Differential changes and interactions of autonomic functioning and sleep architecture before and after 50 years of age

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Abstract We hypothesize that the time when age-related changes in autonomic functioning and in sleep structure occur are different and that autonomic functioning modulates sleep architecture differently before and after 50 years of age. Sixty-eight healthy subjects (aged 20 to 79 years old, 49 of them women) were enrolled. Correlation analysis revealed that wake after sleep onset, the absolute and relative value of stage 1 (S1; S1%), and relative value of stage 2 (S2) were positively correlated with age; however, sleep

efficiency, stage 3 (S3), S3%, and rapid-eye-movement latency (REML) were negatively correlated with age. Significant degenerations of sleep during normal aging were occurred after 50 years of age; however, significant declines of autonomic activity were showed before 50 years of age. Before 50 years of age, vagal function during sleep was negatively correlated with arousal index; however, after 50 years of age, it was positively correlated with S1 and S1%. In addition, sympathetic activity during wake stage was positively related to S2%

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only after 50 years of age. Our results imply that the age-related changes in autonomic functioning decline promptly as individuals leave the younger part of their adult life span and that age-related changes in sleep slowly develop as individuals enter the older part of their adult life span. Furthermore, while various aspects of sleep architecture are modulated by both the sympathetic and vagal nervous systems during adult life span, the sleep quality is mainly correlated with the sympathetic division after 50 years of age.

Keywords Age · Heart rate variability · Miniature polysomnography · Sleep quality · 50 years old

Introduction

Evidence either from subjective or objective measurements has revealed that sleep architecture changes with age (Bonnet and Arand 2007; Frank et al. 1995; Ohayon et al. 2004). Various parameters of sleep quality, such as sleep latency (SL), wake after sleep onset (WASO), stage 1 (S1), and arousal number, increase obviously with age, while stage 3 (S3) and sleep efficiency (SE) have been shown to decline with age. However, evidence on some of these parameters is considered controversial in different age range (Van Cauter et al. 2000). The reasons behind these controversies may be related to the different experimental designs used and to the different types of subjects included in the studies; in the latter case, these may be relatively small in number, include relatively few age groups or have differences in age ranges.

In addition, autonomic nervous system (ANS) functioning is also known to change with age. In this context, the application of heart rate variability (HRV) analysis has recently gained popularity as a means of quantifying ANS functions non-invasively (Fu et al. 2006; Kung et al. 2011; Kuo et al. 1999; Liu et al. 2003). Many reports have shown that age-related changes in vagal indices have different patterns during different age ranges (Liao et al. 1995; Umetani et al. 1998). Vagal functioning develops from birth and reaches a peak value at around 20 years old, and then degenerates until death. The presence of age-related sympathetic activity changes is not conclusive as yet (Moodithaya and Avadhany 2012). Furthermore, ANS activities are also known to vary with differences in conscious state, differences in posture, and differences

in mood or mind state; however, few studies have compared the effects of age-related changes during specific conscious states and in specific postures, especially during sleep (Brandenberger et al. 2003; Crasset et al. 2001). Other evidence has revealed that various ANS activities are co-effected by body mass index (BMI) (Lucini et al. 2013; Sjoberg et al. 2011; Skrapari et al. 2007) and by blood pressure (Guzzetti et al. 1988; Lucini et al. 2002).

The most clear cut turning point in the life of a female human being is the menopause, which happen at around 50 years of age. At present, it is also well accepted that men as well as women enter the climacteric at around 50 years of age. Although men do not undergo such a violent change in their endocrine system as women, their changes also include the endocrine system, the cardiovascular system, sleep quality, and autonomic changes (Kuo et al. 1999; Mooradian and Korenman 2006). Thus, 50 years of age would seem to be a critical turning point in physiological and psychological functioning during the human life span (Eaker et al. 1993; Kuo et al. 1999; Liu et al. 2003). Furthermore, alterations in sleep architecture are known to be related to ANS functioning (Bonnet and Arand 1997; Stein and Pu 2012; Yang et al. 2002, 2003). Many indices of sleep quality have been found to be negatively correlated with sympathetic activity and to be positively correlated with vagal activity (Ako et al. 2003; Loreda et al. 1999) especially during non-rapid eye movement (nREM) sleep. Our previous results in animals found the different conscious states showed the different autonomic functions (Kuo et al. 2004; Kuo and Yang 2005). The spontaneously hypertensive rats exhibited higher sympathetic activity during sleep, especially during quiet sleep (equated with nREM sleep in human). There usually reveal the opposite changes of autonomic activity during REM sleep (Kuo et al. 2008, 2014). The decrease in vagal functioning as an individual age has been shown to be related to the increase of arousals (Bonnemeier et al. 2003); however, whether this relationship changes with age remains unknown. Based on the above findings, we hypothesize that these age-related changes in vagal activity during nREM sleep may occur abruptly at a relatively earlier age, but that the age-related changes in sleep structure may occur later and more slowly at a relatively older age. Thus, we propose that the modulation role of autonomic functioning is different in terms of sleep architecture before and after approximately 50 years of age.

Materials and methods

Subjects

Sixty-eight healthy volunteers (aged 20 to 79 years old, 49 of them women) were recruited by online advertising. They needed to have regular sleep/wake patterns (night sleep) and not to be consuming any medication, alcohol, caffeine, and nicotine. We excluded the participants had the extreme values of the body mass index (BMI). None of the participants had a reported medical history that included psychiatric, neurological, or cardiovascular illnesses. Furthermore, the subjects indicated that they had no history of substance abuse or sedative/hypnotic drug use. All subjects gave written informed consent after the experimental procedures had been described to them. The procedures used in this study were approved by the Institutional Review Board of Taipei Veterans General Hospital.

Data recording

Blood pressure signals were collected by a recorder (WatchBPTM Home Blood Pressure Monitor, Microlife, Taiwan). Electrophysiological signals were recorded by a miniature physiological signal recorder (TD1, Taiwan Telemedicine Device Company, Taiwan) that was carried by each subject. The electrophysiological signal recordings were a simplified version of standard sleep monitoring; four electrophysiological signals (i.e., electrooculogram, EOG; electromyogram, EMG; electroencephalogram, EEG; and electrocardiogram, ECG) were recorded. The EEG was recorded from the C3 point with a reference point at A2. The EOG was recorded from a pair of differential electrodes placed 1 cm above the right outer canthus and 1 cm below the left outer canthus. The EOG recording was able to detect both horizontal and vertical movements of the eyeball in one single channel of recording and is broadly used in current sleep research. Since the EOG was high-pass filtered, it was sensitive to changes in the position of the cornea. The EMG was recorded from a pair of differential electrodes in the submental area. The ECG was recorded from the V5 site on the chest. The recorder was fixed to the chest wall with tape (Kuo et al. 2012a; Tsai et al. 2015). The small size (5.2*3.1*1.2 cm) and light weight (11 g) of the recorder result in a minimum of interference and/or stress on the participants. The recording of the electrophysiological signals was a simplified version of standard sleep monitoring (Rechtschaffen

and Kales 1968) with only four electrophysiological signals (EEG, EOG, EMG, and ECG) being recorded.

Experimental procedure

Participants were initially evaluated using the Pittsburgh sleep quality index (PSQI) and one night of ambulatory polysomnography at home. Throughout the trial period, participants were asked to maintain their regular sleep schedules. Before the electrophysiological recording, the participants were asked to record their demographic data (height, weight, and blood pressure) in the afternoon (from 14:00 to 17:00). Then, the miniature physiological signal recorder was set up. The recordings started at 10:00 pm and lasted for 10 h. During the recording period, the subjects were allowed to undertake normal daily activity except for vigorous physical exercise and they slept at their own homes.

Signal processing

For the sleep stage analysis, the data file was converted into the European Data Format (Kemp et al. 1992) and was then imported into a commercial sleep analysis software program (Somnologica 3.1.2, Embla, USA). Computer assisted sleep analysis was carried out according to the criteria defined by Rechtschaffen and Kales (Rechtschaffen and Kales 1968). Sleep variables such as total sleep time (TST), time (S1, S2, and S3) and percent of total sleep time (S1%, S2%, and S3%) taken up by REM sleep, nREM sleep, and their substages, respectively, sleep latency (SL), sleep efficiency (SE, percent of total sleep time), WASO, number of arousal, the arousal index, and the number of stage changes were calculated. When carrying out an analysis of PSQI, PSQI5a is able to represent sleep latency, while PSQI5b is able to represent sleep disturbance.

For the analysis of HRV, we have designed a special computer program in Pascal language (Borland Pascal 7.0, Borland, USA). Preprocessing of the ECG signals was according to the recommended procedures (heart rate variability: standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996) as detailed in our previous investigations (Kuo et al. 1999; Yang et al. 2002).

Data analysis

The amplitudes of the HRV were measured in the frequency domain using power spectral analysis. The RR signal to be analyzed was truncated into successive 64-s (4096 points) time segments (windows or epochs) with 50 % overlap. The detailed analytical procedures used for HRV analysis have also been described in detail previously (Kuo and Chan 1993; Kuo et al. 1997, 2004; Kuo and Yang 2005; Yang et al. 1996). The spectral analysis of the HRV by Fourier transformation has been categorized into total power (TP), high-frequency (HF), low-frequency (LF), and very-low frequency powers. For each time segment, HF (0.15–0.4 Hz), LF (0.04–0.15 Hz) to HF ratio (LF/HF), and normalized LF (LF%) of the RR spectrogram were quantified. RR and TP are known to be contributed to jointly by the sympathetic and parasympathetic nerves (Kuo et al. 1999). HF is considered to represent vagal control of heart rate. The LF% and the LF/HF ratio are considered by some investigators to reflect sympathetic modulations or alternatively to mirror the sympathovagal balance (heart rate variability: standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996; Yang et al. 1996).

Statistical analysis

The consciousness state was classified into wakefulness and sleep. For each time segment, the TP, LF, and HF of HRV (heart rate variability: standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996) were quantified by integration, that is, by calculation of the area of the power spectral density between two specified frequencies. The LF% and LF/HF were also calculated. TP, LF, HF, and LF/HF were logarithmically transformed to correct for their skewed distributions. According to the Shapiro-Wilk normality tests, one-way analysis of variance or Kruskal-Wallis one-way analysis of variance by ranks was performed. The Tukey's test or the Dunn's test was used for post hoc pairwise multiple comparisons where necessary. The relationships between two parameters were analyzed by Pearson or Spearman correlation analysis. We then used linear multiple regression analysis to confirm that age, BMI, systolic blood pressure (SBP), and diastolic

blood pressure (DBP) showed a significant correlation ($p < 0.05$) with the both HRV and various sleep parameters. Statistical significance was assumed for $p < 0.05$. The results are presented as means $\pm$ SEM.

Results

Basic characters among the different age groups

There were no statistically significant differences in BMI between the different age groups (Table 1). Older groups had a significantly higher SBP and DBP than the younger groups.

Comparison of sleep architecture across the different age groups

Sleep architecture showed significant differences when the various different age groups were compared. Older groups showed significant increases in S1%, WASO, and S2% compared to the younger group. However, some parameters of sleep architecture showed significant declines with age, namely SE, S3, S3%, and REML. On the other hand, some parameters revealed biphasic changes with respect to age, such as number of arousal, arousal index, and REM%, which showed significant increases in the middle-aged group (50–59 years of age), but decreased in the 60 years and more group. However, the analysis did not reveal significant differences in TST, S1, PSQI, PSQI-5a, and REM among the age groups (Fig. 1).

Correlation coefficients between sleep architecture and age among the 20–79, 20–49, and 50–79-year-old groups

If we consider all ages in this study (20–79 years), it was found that S1, S1%, WASO, S2%, PSQI, and PSQI-5b were all positively correlated with age. Furthermore, SE, S3, S3%, and REML were all found to have a negative correlation with age (Fig. 2). The correlation coefficients between the various sleep parameters and age when 20–49 and 50–79-year age groups were compared revealed different patterns. There is no significant correlation among the 20–49-year age group. As regards the 50–79-year age group, S1, S1%, and SL were positively correlated with age. The number of arousal, S3, S3%, arousal index, REM, and REM% were found to be negatively correlated with age. Multiple linear regression analysis

Table 1 Demographic characteristics of the different age groups

Demographics	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years
Number (male/female)	<i>n</i> = 18 (10/8)	<i>n</i> = 12 (5/7)	<i>n</i> = 8 (3/5)	<i>n</i> = 9 (2/7)	<i>n</i> = 11 (5/6)	<i>n</i> = 10 (4/6)
Age (year)	21.6 ± 1.5	33.5 ± 2.8 ¹	45.5 ± 1.9 ¹²	53.2 ± 2.5 ¹²³	66.5 ± 2.3 ¹²³⁴	72.3 ± 1.8 ¹²³⁴⁵
BMI (kg/m ²)	21.5 ± 2.0	22.7 ± 2.1	23.0 ± 2.6	21.5 ± 2.2	22.9 ± 2.8	23.1 ± 3.4
SBP (mmHg)	113.0 ± 10.0	110.2 ± 9.4	122.3 ± 15.7 ²	114.3 ± 9.2	125.4 ± 12.6 ¹²	125.4 ± 12.9 ¹²
DBP (mmHg)	69.6 ± 6.5	76.1 ± 6.6	79.2 ± 8.6 ¹	71.8 ± 10.6	79.8 ± 9.0 ¹	81.7 ± 10.2 ¹

Mean ± SEM

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure¹ *p* < 0.05 vs. 20–29-year age group² *p* < 0.05 vs. 30–39-year age group³ *p* < 0.05 vs. 40–49-year age group⁴ *p* < 0.05 vs. 50–59-year age group⁵ *p* < 0.05 vs. 60–69-year age group

Fig. 1 The objective and subjective sleep parameters for the different age groups. **a** *p* < 0.05 vs. 20–29. **b** *p* < 0.05 vs. 30–39. **c** *p* < 0.05 vs. 40–49. **d** *p* < 0.05 vs. 50–59. **e** *p* < 0.05 vs. 60–69. *TST* total sleep time, *SE* sleep efficiency, *SL* sleep latency, *REML* latency to rapid eye movement sleep, *S1*, *S2*, *S3*, *REM* time of

stage 1, stage 2, stage 3, and REM sleep, *S1%*, *S2%*, *S3%*, and *REM%* the relative values of *S1*, *S2*, *S3*, and REM, *WASO* wake after sleep onset, *arousal index* number of arousal per hour, *PSQI* the Pittsburgh sleep quality index, *PSQI5a* sleep latency of PSQI, *PSQI5b* sleep disturbance of PSQI

Fig. 2 Two-dimensional scattergrams showing the relationships between sleep parameters and age. * $p < 0.05$. r_1 : the correlation coefficient of 20–49-year age group. r_2 : the correlation coefficient of 50–79-year age group. r_3 : the correlation coefficient of 20–79-year age group. *TST* total sleep time, *SE* sleep efficiency, *SL* sleep latency, *REML* latency to rapid eye movement sleep, *S1*, *S2*, *S3*,

REM time of stage 1, stage 2, stage 3, and REM sleep, *S1%*, *S2%*, *S3%*, and *REM%* the relative values of *S1*, *S2*, *S3*, and REM, *WASO* wake after sleep onset, *arousal index* number of arousal per hour, *PSQI* the Pittsburgh sleep quality index, *PSQI-5a* sleep latency of PSQI, *PSQI-5b* sleep disturbance of PSQI

(Supplemental Table 1) revealed that age was predictive of *S2%* among all ages. Age was predictive of *TST*, *S2*, and REM among the 20–49-year age group. In terms of the 50–79-year age group, age was predictive of REM% and arousal index. Figure 1 also reveals these patterns and our results demonstrate that most sleep parameters show significant changes among persons who are aged 50–79 years, but there is relatively have less change with age among persons who are aged 20–49 years old.

Comparison of the HRV during different conscious states across the different age groups

During nREM, the 30 to 69-year-old groups were found to have a significantly lower RR than that of 20–29-

year-old group (Fig. 3). A significant age difference in TP, HF, and LF were found covering all stages. Compared with the 20–29-year age group, all other age groups had significantly lower TP, HF, and LF values across all stages. Compared with the 30–39-year age group during the AW stage, TP, HF, and LF values of the 50–59 and 60–69-year age groups were significantly lower. During the AW stage, the TP and HF values of the 70–79-year age group were lower than those of the 30–39-year age group. During the two sleep stages (nREM and REM), the TP, HF, and LF values among the 50–59-year age group were significantly lowered than those of the 30–39 and 40–49-year age groups. The HF of nREM of the 70–79-year age group was also significantly lower than the values for the 30–39 and

Fig. 3 The parameters of heart rate variability across the various different sleep stages for the different age groups. **a** $p < 0.05$ vs. 20–29. **b** $p < 0.05$ vs. 30–39. **c** $p < 0.05$ vs. 40–49. The averaged means of the RR R-R intervals, TP total power, HF

high-frequency, LF low-frequency, LF/HF LF to HF ratio, LF% normalized LF, AW awake, nREM non-rapid eye movement sleep, REM rapid eye movement

40–49-year age groups. The TP and LF values of REM among the 60 to 79-year age group were significantly lower than those of the 30–39-year age group. The 70–79-year age group had significantly higher LF/HF values than those of the 20–29-year age group and this phenomenon only existed during nREM stage. During the REM stage of sleep, the LF/HF value of 40–49-year age group was significantly lower than that of the 30–39-year age group.

Correlation coefficients between the HRV parameters and the age groups 20–79, 20–49, and 50–79 years of age

If we examine all ages (20–79 years), it was found that RR in nREM was negatively correlated with age. In addition, TP, HF, and LF were also negatively correlated with age during all stages. In contrast, LF/HF and LF% were found to be positively correlated with age only during nREM (Fig. 4). The correlation analysis between HRV parameters and age among the 20–49 and 50–79-year age groups revealed different patterns. Significant correlations were found between HRV parameters and age among 20–49-year age group (Fig. 4) and, importantly, these phenomena did not exist among the 50–79-year age group. RR was negatively correlated with age during sleep. Furthermore, there existed significantly negative correlations for the TP-age, HF-age, and LF-age pairs during all stages. Similar to the patterns presented in Fig. 4, multiple linear regression analysis (Supplemental Table 2) demonstrated that most HRV parameters show significant age-related changes among the 20–49-year age group, but there are relatively less age-related changes among the 50–79-year age group.

Correlation coefficients between HRV parameters and sleep architecture changes among the 20–79, 20–49, and 50–79-year-old groups

Table 2 shows the correlations between HRV parameters during different stages and objective sleep parameters for all individuals. There was a significant correlation for RR-S1% during nREM and REM sleep for all individuals. There were significant negative correlations for RR-S3 and RR-arousal index during both AW and REM stages; furthermore, RR in REM stage was negatively correlated with S3%. If we examine the parasympathetic parameters of HRV, HF during nREM sleep was negatively correlated

Fig. 4 Two-dimensional scattergrams showing the relationships between the parameters of heart rate variability and age across the different sleep stages. * $p < 0.05$. r_1 : the correlation coefficient of 20–49-year age group. r_2 : the correlation coefficient of 50–79-year age group. r_3 : the correlation coefficient of 20–79-year age group. The averaged means of the RR R-R intervals, TP total power, HF high-frequency, LF low-frequency, LF/HF LF to HF ratio, LF% normalized LF, AW awake, nREM non-rapid eye movement sleep, REM rapid eye movement

with WASO for all individuals. Furthermore, HF during nREM sleep was positively correlated with SE, S3, and S3%. TP, HF, and LF in both AW and REM stage were negatively correlated with WASO. HF during AW stage was negatively correlated with S2% and positively correlated with S3%. TP, HF, and LF in REM stage positively correlated with SE. TP and LF were positively correlated with S3 during the REM stage. TP and LF in the AW stage were positively related with S3%. TP and LF during REM were positively correlated with REML. Significant correlations between the sympathetic parameters of HRV and various sleep parameters were only identified during the nREM stage of sleep. In addition, LF/HF and LF% were positively correlated with WASO, S1, and S1%. LF/HF and LF% were negatively correlated with SE and S3%.

The correlations for the three stages of sleep among the 20–49 and 50–79-year age groups between the HRV parameters during different stages and sleep architecture revealed a difference in patterns (Table 3). Among the 20–49-year age group, only TP during nREM stage was negatively correlated with arousal index. HF during REM was negatively correlated with arousal index and LF during AW was positively correlated with S3%. If we examine the 50–79-year age group, both S3 and S3% were negatively correlated with RR during sleep. RR during sleep was positively correlated with S1%. If we examine the parasympathetic parameters, TP during nREM sleep was positively correlated with S1 and S1%; LF during nREM sleep was also positively correlated with SL. There was no significant correlation between the sympathetic parameters during nREM and sleep parameters. However, LF/HF and LF% during AW stage were positively correlated with S2% among 50–79-year age group. These results revealed that there are different ANS mechanisms at work in terms of the various sleep parameters when the 20–49 and 50–79-year-old groups are compared.

Table 2 The correlations between the heart rate variability parameters during different stages and objective sleep parameters across all age groups (20–79 years)

	RR (ms)			TP [ln(ms ²)]			HF [ln(ms ²)]			LF [ln(ms ²)]			LF/HF [ln(ratio)]			LF% (nu)		
	AW	nREM	REM	AW	nREM	REM	AW	nREM	REM	AW	nREM	REM	AW	nREM	REM	AW	nREM	REM
WASO (min)	–	–	–	–0.32*	–	–0.27*	–0.27*	–0.32*	–0.24*	–0.31*	–	–0.29*	–	0.35*	–	–	0.35*	–
TST (min)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
SL (min)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
SE (%)	–	–	–	–	–	0.31*	–	0.30*	0.24*	–	–	0.31*	–	–0.34*	–	–	–0.34*	–
REM (min)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
S1 (min)	–	–	–	–	–	–	–	–	–	–	–	–	–	0.31*	–	–	0.31*	–
S2 (min)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
S3 (min)	–0.25*	–	–0.29*	–	–	0.26*	–	0.27*	–	–	–	0.31*	–	–	–	–	–	–
REM (%)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
S1 (%)	–	0.26*	0.28*	–	–	–	–	–	–	–	–	–	–	0.30*	–	–	0.30*	–
S2 (%)	–	–	–	–	–	–	–0.25*	–	–	–	–	–	–	–	–	–	–	–
S3 (%)	–	–	–0.29*	–	–	–	0.25*	0.26*	–	–	–	0.27*	–	–0.24*	–	–	–0.24*	–
REML (min)	–	–	–	–	–	0.24*	–	–	–	–	–	0.24*	–	–	–	–	–	–
Number of arousal (n)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Arousal index (/h)	–0.25*	–	–0.27*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

The averaged means of the *RR*–*R* intervals, *TP* total power, *HF* high-frequency, *LF* low-frequency, *LF*/*HF* *LF* to *HF* ratio, *LF*% normalized *LF*, *AW* awake, *nREM* non-rapid eye movement sleep, *REM* rapid eye movement, *WASO* wake after sleep onset, *TST* total sleep time, *SL* sleep latency, *SE* sleep efficiency, *REM*, *S1*, *S2*, *S3* time of *REM*, stage 1, stage 2 and stage 3 sleep, *REM*%, *S1*%, *S2*%, and *S3*% the relative values of *REM*, *S1*, *S2*, and *S3*, *REML* latency to *REM* sleep, *arousal index* number of arousal per hour

* $p < 0.05$

Table 3 The correlations between the heart rate variability parameters during different stages and objective sleep parameters across younger (20–49 years) and older (50–79 years) age groups

	20–49 years			50–79 years					
	TP [ln(ms ²)] nREM	HF [ln(ms ²)] REM	LF [ln(ms ²)] AW	RR (ms) nREM	RR (ms) REM	TP [ln(ms ²)] nREM	LF [ln(ms ²)] nREM	LF/HF [ln(ratio)] AW	LF% (nu) AW
WASO (min)	–	–	–	–	–	–	–	–	–
TST (min)	–	–	–	–	–	–	–	–	–
SL (min)	–	–	–	–	–	–	0.41*	–	–
SE (%)	–	–	–	–	–	–	–	–	–
REM (min)	–	–	–	–	–	–	–	–	–
S1 (min)	–	–	–	–	–	0.39*	–	–	–
S2 (min)	–	–	–	–	–	–	–	–	–
S3 (min)	–	–	–	–0.54*	–0.51*	–	–	–	–
REM (%)	–	–	–	–	–	–	–	–	–
S1 (%)	–	–	–	0.39*	0.38*	0.37*	–	–	–
S2 (%)	–	–	–	–	–	–	–	0.37*	0.37*
S3 (%)	–	–	0.35*	–0.50*	–0.48*	–	–	–	–
REML (min)	–	–	–	–	–	–	–	–	–
Number of arousal (<i>n</i>)	–	–	–	–	–	–	–	–	–
Arousal index (/h)	–0.33*	–0.41*	–	–	–	–	–	–	–

The averaged means of the *RR* R-R intervals, *TP* total power, *HF* high-frequency, *LF* low-frequency, *LF/HF* LF to HF ratio, *LF%* normalized LF, *AW* awake, *nREM* non-rapid eye movement sleep, *REM* rapid eye movement, *WASO* wake after sleep onset, *TST* total sleep time, *SL* sleep latency, *SE* sleep efficiency, *REM*, *S1*, *S2*, *S3* time of REM, stage 1, stage 2, and stage 3 sleep, *REM%*, *S1%*, *S2%*, and *S3%* the relative values of REM, S1, S2, and S3, *REML* latency to REM sleep, *arousal index* number of arousal per hour

* $p < 0.05$

Discussion

By simultaneously recording of EEG, EOG, EMG, and ECG signals, the present study explored the sleep quality and autonomic functioning among 20–79-year-old individuals, as well as their interactions. After sleep staging, the changes in ANS activities across the different conscious states varied with age and this allowed the various relationships between ANS and sleep architecture across the different age ranges to be revealed. The novel finding of this study is that ANS has different effects on sleep architecture before and after 50 years of age and that the changes in ANS and sleep during the aging process are quite different. The age-related changes in autonomic functioning promptly decline as individuals pass from their 40s to their 50s; however, the age-related changes in sleep architecture only change slowly among the older adults. Therefore, 50 years of age may be the critical turning point in these two systems and the autonomic functions involved in sleep

architecture would seem to undergo a dramatic shift before and after 50 years of age.

By means of sleep staging, we were able to collect more stable values for the various autonomic functions of interest. Compared to sleep architecture, the degeneration in autonomic functioning with age occurred earlier. As 30 years of age, vagal functioning had deteriorated significantly; however, in contrast, sympathetic functions did not show any apparent changes. Later, significant deterioration in sympathetic activity did occur, but only after 70 years of age and only during the nREM stage of sleep. The correlation analyses showed that vagal activity was negatively correlated with age only among 20–49 years of age (Fig. 4), but the phenomena disappeared after 50 years of age. After considering the effects of other factors, such as BMI and blood pressure, we found age did not affect greatly sympathetic activity, even among younger or older age groups. These findings revealed that the degeneration of autonomic functioning occurred before 50 years of age and

degenerated continually and slowly after 50 years of age.

Previous studies have revealed that SE and SWS decrease, while WASO increases with age (Frank et al. 1995; Ohayon et al. 2004; Rao et al. 1999). Other reports have revealed that S1%, S2%, WASO, and SL increase while S3% decreases with age (Ohayon et al. 2004). One report further postulated that the reductions in SWS are partly responsible for reduced growth hormone secretion during midlife and later life (Van Cauter et al. 2000). According to the above findings, it would seem that sleep architecture changes with age and each sleep parameter varies with age in quite different manners. Our findings are similar to these previous findings regarding age-related changes in sleep architecture. Furthermore, we used two-dimensional scattergrams to show the relationships between the various sleep parameters and age and we found that most of sleep parameters had an age of 50 years old as the critical turning point. A meta-analysis study showed TST and REM% decrease with age, while REML does not change with age (Ohayon et al. 2004). However, we only found a decrease in REM% after 50 years old and REML was negatively correlated with age for all age groups. Only a few studies have separated life span into younger and older parts specifically (Van Cauter et al. 2000). One study revealed that WASO, S1, S3, and SE declined before 50 years (Bonnet and Arand 2007). Our results showed that only S2 and PSQI-5b degenerated significantly. On the other hand, our findings were similar to one study (Van Cauter et al. 2000) that most age-related declines in sleep (WASO, number of arousal, arousal index, and REM%) occur apparently only later in life. The significant correlations between age and sleep parameters only exist among 50–79 years of age (Fig. 2). Therefore, we suggest the turning point with respect to sleep architecture is almost certainly located around 50 years old. In addition, we excluded some potential confounding factors (BMI, SBP, and DBP) that might affect sleep architecture. TST, S2, and REM were found to have positive correlations with age before 50 years old; however, REM% and arousal index only showed a significant correlation with age after 50 years of age. Therefore, during the younger life span, age affects sleep patterns only after excluding the confounding factors. After 50 years of age, age is relatively a main factor for sleep patterns. Our results imply that sleep architecture exhibits greater apparent declines among older individuals, namely those aged 50 years or more.

Sleep patterns and ANS functioning show different change patterns before and after 50 years of age. HRV parameters grow to maturity before 50 years old and degenerated gradually after 50 years of age. The changes in ANS functioning are about 40 years ahead of most of sleep architecture changes in this study. These phenomena imply that ANS functions may be involved in these growth-related and age-related sleep changes. We found that age is predictive of S2% and it is also predictive of various HRV parameters (TP, HF, and LF in all stages) across the adult life span. Correlation coefficient analyses then showed that some sleep parameters are significantly correlated with vagal activity among individuals who are younger (20–49 years old). However, among older individuals (50–79 years old), sleep (S2%) is showed significant correlation with sympathetic activity. These phenomena were also present in the age-related changes of ANS functioning. Therefore, the aging-related effects on sleep would seem to be mainly related to a decrease in vagal activity and the elevation in sympathetic activity.

The prevalence of cardiovascular diseases is elevated after 50 years of age and this is very obvious after 60 years of age (Mozaffarian et al. 2015; Tuzcu et al. 2001; Van Cauter et al. 2000). Sex hormone related changes in ANS functioning (Liu et al. 2003) and sleep architecture changes (Sowers et al. 2008) are significant if individuals before and after menopause are compared; furthermore, there would seem to exist interactions between sleep-related problems and the autonomic imbalance in menopausal women (Kung et al. 2011). Specifically, the prevalence of obstructive sleep apnea (OSA) and the incidence of cardiovascular events increase after menopause (Young et al. 2002). In this study, we found both ANS and sleep patterns change with age and that these changes are different before and after 50 years of age. The abovementioned phenomena support the hypothesis that the 50 years of age is a critical turning point in the human life span.

The decrease in sympathetic activity is associated with synchronized sleep and it has been shown that there is an elevation in sympathetic activity during REM sleep (Kuo et al. 2008, 2012a; Scholz et al. 1997). However, this increase in sympathetic activity has been shown to be related to arousals during sleep (Chen et al. 2013; Kiyani et al. 2010). Thus, disturbed sleep may be affected by cardiac sympathetic nervous system regulation (Chen et al. 2013; Chung et al. 2009; Kuo et al. 2012b; Nielsen et al. 2010). On the other hand, there

may exist different mechanisms in young and old subjects in terms of ANS modulation during sleep (Brandenberger et al. 2003). Up to the present, no study has explored whether different ages result in different mechanisms in terms of sleep-related ANS modulation (Stein and Pu 2012). In this study, we recorded sleep and ANS activity simultaneously among individuals aged from 20 to 79 years and found the decrease in deep sleep was associated with an elevation in sympathetic activity. After separating our study population into younger and older groups, there exist different phenomena in terms of the relationship between sleep patterns and HRV before and after 50 years of age. Therefore, we believe that the ANS plays different roles in sleep patterns during growing up and as individuals age.

It is well-known that the ANS matures with age before 20 years old and then declines with age progressively (Kuo et al. 1999; Liao et al. 1995; Moodithaya and Avadhany 2012; Umetani et al. 1998). Similar to results to these for sleep architecture were only demonstrated using a relative small number of subjects (Finley and Nugent 1995; Melo et al. 2005; Yeragani et al. 1997), were only included few age groups for comparison (Melo et al. 2005; Moodithaya and Avadhany 2012; Yeragani et al. 1997), were only recorded for 5 min during the day time without discriminating the specific time of the day or, although 24 h of signals were recorded, these were not discriminated in terms of the conscious status (Bonnemeier et al. 2003). Only a few studies have explored the turning point in autonomic functioning in relation to the aging process (Kuo et al. 1999; Umetani et al. 1998). In addition, the different recording methods used may have caused the controversial results. In our opinion, several confounding factors may exist. Firstly, different conscious states have different ANS activities which are easily disturbed by many factors. Secondly, diurnal change may also affect the autonomic functioning. Finally, most of the studies did not control for many confounding factors such as BMI and BP. Vagal functioning declined before 50 years old and we found that various vagal-related parameters (TP, HF, and LF in nREM) show significant decreases starting at 20 years old. These changes were found to slow sharply at 50 years of age and this agrees with various previous findings (Kuo et al. 1999; Liao et al. 1995; Moodithaya and Avadhany 2012; Umetani et al. 1998). On the other hand, sympathetic activity did not show significant changes with age. The age effects in terms of sympathetic activity alterations are mostly related to other parameters such as BMI and blood pressure. In the present study, we

have controlled for more confounding factors and been able to exclude many factors, therefore, our findings are more reliable. Nevertheless, gender effects may still play a significant role in the changes which needs to be investigated in a future study.

Although we have identified and controlled for many factors, there are still some limitation to the present study. Firstly, although we have controlled for age and BMI in each age group, the gender ratio in each group is less well controlled. Secondly, the volunteers in this study come from a variety of different life backgrounds. The younger subjects were university or graduate students; while the older subjects were white-collar employed persons, housewives, and retirees. The life stresses, environment, and educational background of these subjects are quite different. Thirdly, we used a portable PSG to record the physiological signals at home. The environments of the subjects' home may have differences in humidity and temperature, which also may have affected the results. Fourthly, we excluded all types of disease by questionnaire and/or interview; nevertheless, some of our participants may have undiagnosed sleep disorders. Finally, age-related organ dysfunction and damage may also change cardiovascular regulation (Mitchell 2008) and we cannot exclude abnormalities associated with organ dysfunction as a factor that may have affected the HRV results.

Changes in ANS activity and sleep patterns were found to vary with age and interacted with each other; however, these changes showed different patterns. While cardiovascular functioning seems to predominate with respect to affecting age-related sleep degeneration, in contrast, sympathetic activity remains constant throughout the adult life span. Despite our findings being relatively small in terms of change, the fact that they are significant has important long-term cardiovascular health implications. Our findings imply that any improvement in ANS functioning has benefits not only in itself but also will affect sleep quality. The age of 50 years could be an important turning point in terms of treatment. Future studies should investigate whether treatment affecting ANS functioning is able to improve age-related sleep problems.

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Compliance with ethical standards The procedures used in this study were approved by the Institutional Review Board of Taipei Veterans General Hospital.

Conflict of interest The authors declare that they have no competing interests.

Informed consent All subjects gave written informed consent after the experimental procedures had been described to them.

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