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Comparison between heart rate variability and pulse rate variability during different sleep stages for sleep apnea patients

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Abstract.
BACKGROUND: The usefulness of heart rate variability (HRV) in the clinical research has been verified in numerous studies. However, it is controversy that using pulse rate variability (PRV) as a surrogate of HRV in different clinical applications.
OBJECTIVE: We aimed to investigate whether PRV extracted from finger pulse photoplethysmography (Pleth) signal could substitute HRV from ECG signal during different sleep stages by analyzing the common time-domain, frequency-domain and non-linear indices.
METHODS: Seventy-five sleep apnea patients were enrolled. For each patient, ECG and Pleth signals were simultaneously recorded for the whole night using Alice Sleepware Polysomnographic System and the sleep stage signals were automatically calculated by this System. Time-domain, frequency-domain and non-linear indices of both HRV and PRV were calculated for each sleep stage.
RESULTS: Mann-Whitney U-test showed that for both time-domain and frequency-domain indices, there were no statistical differences between HRV and PRV results during all four sleep stages. For non-linear indices, sample entropy reported statistical differences between HRV and PRV results for N1, N2 and REM sleeps (all $P < 0.01$) whereas fuzzy measure entropy only reported statistical differences for REM sleep ($P < 0.05$). SDNN, LF and LF/HF indices decreased for both HRV and PRV with the sleep deepening while HF and non-linear indices increased. In addition, there were strong and significant correlation between HRV and PRV indices during all four sleep stages (all $P < 0.01$).
CONCLUSIONS: PRV measurement could present the similar results as HRV analysis for sleep apnea patients during different sleep stages.

Keywords: Heart rate variability, pulse rate variability, sleep apnea, sleep stage

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1. Introduction

An apnea has been defined as a cessation of airflow at the nose and mouth lasting at least 10 s. A sleep apnea syndrome is diagnosed if, during seven hours of nocturnal sleep, at least 30 apneic episodes are observed [1]. For measuring the severity of sleep apnea, apnea hypopnea index (AHI) is usually used in clinical practice and is defined as the average number of apnea hypopnea events during the total sleep period [2]. A wide range of studies have suggested that sleep apnea causes changes in the normal variation of heart rate during sleep and affects sleep quality. Sleep stages can be classified as one rapid eye movement (REM) sleep and three non-rapid eye movement (NREM) sleep, i.e., N1, N2 and N3 sleep, according to the guideline of American Academy of Sleep Medicine (AASM) [3]. It has been proven that the activity of autonomic nervous system (ANS) is strongly linked with the sleep stages [4]. During NREM sleep, parasympathetic modulation becomes stronger while during REM sleep, ANS is greatly influenced by the surges in sympathetic activity [5].

Usually, heart rate variability (HRV) is used for evaluating the ANS activities in clinical practice. HRV is performed by measuring the changes of successive R-R intervals from the electrocardiogram (ECG) to observe the regularity of heart rate signal and it could provide the meaningful information for clinical intervention [6,7]. Recently, it is controversy that using pulse rate variability (PRV) as a surrogate of HRV in various physiological and disease states [8–13]. Similar to HRV, PRV is defined as the variation between pulse rate time intervals (P-P intervals). Compared with the complicated ECG cable connections and the ECG electrodes, PRV could be easier acquired by a simple technique of pulse photoplethysmography (Pleth) signal during the sleep [14]. It is reported that sleep apnea leads to more changes in pulse wave amplitude of Pleth than that in heart rate [15].

In this study, we synchronously recorded ECG and finger Pleth signals to perform both HRV and PRV analysis during different sleep stages for sleep apnea patients. We aimed to investigate whether PRV extracted from finger Pleth could substitute HRV from ECG during different sleep stages by analyzing the common time-domain, frequency-domain and non-linear variability indices and thus to better understand how the sleep stages affect the HRV and PRV indices for sleep apnea patients.

2. Methods

2.1. Patients

Seventy-five sleep apnea patients were enrolled in this study. Patients reporting smoking or heavy drinking habits were excluded before participation. For each patient, informed consent was required prior to the participation. The study was ethically approved by the ethical committee of the Shandong Province of Traditional Chinese Medicine Hospital and the patients gave their informed consent.

2.2. Data acquisition and processing

For each patient, multi-channel signals were synchronously recorded for a whole night by the Alice Sleepware Polysomnographic System. The signals included ECG, Pleth, electroencephalogram, left and right electrooculogram, leg movements, body positions, thoracic and abdominal wall expansion, oronasal airflow and arterial oxygen saturation (SpO_2). Figure 1 shows an example of the synchronously recorded multi-channel signals with a length of 5 minutes. Four sleep stages were automatically identified by the Alice Sleepware Polysomnographic System: N1 sleep, N2 sleep, N3 sleep and REM sleep.

Table 1
Basic characteristics for the 70 sleep apnea patients

Variable	Mean ± SD	95% CI
Age (years)	48 ± 10	45–51
Sex (F/M)	30/40	–
Height (cm)	168 ± 8	166–170
Weight (kg)	76 ± 14	73–80
BMI (kg/m^2)	27 ± 4	26–28
AHI	37 ± 26	31–44

Note: BMI, body mass index; AHI, apnea hypopnea index; SD, standard deviation; CI, confidence interval.

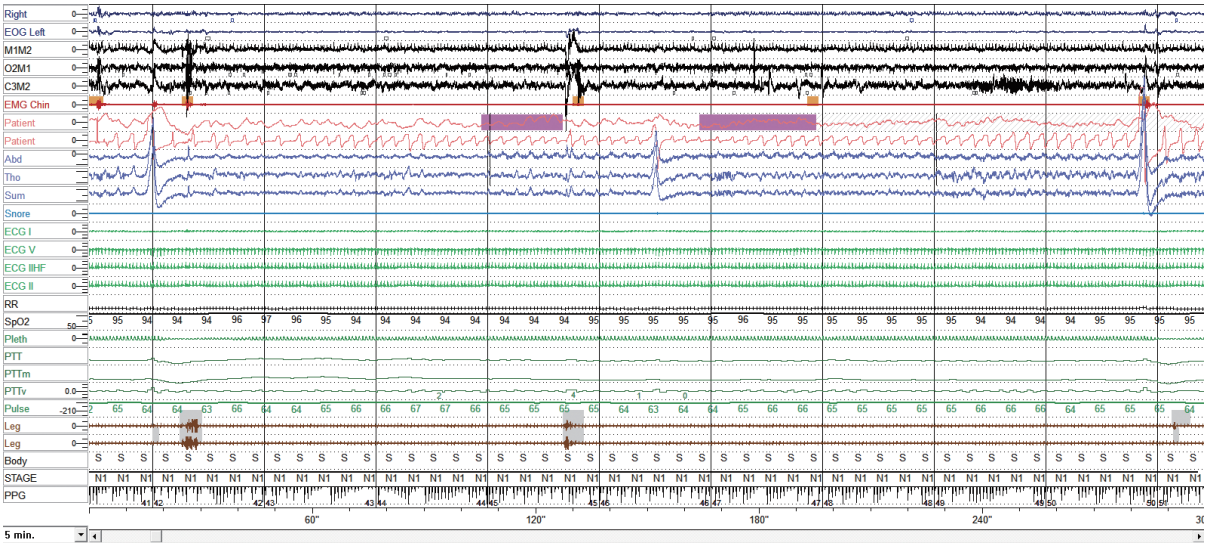

Fig. 1. Example of the synchronously recorded multi-channel signals with a length of 5 minutes. Two sleep apnea events were marked in pink.

The automatic identification of the sleep stages was manually reviewed and corrected by two experienced operators.

Due to the long-term signal recording, three recordings had very noisy multi-channel signals resulting in the impossibility for identifying the sleep stages. In addition, two recordings did not show the obvious sleep apnea symptoms during the whole night. So these five recordings were excluded in the following analysis. Thus 70 sleep apnea patients' recordings were reserved with good signal quality and clear sleep stage classification. Among 70 patients, there were 19 mild sleep apnea patients with AHI between 5 and 14, 9 moderate sleep apnea patients with AHI between 15 and 29, and 42 severe patients with AHI no less than 30. Table 1 shows the basic characteristics for the 70 sleep apnea patients. Table 2 shows their corresponding sleep information.

For each sleep stage, the sleep apnea events were detected according to the guideline of AASM, i.e., sleep events were classified as sleep apneas if the amplitude of the oronasal airflow reduced to be less than 10% of baseline breaths for at least 10 s, or SpO_2 has a decrease of at least 4% from baseline value [1]. Figure 1 also shows two sleep apnea events marked in pink.

ECG and Pleth signals were used for the analysis of HRV and PRV during different sleep stages for sleep apnea patients. Firstly, the R-wave peaks of ECG and the peaks of Pleth were detected and the

Table 2
Statistical results of the sleep information for the 70 sleep apnea patients

Variable	Mean ± SD	Min	Max
Lights out (h:min)	21:53*	20:26	23:04
Lights on (h:min)	6:11*	3:56	7:26
Sleep onset (h:min)	22:21*	21:26	23:33
Total recording time (TRT) (min)	498 ± 50	215	594
Total sleep time (TST) (min)	427 ± 62	277	541
N1 sleep latency (min)	21 ± 21	2	67
N2 sleep latency (min)	20 ± 21	12	106
N3 sleep latency (min)	90 ± 88	7.5	351
REM sleep latency (min)	146 ± 91	3.5	333
Wake after sleep onset (min)	57 ± 44	5.5	175
Sleep efficiency (TST/TRT) (%)	85 ± 10	49	99
N1 sleep (% of TST)	41 ± 19	4.5	86
N2 sleep (% of TST)	38 ± 15	2.7	76
N3 sleep (% of TST)	7 ± 8	0	38
REM sleep (% of TST)	14 ± 7	0.3	39
Number of arousal per hour	22 ± 17	2	76

*Note: only mean value from the 70 patients is provided.

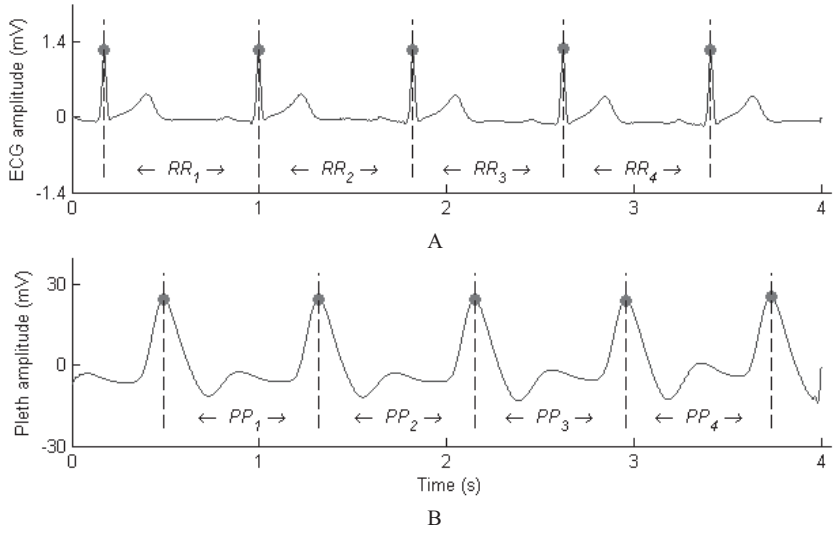

Fig. 2. Demonstration of construction of RR (A) and PP (B) interval time series from the ECG and Pleth signals.

adjacent peaks formed the RR or PP interval time series. Figure 2 shows an example of the detected R-wave peaks of ECG and the peaks of Pleth, as well as the constructed RR and PP interval time series (RR_i and PP_i). Then, the RR and PP time series were segmented by a 5-minute time window. Finally, the 5-minute RR and PP segments with at least one sleep apnea event were extracted and used for the analysis of HRV and PRV. Thus, 126 5-minute RR and PP segments during N1 sleep, 211 segments during N2 sleep, 73 segments during N3 sleep and 148 segments during REM sleep were selected. For each 5-minute segment, the ectopic beats were identified and were excluded for the following HRV and PRV calculation. We manually verified that the percentages of the ectopic beats for each segment were less than 3%.

2.3. Indices calculation

The following indices were calculated for the 5-minute RR and PP segments respectively to obtain the corresponding HRV and PRV indices.

2.3.1. Time-domain indices

The standard deviation of RR or PP time series (SDNN) was used as time-domain index [12,16]. SDNN could indicate the autonomic influence of sympathetic and parasympathetic activities on RR and PP time series [17].

2.3.2. Frequency-domain indices

Frequency-domain analysis for RR and PP time series provides a quantitative evaluation of sympathetic and parasympathetic activation. The low frequency (LF) component (between 0.04–0.15 Hz) reflects both sympathetic and parasympathetic nervous systems and the high frequency (HF) component (between 0.15–0.40 Hz) mainly reflects vagal activity [18,19]. Burg modern spectrum estimation was used to acquire frequency parameters. The spectral powers of LF and HF were normalized using LFn = LF/(LF + HF) and HFn = HF/(LF + HF). The ratio of LF to HF (LF/HF) reflects sympathetic and parasympathetic control balance. LFn, HFn and LF/HF were used as the frequency-domain HRV and PRV indices.

2.3.3. Non-linear indices

Sample entropy (SampEn) proposed by Richman et al. [20] and fuzzy measure entropy (FMEn) proposed by Liu et al. [21–23] were used as the non-linear indices. Both of them could provide the inherent non-linear complexity for the analyzed RR and PP interval time series.

2.4. Statistical analysis

The non-parametric test was used for the results of HRV and PRV indices because of non-Gaussian distribution of the variables as ascertained by the single sample $K - S$ test. The statistical differences between HRV and PRV indices among different sleep stages were firstly compared by the Mann-Whitney U-test. Then correlations between HRV and PRV indices for each sleep stage were tested. Finally we analyzed how HRV and PRV indices change with the change of sleep stages. All statistical analyses were performed using the SPSS software (Ver. 20, IBM, USA). A statistical significance was accepted at $P < 0.05$.

3. Results

3.1. Comparison between HRV and PRV results during different sleep stages

Figure 3 shows the results of HRV and PRV indices during different sleep stages, as well as the corresponding Mann-Whitney U-test results. For both time-domain and frequency-domain indices, there were no statistical differences between HRV and PRV results during all four sleep stages. For non-linear indices, SampEn reported statistical differences between HRV and PRV results for N1, N2 and REM sleeps (all $P < 0.01$) whereas FMEn only reported statistical differences for REM sleep ($P < 0.05$). Table 3 shows the results of mean values and standard deviations (SDs) for HRV and PRV indices during different sleep stages. As shown in Table 3, the SDs of HRV indices were slightly larger than those of PRV indices except the index of SDNN. For SDNN, HRV and PRV had the same SDs during N2, N3 and REM sleep, while HRV has slightly smaller SDs than PRV for N1 sleep.

Table 3
The results of mean values and standard deviations of HRV and PRV indices during different sleep stages

Index	Variability	Mean values				Standard deviations			
		N1	N2	N3	REM	N1	N2	N3	REM
Time-domain									
SDNN (ms)	HRV	74	56	52	64	35	27	31	31
	PRV	79	59	53	66	41	27	31	31
Frequency-domain									
LFn	HRV	0.56	0.52	0.40	0.57	0.21	0.19	0.23	0.18
	PRV	0.51	0.49	0.38	0.53	0.19	0.18	0.22	0.17
HFn	HRV	0.44	0.48	0.60	0.43	0.21	0.19	0.23	0.18
	PRV	0.49	0.51	0.62	0.47	0.19	0.18	0.22	0.17
LF/HF	HRV	1.99	1.66	1.28	1.88	1.96	1.71	2.16	1.68
	PRV	1.60	1.36	1.10	1.48	1.64	1.29	1.72	1.07
Non-linear									
SampEn	HRV	1.41	1.54	1.63	1.40	0.36	0.39	0.41	0.40
	PRV	1.53	1.64	1.73	1.54	0.34	0.34	0.32	0.36
FMEn	HRV	1.17	1.33	1.60	1.12	0.45	0.49	0.50	0.47
	PRV	1.27	1.42	1.71	1.24	0.44	0.47	0.45	0.45

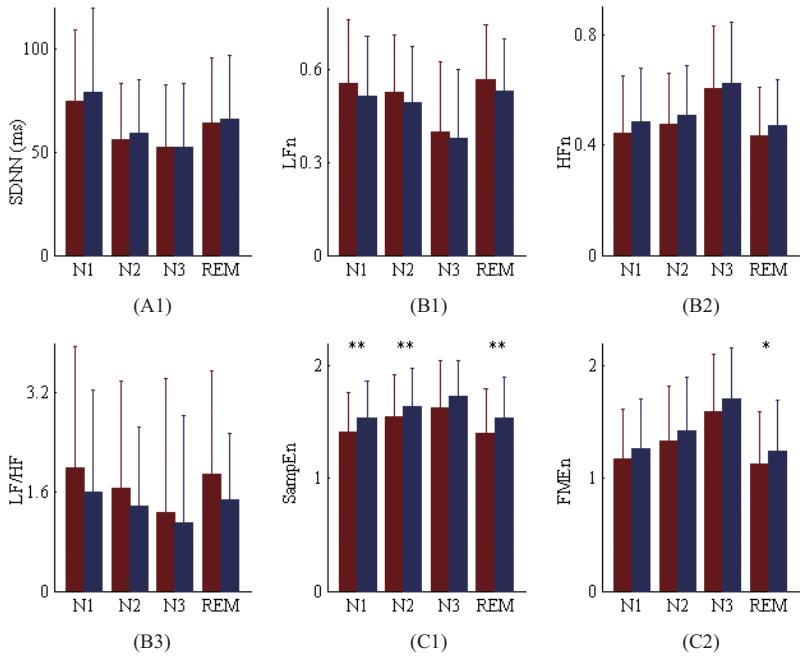

Fig. 3. Results of HRV (left bar in each sleep stage) and PRV (right bar in each sleep stage) indices during different sleep stages: (A1) for time-domain index SDNN, (B1)–(B3) for frequency-domain indices and (C1)–(C2) for non-linear indices. '*' means the significant difference between HRV and PRV results at significance level of $P < 0.05$; '**' means the significant difference between HRV and PRV results at significance level of $P < 0.01$.

3.2. How HRV and PRV results change during the four sleep stages

As shown in Fig. 3 and Table 3, for both HRV and PRV results, indices of SDNN, LFn and LF/HF had similar trends, i.e., they firstly decreased with the sleep stage change from N1 to N2, and further to N3 sleep, and then suddenly increased when the sleep transferred to REM sleep. However, indices of HFn,

SampEn and FMEn reported the opposite trends, i.e., they firstly increased with the sleep stage change from N1 to N2, and further to N3 sleep, and then suddenly decreased when the sleep transferred to REM sleep.

For time-domain index SDNN, as expected, it became smaller and smaller from N1 to N3 sleep. For frequency-domain indices, LFn decreased with sleep deepening and became largest during REM sleep while HFn increased from N1 to N3 sleep and became smallest during REM sleep, resulting in a significant decrease of LF/HF from N1 to N3 sleep. For non-linear indices, both SampEn and FMEn were significantly higher during N3 sleep compared with other three sleep stages and became larger and larger from N1 to N3 sleep.

From Table 3, it is worth to note that, for index of FMEn, it reported the lowest HRV and PRV results for REM sleep. Then with the sleep deepening, i.e., from N1 to N3 sleep, FMEn values showed stable increasing trends for both HRV and PRV results, indicating the ability of FMEn for identifying different sleep states. HFn showed the similar monotonically increasing trends during the four sleep stages (from REM sleep to N1, N2 and N3 sleep) as shown in FMEn for both HRV and PRV. Meanwhile, LFn showed the similar monotonically decreasing trends during the four sleep stages. However, other indices did not report the monotonous trends from REM sleep to N1, N2 and N3 sleep for identifying the four sleep stages. These results verified that FMEn, LFn and HFn performed better than other indices for the identification of sleep stages.

3.3. Correlations between HRV and PRV indices

Figure 4 shows the correlation plots for HRV and PRV indices during all four sleep stages, as well as the Pearson's correlation coefficients (R) and P values. There were strong and significant correlation between HRV and PRV indices during all four sleep stages (all $P < 0.01$). In general, HRV and PRV indices had better correlation during N3 sleep than other sleep stages except the indices of SampEn and FMEn. SampEn had the highest correlation during REM sleep and FMEn had the highest correlation during N1 sleep.

4. Discussion and conclusion

Previous studies have confirmed that there were significant differences between the REM and NREM sleep stages when performing the HRV analysis [24–26]. There was a consensus from the HRV analysis that SDNN, LF and LF/HF indices decreased with the sleep deepening while HF and non-linear indices increased [27–30]. This study provided some preliminary observations on confirming a PRV measurement could present the similar results compared with HRV analysis for sleep apnea patients during different sleep stages. The comparisons between the previous studies based on HRV analysis from ECG signal and the current study based on HRV and PRV analysis from ECG and Pleth signals were summarized in Table 4. It is worth to note that in some previous studies, old R&K standard [31] was used for the classification of sleep stages, which was divided into REM sleep stage and non-REM sleep stages (S1, S2, S3 and S4). In this study, we used the new standard to classify the sleep stages into REM sleep and three non-REM sleep stages (N1, N2, N3) [3]. In addition, some studies also used the light sleep (LS) to denote the S1 and S2 (or N1 and N2) sleep, as well as used the slow wave sleep (SWS) or deep sleep (DS) to denote S3 and S4 (or N3) sleep [27,29].

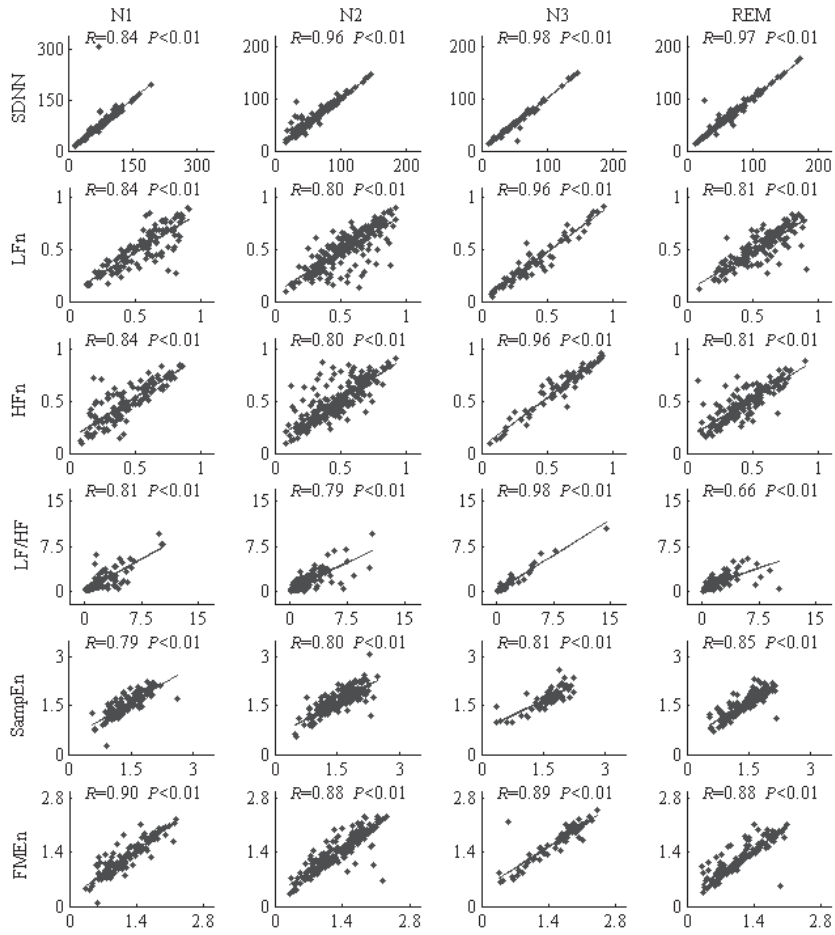

Fig. 4. Correlation plots for HRV and PRV indices during all four sleep stages. *R* denotes the Pearson's correlation coefficients. The vertical axis represents HRV indices and the horizontal axis represents PRV indices.

For comparison, the common sample rates of 128, 200 and 500 Hz were used for the ECG recording from the previous studies. However, our study used a higher sample rate of 1,000 Hz to make to accurately locate the QRS peaks and pulse peaks. Besides, the current study simultaneously analyzed both HRV and PRV indices derived from the ECG and Pleth signals, with more comprehensive sleep stage division. The correlation analysis between HRV and PRV indices was also performed. We observed a decrease of SDNN with the sleep deepening, which was consistent with the studies from Kesek et al. [27] and Mork et al. [30]. We got the largest LF values from the REM sleep and became smaller from N1 to N3 sleep, which was consistent with the Busek et al. [19], Kesek et al. [27], Mork et al. [30], but was inconsistent to the reports from the Toscani et al's study [32]. We obtained the largest HF values from the N3 sleep and it was consistent with the reports from Toscani et al. [32], Kesek et al. [27] and Mork et al. [30], but opposite to Busek et al.'s study [19]. Refer to LF/HF, our results were high consistent with the Toscani et al.'s study [32]. Meanwhile, the non-linear analysis demonstrated that the complexity of RR interval time series during the NREM sleep was significantly higher than that during the REM sleep, and the complexity became to higher levels with the sleep deepening, which was also confirmed by the previous study using [29].

Table 4
Comparisons between the previous studies based on HRV analysis from ECG signal and the current study based on PRV analysis from PPG signal

Index	Study	Subject number	Signal source	Sample rate (Hz)	Signal length (min)	Sleep stage			
						N1	N2	N3	REM
SDNN (ms)	Kesek et al. [27]	387	ECG	200	5	54* (LS)		38* (SWS)	66*
	Mork et al. [30]	22	ECG	–	5	–	51 ± 14	31 ± 13	58 ± 20
	This work	**70**	**ECG**	**1000**	**5**	**74 ± 35**	**56 ± 27**	**52 ± 31**	**64 ± 31**
			Pleth			**79 ± 41**	**59 ± 27**	**53 ± 31**	**66 ± 31**
LF	Bušek et al. [19]	11	ECG	500	5	–	970 ± 571 (S2)	–	671 ± 538 (S4)	1222 ± 798
	Toscani et al. [32]	7	ECG	128	3	106 ± 90 (S1)	79 ± 33 (S2)	70 ± 62 (S3)	85 ± 109 (S4)	93 ± 54
	Kesek et al. [27]	387	ECG	200	5	2738* (LS)		1630* (SWS)		3137*
	Mork et al. [30]	22	ECG	–	5	–	58 ± 16	39 ± 14		64 ± 15
	Virtanen et al. [28]	71	ECG	–	3–5	–	1047 ± 233 (S2)	553 ± 113 (SWS)		582 ± 124
	This work	**70**	**ECG**	**1000**	**5**	**0.56 ± 0.21**	**0.52 ± 0.19**	**0.40 ± 0.23**		**0.57 ± 0.18**
			Pleth			**0.51 ± 0.19**	**0.49 ± 0.18**	**0.38 ± 0.22**		**0.53 ± 0.17**
HF	Bušek et al. [19]	11	ECG	500	5	–	2277 ± 2878 (S2)	–	1777 ± 2789 (S4)	2073 ± 3158
	Toscani et al. [32]	7	ECG	128	3	96 ± 99 (S1)	132 ± 127 (S2)	309 ± 632 (S3)	377 ± 767 (S4)	124 ± 131
	Kesek et al. [27]	387	ECG	200	5	1634* (LS)		1748* (SWS)		1212*
	Mork et al. [30]	22	ECG	–	5		38 ± 11		52 ± 15	30 ± 13
	Virtanen et al. [28]	71	ECG	–	3–5	–	1287 ± 286 (S2)	1161 ± 313 (SWS)		682 ± 269
	This work	**70**	**ECG**	**1000**	**5**	**0.44 ± 0.21**	**0.48 ± 0.19**	**0.60 ± 0.23**		**0.43 ± 0.18**
			Pleth			**0.49 ± 0.19**	**0.51 ± 0.18**	**0.62 ± 0.22**		**0.47 ± 0.17**
LF/HF	Bušek et al. [19]	11	ECG	500	5	–	1.07 ± 0.82 (S2)	–	0.98 ± 0.79 (S4)	2.40 ± 1.96
	Toscani et al. [32]	7	ECG	128	3	1.43 ± 2.61 (S1)	1.09 ± 1.65 (S2)	0.74 ± 1.23 (S3)	0.57 ± 0.90 (S4)	1.27 ± 1.79
	Kesek et al. [27]	387	ECG	200	5	1.70* (LS)		0.98* (SWS)		2.64*
	Mork et al. [30]	22	ECG	–	5	–	2.1 ± 0.9	0.9 ± 0.7		3.6 ± 2.8
	Virtanen et al. [28]	71	ECG	–	3–5	–	1.32 ± 0.18 (S2)	0.81 ± 0.08 (SWS)		3.42 ± 0.40
	This work	**70**	**ECG**	**1000**	**5**	**1.99 ± 1.96**	**1.66 ± 1.71**	**1.28 ± 2.16**		**1.88 ± 1.68**
			Pleth			**1.60 ± 1.64**	**1.36 ± 1.29**	**1.10 ± 1.72**		**1.48 ± 1.07**
SampEn	Xiao et al. [29]	45	ECG	500	5	–	1.27 ± 0.15 (LS)	–	1.38 ± 0.14 (DS)	1.14 ± 0.19
	This work	**70**	**ECG**	**1000**	**5**	**1.41 ± 0.36**	**1.54 ± 0.39**	**1.63 ± 0.41**		**1.40 ± 0.40**
			Pleth			**1.53 ± 0.34**	**1.64 ± 0.34**	**1.73 ± 0.32**		**1.54 ± 0.36**

Note: All values are denoted as mean ± SD. '*' means only mean values are provided. LS denotes S1 and S2 (or N1 and N2) sleep, SWS or DS denotes S3 and S4 (or N3) sleep, LS, SWS and DS appeared in the original references.

The potential limitations in this study should be reported. First, we did not include all 75 sleep apnea patients for HRV and PRV analysis due to the impossibility of sleep stage identification caused by the poor signal quality. In addition, not all four sleep stages were presented in certain sleep stage signals especially for sleep apnea patients [24], which also reduce the available number of the sleep apnea patients. Secondly, the sleep stage signal was automatically obtained from the Alice Sleepware Polysomnographic System. However, for each of the chosen 70 sleep apnea patients, we made the manual confirmation for the accuracy of the sleep stage signal. Thirdly, PP interval was usually acquired by locating the pulse starting points, but in this study, it was obtained from the interval of pulse peaks to reduce the possible risk of the location errors for the pulse starting points during the long-term Pleth recording in the whole night. In addition, sleep apnea patients are easier to wake up from deep sleep and have much sleep stage conversions than the normal subjects. However, in the current study, we only focused on the sleep apnea patients. We identify the comparison between the sleep apnea patients and normal subjects should be our future work.

In clinical practice, this is a need to confirm if the PRV analysis from the easy Pleth measurement can replace the HRV analysis. Although there were significant differences for HRV and PRV non-linear indices, there were no significant differences for time-domain and frequency-domain indices and HRV and PRV indices were highly correlated in different sleep stages. Our results indicated that the suitability of rashly replacing the HRV with PRV results in clinical analysis.

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Conflict of interest

The authors declare no conflict of interest.

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