ORIGINAL ARTICLE

The Application of Yin-Yang Concept on Heart Rate Variability Patterns in Menopausal Women with Insomnia*

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ABSTRACT **Objective**: To develop heart rate variability (HRV) patterns for peri- and postmenopausal insomnia (PI) by the yin/yang concept of Chinese medicine (CM). **Methods**: Seventy-four peri- and postmenopausal women (average age 56.6 ± 1.0 years) with insomnia were enrolled in the study. HRV and the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI) were recorded. The Autonomic Nervous System (ANS), Sympathetic and Parasympathetic Indices were derivative from the low frequency (LF), high frequency (HF) and ratio of LF to HF (LF/HF) components of the HRV. A deficiency or the excess pattern for PI was used for ANS index values > 0 or < 0, respectively. The deficiency pattern of PI was further divided into deficiency-yang (ANS index < 0, Sympathetic-Parasympathetic index > 0) and the deficiency-yin patterns (ANS index < 0, Sympathetic-Parasympathetic index < 0). The classification of the excess-yang and the excess-yin patterns of PI was carried out in the same way. The CPSQI and HRV parameters were compared to each of these patterns. **Results**: The deficiency pattern (60.8 %) occurred more frequently than the excess pattern (39.2%) among PI participants. There were significantly longer bouts of insomnia, prolonged sleep latency, lower LF, HF, and LF/HF of HRV among individuals with the deficiency pattern than among those with the excess pattern among PI participants (P<0.05). The deficiency-yang pattern of PI participants had significantly prolonged sleep latency and decreased sleep efficiency, a higher LF/HF but a lower HF while compared to those with the deficiency-yin pattern (P<0.05). **Conclusions**: The results show a possible method of integration of biomedicine and CM by using physiological signals (HRV) combined with the concepts of CM (deficiency/excess and yin/yang) in order to develop diagnostic patterns of PI. This method may be applicable to the trials involving the use of acupuncture or Chinese herbs to treat PI.

KEYWORDS Chinese medicine, patterns differentiation, peri- and postmenopausal insomnia, heart rate variability

Insomnia, defined as problems associated with sleep onset, sleep maintenance, and easy awakening in the presence of adequate circumstance for sleep, is a common problem in women with menopause transition.(1-3) Epidemiological studies have showed that 42%–75% of peri- and postmenopausal women have insomnia.(4-6) Because peri- and postmenopausal insomnia (PI) are linked with significant rates of functional impairment, mental health concerns, and poor quality of life,(7-9) the optimal evaluation and management of insomnia in this population of women is important.

There are many factors that contribute to PI, including aging, symptoms of hot flashes, anxiety and depressive disorders, primary sleep disorders (i.e. obstructive sleep apnea, periodic limb movement disorder), musculoskeletal pain, comorbid medical conditions and medications, as well as with psychosocial and behavioral factors.(10-12) Therefore, PI is a heterogeneous disorder, which the etiologies are hard to be distinguished clearly clinically. However, PI might be regarded as a disturbance of homeostasis, including physiological and psychological systems of the body, within women during menopause transition.(13,14)

The activity of the autonomic nervous system

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(ANS) play a vital role in orchestrating physiological homeostasis within the human body.[15] Heart rate variability (HRV), a non-invasive method, has been used to measure ANS functioning in humans.[16] The resting HRV is seen as an index of the functional integrity of the central autonomic network, the neural system responsible for many aspects of homeostatic regulation (including affective, physiological, cognitive, and behavior elements).[17] Several studies showed that altered HRV may be associated with symptoms (such as hot flashes) in peri- and postmenopausal women.[18,19] Furthermore, one study demonstrated that the sympathetic component of HRV had a significant increase in symptomatic degree of sleep disturbances in peri- and postmenopausal women.[20]

The low frequency (LF, 0.04–0.15 Hz) component of HRV is jointly contributed to by both the sympathetic and parasympathetic nerves. The high frequency (HF, 0.15–0.4 Hz) component of HRV represents parasympathetic drive to the heart; while the ratio of LF to HF (LF/HF) is regarded as measuring sympathetic modulation.[16] The parasympathetic and sympathetic components of HRV can be characterized as polar opposites, which is similar to the philosophy of yin and yang in Chinese medicine (CM).[21] Therefore, we hypothesized that HRV patterns of PI, which was developed by the yin/yang concept of CM, may be helpful to understand different symptomatic presentations and possible mechanisms in PI.

The purpose of this study is to develop a possible model of integration of biomedicine (mainstream medicine) and CM by using physiological signals (HRV) combined with the concepts of CM (yin/yang) for diagnostic patterns of PI.

METHODS

Diagnostic Criteria

The menopausal status of the participants was defined on the basis of their menstrual characteristics: 'perimenopausal' women had a menstrual period in the past 12 months but had experienced irregularity in the past 3 months; 'postmenopause' was considered to be those women whose last menstrual period had occurred more than 12 months previously.[22,23]

Inclusion and Exclusion Criteria

Perimenopausal women with chief complaint of insomnia were included. The insomnia consisted of difficulties in initiating or maintaining sleep. On the basis of a clinical interview and a medical examination, the inclusion criteria for PI were as follows: (a) a complaint of insomnia; (b) the complaint that the insomnia was temporally associated with menopause; (c) that the disorder had been present for at least 3 months; and (d) that the patient had vasomotor symptoms.[24]

Subjects were excluded if they (a) had definite symptoms associated with sleep-breathing disorders; (b) had various parasomnias; (c) reported an irregular sleep-wake schedule; (d) had a history of psychiatric illness or (e) were taking hormone replacement therapy. In addition, subjects with diabetic neuropathy, cardiac arrhythmia, severe liver disease, severe renal disease, or were taking drugs that would affect their HRV were excluded.

Participants

The subjects were recruited from patients who visited the Center for Traditional Medicine, Taipei Veterans General Hospital, Taiwan, China from July 2010 to June 2011. All study procedures were approved by Institutional Review Board of the Taipei Veterans General Hospital in Taiwan, China (registered No. 201006001IC), and all participants gave written informed consent for the study.

Processing of the Electrocardiogram Signal

The procedure of HRV analysis was carried out according to the standard method and has been reported previously.[25,26] In brief, electrocardiogram (ECG) was taken for 5 min in the daytime while each subject lay quietly and breathed normally. ECG signal acquisition, storage and processing were performed using a HRV analyzer (SS1C, Enjoy Research Inc., Taiwan, China). The signals were recorded using an 8-bit analog-to-digital converter with a sampling rate of 512 Hz. The digitized ECG signals were analyzed online and were simultaneously stored on a hard disk for offline verification. The computer algorithm then identified each QRS complex and rejected each ventricular premature complex or noise according to its likelihood using a standard QRS template. Normal and stationary R-R interval values (RR) were re-sampled and interpolated at a rate of 7.11 Hz to produce continuity in the time domain. This interpolation produced 2,048 data points in 288 s for the following Fourier transformation. PI participants who were taking hypnotics were asked not to use them for 36 h before HRV measurement.

Power Spectral Analysis of HRV

Power spectral analysis was performed using fast Fourier transformation (FFT). The baseline shift was deleted and a Hamming window was used to attenuate the leakage effect.[27] For each time segment (288 s, 2048 data points), our algorithm estimated the power spectrum density based on the FFT. The resulting power spectrum was corrected for attenuation resulting from the sampling and the Hamming window. The power spectrum was subsequently quantified into standard frequency-domain measurements as defined previously,[16,25,26] including total power (TP), very low-frequency power (VLF, 0.003–0.04 Hz), LF (0.04–0.15 Hz), HF (0.15–0.40 Hz), and LF/HF. LF, HF, and LF/HF were logarithmically transformed to correct for their skewed distributions.[25]

Development of ANS, Sympathetic and Parasympathetic Indices from HRV Parameters

We defined the parameters of HRV (including LF, HF and LF/HF) based on the general population in Taiwan using 1070 normal volunteers (598 women and 472 men) aged between 40 and 79 years in order to obtain comparable values.[25] Based on the fact that the LF component of HRV is jointly contributed by both the sympathetic and parasympathetic nerves, the ANS index was defined as: ANS Index = ($LF_{measure}$—mean of LF_{normal})/standard deviation of LF_{normal}, where $LF_{measure}$ is the LF component of the HRV in PI women in this study and LF_{normal} is the LF component of HRV obtained from the general population. If the ANS Index is positive, it indicates that the individual has higher autonomic nervous activity than the mean value of the population and this was defined as an excess pattern. In contrast, the individual was defined as having a deficiency pattern if the ANS Index was negative (Figure 1).

The formulae for the Sympathetic and Parasympathetic Index were as follows, respectively: Sympathetic Index = ($LF/HF_{measure}$—mean of LF/HF_{normal})/standard deviation of LF/HF_{normal} and Parasympathetic Index = ($HF_{measure}$—mean of HF_{normal})/standard deviation of HF_{normal}, where $LF/HF_{measure}$ and $HF_{measure}$ are the LF/HF and HF components of the HRV obtained from PI women in this study, while $LF/HF_{measure}$ and HF_{normal} are the LF/HF and HF components of the HRV obtained from the general population. If the Sympathetic Index minus the Parasympathetic Index is positive, this represents an individual has higher sympathetic nervous activity which is called a yang state. In contrast, if the Sympathetic Index minus the Parasympathetic Index is negative, this represents an individual has higher parasympathetic nervous activity which is called a yin state (Figure 1).

Patterns Differentiation among PI Women

We categorized that PI into a deficiency or excess pattern according to whether the ANS Index was negative or positive, respectively. After this, the deficiency pattern of the PI group was further classified into the deficiency with yang predominance (deficiency-yang) and deficiency with yin predominance (deficiency-yin) patterns according to whether the Sympathetic Index minus Parasympathetic Index is positive or negative respectively. As the same, the excess pattern of the PI group was classified into the excess with yang predominance (excess-yang) and excess with yin predominance (excess-yin) patterns in the same way (Figure 1). Finally, the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI) and HRV parameters were compared between the deficiency/excess, deficiency-yang/deficiency-yin and excess-yang/excess-yin patterns among the PI individuals.

Sleep Quality Measurement

The CPSQI has been previously validated and was used as a subjective sleep quality questionnaire in this study. A CPSQI score of more than 5 is regarded as insomnia.[28] The CPSQI contains 19 self-rated questions. The 19 items were combined to form 7 component scores, each of which has a range of 0 to 3 points. The 7 components include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication and daytime dysfunction. In all cases, a score of "0" indicates no difficulty, while a score of "3" indicates severe difficulty. The 7 component scores are then added to yield one "global" score, with a range of 0–21 points, where "0" indicating no difficulty and "21" indicating severe difficulties in all areas.[29]

Statistical Analysis

Values were expressed as means ± standard error mean ($\bar{x} \pm SE$). The Student's *t*-test was used for the comparisons of age, body mass index, duration of insomnia, CPSQI and HRV parameters across the different groups. Statistical significance was assumed for *P*<0.05.

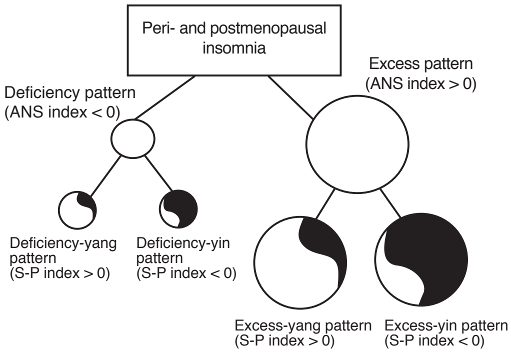

Figure 1. A Flow Chart Presented with Pattern Differentiation of PI

Notes: PI was separated into a deficiency or excess pattern based on whether the ANS Index was negative or positive, respectively. Next, the deficiency pattern of PI was further classified into deficiency-yang and deficiency-yin patterns according to whether the value of the S-P index is positive or negative, respectively. The excess pattern of PI was classified into the excess with yang predominance (excess-yang) and excess with yin predominance (excess-yin) patterns using the same approach.

RESULTS

Seventy-four PI women (average 56.6 ± 1.0 years) were included in this study. There were 45 subjects (60.8%) belonging to the deficiency pattern of PI and 29 subjects (39.2%) belonging to excess pattern of PI. There was a significantly longer duration of insomnia and more prolonged sleep latency among those with the deficiency pattern than among those with the excess pattern (*P*<0.05). As for the HRV parameters, the deficiency pattern of PI showed significantly lower values for LF, HF, TP, and LF/HF of the HRV than those with the excess pattern of PI (*P*<0.01; Table 1).

When analyzed with respect to the deficiency-yang and the deficiency-yin patterns of PI, the deficiency-yang pattern had significantly prolonged sleep latency and decreased sleep efficiency compared to the deficiency-yin pattern (*P*<0.05). The deficiency-yang pattern had significantly higher LF/HF but lower HF than those with the deficiency-yin pattern (*P*<0.05; Table 2).

When analyzed with respect to the excess-yang and the excess-yin patterns of PI, the excess-yang pattern had significantly higher LF/HF but lower HF than the excess-yin pattern (*P*<0.05). No other significant differences in terms of age, duration of insomnia or CPSQI parameters were found when the excess-yang and the excess-yin patterns of PI were compared (Table 3).

Table 1. Comparison of Basline Characters between Deficiency and Excess Patterns, in PI Women ($\bar{x} \pm$ SE)

Item	Deficiency (45 cases)	Excess (29 cases)	*P* value
ANS Index	–0.9 ± 0.1**	0.7 ± 0.1	<0.001
Age (Year)	57.2 ± 1.0	55.5 ± 1.1	0.151
BMI (kg/m^2)	22.2 ± 1.8	23.6 ± 2.2	0.635
Insomnia duration (Year)	7.1 ± 1.0*	4.7 ± 0.8	0.017
Subjective sleep parameters			
CPSQI	14.0 ± 0.4	12.8 ± 0.6	0.397
Sleep latency (min)	80.5 ± 11.3*	50.6 ± 6.4	0.027
Total sleep time (h)	5.0 ± 0.2	4.6 ± 0.3	0.254
Sleep efficiency (%)	71.6 ± 0.2	74.8 ± 0.4	0.539
HRV parameters			
RR (ms)	851.3 ± 17.3	886.2 ± 22.9	0.233
LF [Hz, ln(ms^2)]	4.5 ± 0.2**	5.7 ± 0.1	<0.001
HF [Hz, ln(ms^2)]	4.4 ± 0.1**	5.1 ± 0.2	0.001
TP [Hz, ln(ms^2)]	6.2 ± 0.1**	7.2 ± 0.1	<0.001
LF/HF [ln(ratio)]	0.0 ± 0.1**	0.8 ± 0.2	0.001

Notes: *P<0.05, **P<0.01 vs. excess pattern. BMI: body mass index

Table 2. Comparison between Deficiency-Yang and Deficiency-Yin Patterns in PI Women ($\bar{x} \pm$ SE)

Item	Deficiency-yang (14 cases)	Deficiency-yin (31 cases)	*P* value
S-P Index	1.2 ± 0.3**	–1.2 ± 0.2	<0.001
ANS Index	–0.9 ± 0.2	–0.9 ± 0.1	0.966
Age (Year)	56.4 ± 1.7	59.5 ± 2.1	0.258
BMI (kg/m^2)	22.6 ± 1.4	22.0 ± 1.1	0.567
Insomnia duration (Year)	8.7 ± 2.4	8.9 ± 1.8	0.947
Subjective sleep parameters			
CPSQI	15.2 ± 0.8	13.7 ± 0.7	0.160
Sleep latency (min)	117.7 ± 25.2*	60.0 ± 7.5	0.035
Total sleep time (h)	4.8 ± 0.4	5.1 ± 0.3	0.555
Sleep efficiency (%)	63.5 ± 0.0*	76.0 ± 0.0	0.027
HRV parameters			
RR (ms)	830.6 ± 18.0	859.8 ± 24.8	0.350
LF [Hz, ln(ms^2)]	4.3 ± 0.2	4.6 ± 0.2	0.404
HF [Hz, ln(ms^2)]	3.8 ± 0.3*	4.6 ± 0.1	0.019
TP [Hz, ln(ms^2)]	6.1 ± 0.2	6.3 ± 0.2	0.491
LF/HF [ln(ratio)]	0.8 ± 0.2**	0.0 ± 0.2	0.002

Notes: *P<0.05, **P<0.01 *vs.* deficiency-yin pattern

Table 3. Comparison between Excess-Yang and Excess-Yin Patterns in PI Women ($\bar{x} \pm SE$)

Item	Excess-yang (14 cases)	Excess-yin (15 cases)	*P* value
S-P Index	0.8 ± 0.3**	–1.5 ± 0.3	0.001
ANS Index	0.7 ± 0.3	0.4 ± 0.1	0.226
Age (Year)	57.3 ± 2.6	55.0 ± 1.5	0.451
BMI (kg/m^2)	23.1 ± 0.7	23.6 ± 0.9	0.453
Insomnia duration (Year)	3.9 ± 2.6	5.4 ± 1.0	0.396
Subjective sleep parameters			
CPSQI	13.0 ± 1.2	13.6 ± 1.0	0.718
Sleep latency (min)	43.8 ± 5.6	54.8 ± 9.8	0.346
Total sleep time (h)	4.9 ± 0.5	4.4 ± 0.3	0.369
Sleep efficiency (%)	80.4 ± 0.5	71.4 ± 0.0	0.279
HRV parameters			
RR (ms)	852.0 ± 32.0	906.7 ± 30.6	0.239
LF [ln(ms^2)]	6.0 ± 0.3	5.6 ± 0.1	0.225
HF [ln(ms^2)]	4.5 ± 0.3*	5.4 ± 0.1	0.026
TP [ln(ms^2)]	7.2 ± 0.3	7.1 ± 0.1	0.754
LF/HF [ln(ratio)]	1.4 ± 0.1**	0.2 ± 0.1	<0.001

Notes: $^*P<0.05$, $^{**}P<0.01$ *vs.* excess-yin pattern

DISCUSSION

There are several methods of integration of biomedicine and CM, for example, joining of biomedicine and CM as a therapeutic method for some kind of diseases,(30.31) or diagnosis of a biomedical disease (such as rheumatoid arthritis) by pattern differentiation of CM.(32,33) This study provides a possible method that by using physiological signals (HRV) combined with the concepts of CM (deficiency/ excess and yin/yang) in order to develop diagnostic patterns of PI. The advantages of this method are that it is objective, reproducible, and easily carried out. In future studies, this approach may be applied to clinical trials for the use of acupuncture or Chinese herbs to treat PI.(34)

As identified by CM, the deficiency pattern of insomnia is more common than the excess pattern.(35) In addition, an important concept of CM is that "the longer the duration of a disease, the more probably is it to have a deficiency status."(36) The results of this study show that the deficiency pattern is more than the excess pattern of PI (60.8% *vs*. 39.2%), and the deficiency pattern of PI involved a longer duration of insomnia. Taken together, the above findings show that the pattern differentiation of PI in this study resembles closely the finding from ancient CM records.

It is interesting that the deficiency pattern of PI showed prolonged sleep latency compared to the excess pattern. Hot flushes in peri- and postmenopausal women are associated with nighttime wakefulness and sleep fragmentation but have not been found to be related to sleep efficiency, total sleep time, or sleep latency.(37) Therefore, the prolonged sleep latency in the deficiency pattern of PI may be due to other factors other than hot flushes. It has been suggested that subjects with chronic insomnia are in a state of sympathetic ANS predominance and neuroendocrine alteration.(38) The deficiency pattern of PI had a significantly lower HRV (including LF, HF, TP, and LF/HF) than the excess pattern. It has been reported that lower HRV is associated with stress-induced inflammation responses [such as interleukin (IL)-6 and tumor necrosis factor] and stress hormones (such as cortisol).(39) It has been further suggested that the daytime shift of IL-6 and tumor necrosis factor secretion, combined with a 24-h hypersecretion of cortisol, contribute to the insomniacs' daytime fatigue and their difficulty falling asleep. Therefore, the lower HRV in the deficiency pattern of PI may reflect neuroendocrine alterations and inflammation responses in the body, which may explain the prolonged sleep latency.

In a further classification of the deficiency pattern of PI, the deficiency-yang pattern showed significantly higher LF/HF but lower HF than those of the deficiency-yin pattern. This means that the deficiency-yang pattern of PI had relatively lower parasympathetic but higher sympathetic activity. It has been reported that parasympathetic activity has an active role involved in the transition from awake to sleep in rats.(40) In a human study, insomnious patients presented with a higher sympathovagal balance compared to normal subjects both before and after sleep onset.(41) These results seem to help explain why the deficiency-yang pattern individuals had difficulty falling asleep and subsequently had lower sleep efficiency than the deficiency-yin pattern individuals.

Although the excess-yang pattern of PI had significantly higher LF/HF but lower HF than those of excess-yin pattern, there were no significant differences in parameters of CPSQI between excess-yang and excess-yin patterns of PI. This may be because the higher HRV, which has fewer effects on neuroendocrine systems and the inflammatory response, is the predominant factor associated with the excess pattern of PI.

In conclusion, we have developed a quantitative HRV pattern diagnosis for PI based on CM concept. The results for the pattern differentiation of PI in this study are consistent with CM's historical records and also can be explained using modern sleep medicine. In the future, this approach may be applied to clinical trials of acupuncture or Chinese herbs when they are used to treat PI.

Conflict of Interest

There are no financial conflicts to disclose.

Author Contributions

Kung YY conducted the database search, study design, analyzed the data, and drafted the manuscript. Kuo TBJ assessed the study design and supervised the experimental techniques. Huang YT and Chiu JH help Kung YY complete the study. Yang CCH supervised Kung YY to perform data collection and revised the manuscript. All authors have read and approved the final version of the manuscript.

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