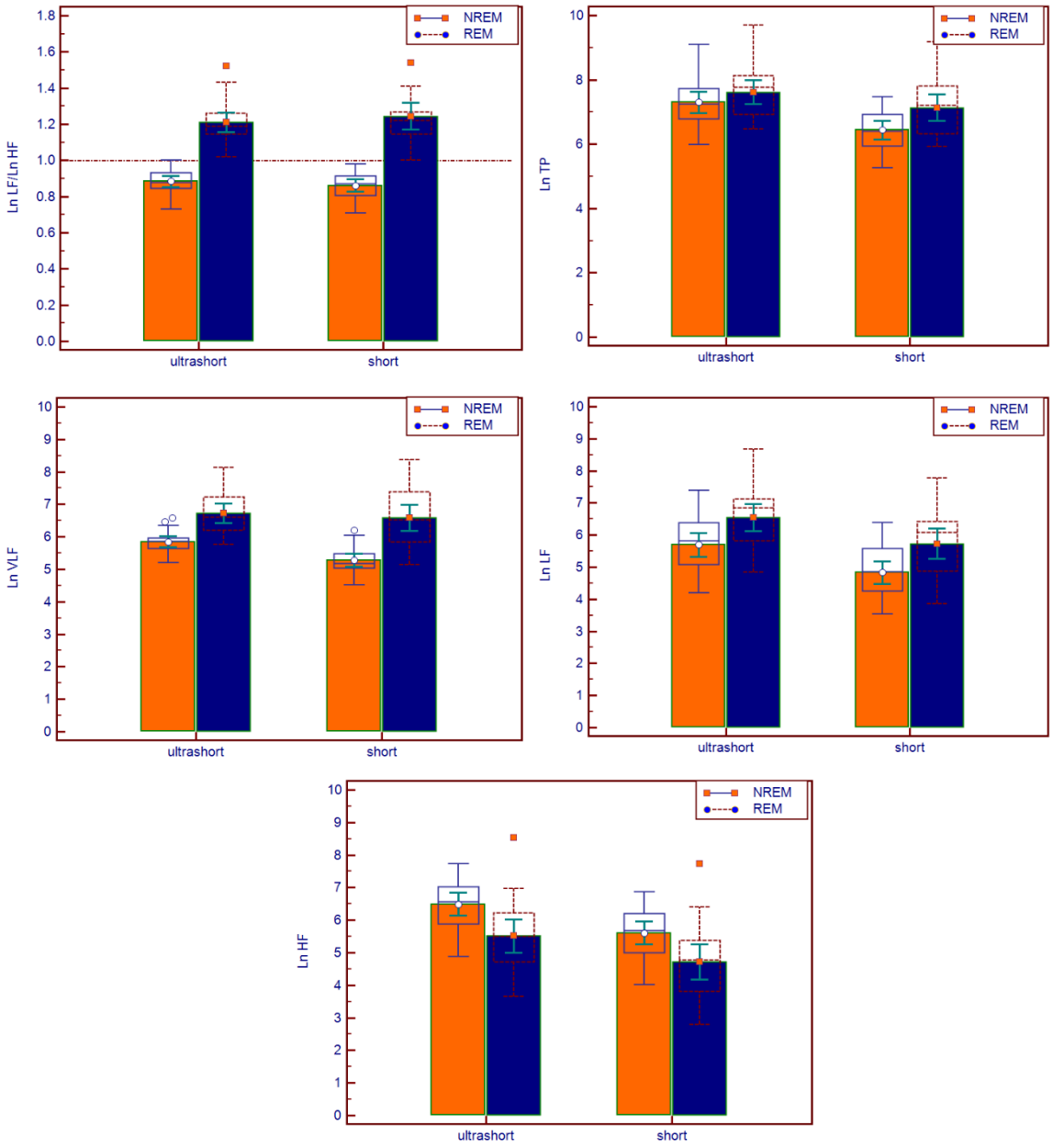

Fig. 3. **Comparison between the mean of the mean REM and NREM values from the ultrashort-term (n=240) and short-term (n=150) windows for 21 individual patients.**

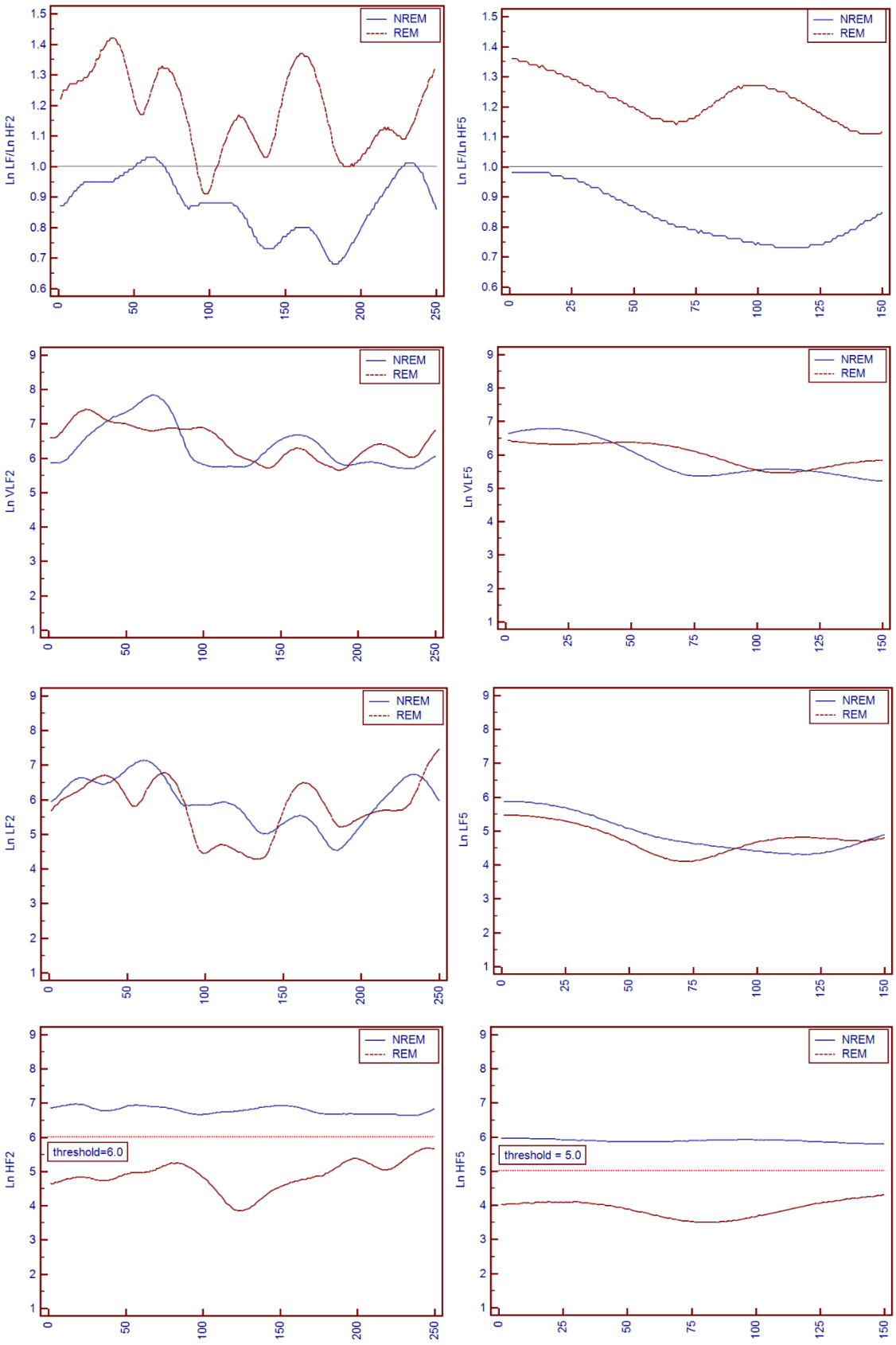

Fig. 4 Spectrogram of the REM and NREM from the ultrashort-term (suffix 2) and short-term windows (suffix 5) for a single subject.

Table 3 Ultrashort-term- and short-term-window Pearson correlation results (95% CI).

Parameter	REM		NREM	
	Correlation coefficient, r	p-value	Correlation coefficient, r	p-value
Ln LF/Ln HF	0.9667	<0.0001	0.9588	<0.0001
Ln TP	0.9522	<0.0001	0.9567	<0.0001
Ln VLF	0.9361	<0.0001	0.9801	<0.0001
Ln LF	0.9745	<0.0001	0.9896	<0.0001
Ln HF	0.9783	<0.0001	0.9957	<0.0001

Discussion

To overcome the shortcomings associated with a short-term window, we introduced an STFT with an ultrashort-term window and a time resolution of 2 s. We found that HRV parameters obtained by an ultrashort-term HRV analysis with a time shift of 2 s were significantly correlated with a short-term HRV analysis in terms of the discrimination performance between REM and NREM ($p<0.0001$, 95% CI). Additionally, an ultrashort-term window could clearly detect rapid dynamic changes in ANS activity from spectral profiles, a function that a short-term window cannot provide. Interestingly, we found that Ln HF spectral profiles could be used to distinguish sleep stages (REM and NREM) with threshold of 6.0 for all patients and to track the rapid activation of parasympathetic tone during sleep if the HRV dataset was normalized. Therefore, an ultrashort-term window with a time shift of 2 s was useful and may replace the traditionally used short-term windows for various sleep interpretations. The SD as a new indicator for distinguishing sleep stages was found to be better in ultrashort-term windows than in short-term windows.

A short-term HRV analysis showed smoother spectral profiles than ultrashort-term HRV analysis in terms of HRV fluctuations. Thus, a short-term window may make it easier to evaluate an entirely autonomic state during sleep, including discrimination performance between REM and NREM. Changes in Ln LF/Ln HF during both REM and NREM were found due to the decrease or increase in Ln HF. Among the frequency-domain HRV parameters, Ln HF fluctuated the least while maintaining a wider gap than Ln LF, and remained more consistent in NREM than in REM. This indicated that monitoring Ln HF in real time during the night period may be helpful in terms of building a health status score for a healthy person as well as devising customized treatments for patients with underlying diseases. Ln VLF components in ultrashort-term windows were considered to reflect slow regulatory mechanisms, such as the rennin-angiotensin and thermoregulatory systems, during NREM sleep, because the mean Ln VLF in the two windows remained relatively unchanged despite large changes in both Ln LF and Ln HF during REM and NREM (Usui and Nishida, 2017). We propose that sleep efficiency could be associated with power spectral estimates, but these relationships still need to be proved.

However, we have the limitations that there exist no sophisticated methods to prove the validity of ultrashort-term HRV features for sleep interpretation, compared to short-term HRV features. Also, a short-term window is subject to inherent limitations, such as failure to detect dynamic ANS activity, in particular the rapid changes in Ln HF and Ln LF/Ln HF. In addition, only 21 subjects from each sleep stage may make it hard to determine if a predetermined line between Ln HF and Ln LF for spectral profiles is a potential index to classify sleep stages with high accuracy. In the future, ultrashort-term HRV features obtained by STFT while changing various time resolution and window sizes should be investigated for exploring the efficacy of sleep-stage classification.

4. Implications

The STFT-based power spectral estimates for HRV sleep analysis were applied by using two different window sizes with a time resolution of 2 s to investigate the characteristics of frequency-domain HRV parameters during both REM and NREM. The SD representing HRV fluctuations showed great differentiation performance between REM and NREM in the ultrashort-term window. The results obtained by both windows supported other results, which demonstrated an increase in Ln HF component and a decrease in the Ln LF component when the sleep stage transitioned from REM to NREM. Our findings show the better characteristics of spectral profiles in ultrashort-term windows than short-term windows for the detection of rapid ANS activities. For instance, the number of crossing points at a threshold of 1.0 for Ln LF/Ln HF may become a therapeutic index during both REM and NREM. Additionally, we showed that as a newly proposed indicator, the SD obtained from STFT HRV analysis in ultrashort-term windows could be applied to discriminate between sleep stages.

In conclusion, sleep HRV analysis using an ultrashort-term window with a time shift of 2 s for the STFT method could be used to identify sleep stages as well as rapid physiological changes in response to instant sleep events. In future studies, we will apply an extremely ultrashort-term window based on the STFT with a time resolution of every heartbeat for sleep HRV analysis. This may take the form of a 1 min or 30 s window size for the evaluation of more detailed ANS activity, including discrimination between REM and NREM, light (N1 and N2), and deep sleep (N3) stages, in-between sleep stages, and transitions from REM to NREM or vice versa.

Acknowledgements

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Declaration of Interest

All authors have indicated no financial conflicts of interest.

Ethics Approval

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Hallym Medical University Chuncheon Sacred Hospital (IRB No. 2020-03-022). Additionally, the requirement for written informed consent was waived because of the retrospective study design.

Informed Consent

The need for written informed consent was waived because this study was designed to be

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