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Original Article

Enhancement of sleep stability with Tai Chi exercise in chronic heart failure: Preliminary findings using an ECG-based spectrogram method

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Abstract

Objective: To assess the effects of a 12-week Tai Chi exercise program on sleep using the sleep spectrogram, a method based on a single channel electrocardiogram (ECG)-derived estimation of cardiopulmonary coupling, previously shown to identify stable and unstable sleep states.
Methods: We retrospectively analyzed 24-h continuous ECG data obtained in a clinical trial of Tai Chi exercise in patients with heart failure. Eighteen patients with chronic stable heart failure, left ventricular ejection fraction $\leqslant$40% (mean [±standard deviation] age, 59 ± 14 years, mean baseline ejection fraction 24% ± 8%, mean) were randomly assigned to receive usual care ($N = 10$), which included pharmacological therapy and dietary and exercise counseling, or 12 weeks of Tai Chi training ($N = 8$) in addition to usual care. Using the ECG-based sleep spectrogram, we compared intervention and control groups by evaluating baseline and 12-week high (stable) and low (unstable) frequency coupling (HFC & LFC, respectively) as a percentage of estimated total sleep time (ETST).
Results: At 12 weeks, those who participated in Tai Chi showed a significant increase in HFC (+0.05 ± 0.10 vs. −0.06 ± 0.09 % ETST, $p = 0.04$) and significant reduction in LFC (−0.09 ± 0.09 vs. +0.13 ± 0.13 % ETST, $p < 0.01$), compared to patients in the control group. Correlations were seen between improved sleep stability and better disease-specific quality of life.
Conclusions: Tai Chi exercise may enhance sleep stability in patients with chronic heart failure. This sleep effect may have a beneficial impact on blood pressure, arrhythmogenesis and quality of life.

Keywords: Exercise; Heart failure; Heart rate variability; Mind-body; Sleep stability

1. Introduction

Sleep fragmentation is a well-known clinical feature in patients with heart failure. Standard polysomnographic categorization of sleep quality shows several changes, including reduced total sleep time, reduced sleep efficiency, frequent stage shifts, increased stage 1 non-rapid eye movement (NREM) sleep, reduced to absent slow wave sleep, and a high microarousal index [1]. Insomnia is a common symptom in patients with heart failure. The mechanisms involved include sleep-disordered breathing, poor sleep hygiene, direct (e.g., beta-blocker) and indirect (e.g., diuretic causing nocturia) medication effects, orthopnea/paroxysmal nocturnal dyspnea, and possibly neurohumoral activation itself.

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Recurrent arousals can severely fragment sleep, contributing to impaired cognitive function and quality of life [2]. In addition, repeated episodes of apnea and hypopnea can have deleterious effects on cardiac physiology and function, causing arterial oxyhemoglobin desaturations, nocturnal hypertensive surges amplified by arousals, triggering of arrhythmias, and an amplification of neurohumoral activation [3,4]. Improving sleep and sleep-breathing, therefore, is considered an important therapeutic target in the heart failure population.

A relatively new and complementary approach to quantify sleep physiology is the domain of *sleep stability*. Originally described solely by the electroencephalographic feature of cyclic alternating pattern (CAP and non-CAP) NREM sleep [5], recent work has shown that integrated oscillations of multiple, linked, physiological systems occur during sleep, and that sleep stability may be better described using a more complex, multisystems approach. For example, features of CAP on electroencephalogram (EEG) are usually associated with temporal instability of respiration, lack of nocturnal blood pressure "dipping," cyclic bursts of sympathetic activity, lower thresholds for arousals, and non-restorative sleep, a state referred to here as NREM unstable sleep. When the CAP features are absent on EEG (the "non-CAP" state), blood pressure "dipping" occurs, respiration demonstrates temporal stability, and arousal thresholds are elevated, a state referred to here as stable NREM sleep [6].

We developed a method to quantify sleep stability from a single channel electrocardiogram (ECG), mathematically combining heart rate variability (modulated by the autonomic nervous system) and the amplitude modulation of the R-wave associated with mechanical effects of respiration. This method that is based on cardiopulmonary coupling generates a "sleep spectrogram" and provides a visual and numerical estimate of sleep stability and instability. We have previously shown that high-frequency cardiopulmonary coupling during sleep is a feature of stable sleep state and is usually associated with a non-CAP EEG, while low-frequency cardiopulmonary coupling is a feature of unstable sleep state and is usually associated with a CAP EEG [7]. Thus, the sleep spectrographic technique integrates respiration, sleep and autonomic function, three critical variables of state physiology.

This fully-automated ECG-based method also has the advantage of not being constrained by the exact morphology and amplitude of EEG activity during sleep, which can be altered by age, individual differences, skull thickness, medications and disease processes. Arousing stimuli or states (e.g., disease, pain, stress, and certain medications) may contribute to unstable sleep, reducing high- and increasing low-frequency cardiopulmonary coupling during sleep. In contrast, interventions that promote stable sleep may have therapeutic value, particularly in disease states such as heart failure, where sleep fragmentation is so common.

Tai Chi is a meditative exercise with origins in traditional Chinese martial and healing arts. It is widely practiced in Asia, particularly among the elderly, and has gained increasing popularity in the United States. Recent literature has suggested that it may be particularly suitable for the elderly or de-conditioned patient with cardiac disease. Tai Chi incorporates slow-moving, gentle physical activity, balance, and weight shifting, with meditation, relaxation, deep breathing, and imagery. Reported benefits of Tai Chi include increased balance and decreased incidence of falls [8,9]; increased strength and flexibility [8,10,11]; reduced pain and anxiety [12]; improved self-efficacy [13,14]; improved sleep [15] and enhanced cardiopulmonary function [16–19]. Improved exercise capacity and quality of life have been reported in patients with heart failure [20,21].

We hypothesized that Tai Chi may enhance sleep quality and stability in patients with chronic heart failure, and applied the sleep spectrographic technique to 24 h continuous ECG data available from a previously published trial of Tai Chi in heart failure [21].

2. Methods

2.1. Subjects, recruitment, and intervention

A total of 30 patients with chronic stable heart failure and left ventricular systolic dysfunction (ejection fraction $\leqslant$40%) were recruited from advanced heart failure specialty clinics at Beth Israel Deaconess Medical Center and the Brigham and Women's Hospital in Boston, MA. Patients were randomized to either a 12-week Tai Chi exercise class in addition to their usual care, or to usual care alone. Usual care included pharmacologic therapy, dietary counseling, and general physical activity advice per American College of Cardiology/American Heart Association consensus guidelines [22]. Patients who had major changes in their cardiac medical regimen in the prior three months, a major cardiac event or procedure in the prior three months, unstable arrhythmias or major valvular disease, or were currently participating in a conventional cardiac rehabilitation program were excluded. The subset of data from 18 patients derived from the original 30 who had appropriate 24 h ECG data (described below) were available for analysis.

The intervention consisted of one-hour classes held twice weekly for 12 weeks. Classes included warm-up exercises of weight shifting, arm swinging, visualization techniques for scanning the body and releasing tension, and gentle stretches of the neck, shoulders, spine, arms and legs. The five core Tai Chi movements were adapted from Master Cheng Man-Ch'ing's Yang-style Tai Chi and performed in cyclic repetition [23]. Patients were

encouraged to practice at home with a 35 min instructional videotape at least three times per week. Further description of the methods and intervention protocol are detailed elsewhere [21].

2.2. Quality of life, exercise capacity, and neurohormonal markers

As part of the protocol for the larger randomized controlled trial, outcomes testing occurred at baseline and 12 weeks. Quality of life was measured using the Minnesota Living with Heart Failure (MLHF) Questionnaire. This well-validated instrument consists of 21 items covering physical, psychological, and socioeconomic dimensions of illness and quantifies the disability related to each item on a six-point response scale. Scores range from 0 to 105, with a lower score denoting a more favorable functional status [24].

To measure exercise capacity, patients performed a standardized 6-min walk-test which measures the distance walked at a comfortable pace in 6 min. This test has been used to assess functional capacity and predict survival in heart failure drug trials [25]. In addition, patients performed a symptom-limited exercise test using a bicycle ramp protocol to determine peak oxygen uptake (peak VO_2). Testing was performed on an electronically calibrated upright bicycle, with expired gas analysis under continuous ECG monitoring. Blood pressure was taken at 3-min intervals and just prior to stopping exercise. Respiratory gas analysis was performed on a breath-by-breath basis using a Sensormedic metabolic cart (Yorba Linda, CA). Peak values were averaged from the final 20 s of the test.

B-type natriuretic peptide (BNP) samples were analyzed on whole blood collected in ethylenediamine tetraacetic acid (EDTA) using the Biosite Triage BNP Test (San Diego, CA) fluorescence immunoassay. BNP is a circulating cardiac peptide that is a useful marker in the diagnosis and management of heart failure. Levels correlate positively with the degree of left ventricular dysfunction. Serum levels of BNP >100 pg/mL support a diagnosis of symptomatic heart failure [26].

Catecholamine samples were drawn on ice in heparinized tubes after 20 min rest with intravenous catheter in place. After centrifugation, plasma was separated and stored at −70 °C. Analyses for norepinephrine, epinephrine, and dopamine were performed using high-performance liquid chromatography/electrochemical detector.

2.3. Continuous ambulatory ECG recordings

At baseline and 12 weeks, patients underwent 24 h ambulatory ECG monitoring. Recordings were performed using a Marquette Electronics (Milwaukee, Wisconsin) series 8500 Holter monitor, digitized at 128 Hz, and annotated using a Marquette Electronics MARS 8000 Holter scanner. Annotations were manually verified and edited by an experienced technician.

For assessment of standard heart rate variability, as well as cardiopulmonary coupling and sleep stability, 27 of 30 patients provided two complete sets of ECG data. Of these, 9 were further excluded from analysis: 2 patients had a predominant non-sinus rhythm and 7 patients were paced, precluding heart rate variability analysis. We analyzed data on the remaining 18 patients.

In addition to 24-h heart rate variability (HRV) analysis, HRV statistics were also separately calculated for sleep and waking activity. Since the actual times of sleep were not recorded, the period of sleep was defined as the six nighttime hours of lowest heart rate (providing the estimated total sleep time [ETST]). Waking activity was defined as the six daytime hours of highest heart rate.

2.4. Standard heart rate variability

From the 24-h beat annotation files, the time series of normal-to-normal sinus intervals was extracted. Outliers due to false or missed normal beat detections were removed using a sliding window average filter with a window of 41 data points and rejection of central points lying outside 20% of the window average. The time domain HRV statistics of AVNN (average of all normal sinus to normal sinus NN intervals), SDNN (standard deviation of all NN intervals), SDANN (standard deviation of the average of NN intervals in all 5-min segments), SDNNINDX (mean of the standard deviations of NN intervals in all 5-min segments) , rMSSD (square root of the mean of the squares of differences between adjacent NN intervals), pNN10, pNN20, pNN30, pNN40 and pNN50 (percentage of differences between adjacent NN intervals that are greater than 10, 20, 30, 40, and 50 ms, respectively) and the frequency domain measures of Total Power, ULF (total spectral power up to 0.003 Hz), VLF (between 0.003 and 0.04 Hz), LF (between 0.04 and 0.15 Hz), HF (between 0.15 and 0.4 Hz), LF/HF ratio and log–log power slope were calculated. To eliminate the need for evenly sampled data required by the standard Fast Fourier Transform, frequency domain spectra were calculated using the Lomb periodogram for unevenly sampled data [27–29].

2.5. Sleep spectrogram technique

Details of the sleep spectrographic technique have been previously published [7]. In brief, using a single lead ECG, an automated beat detection algorithm is used to detect beats and classify them as either normal or ectopic. In addition, amplitude variations in the QRS complex (which represents ventricular depolarization) due to shifts in the cardiac electrical axis relative to the electrodes during respiration and changes in tho-

racic impedance as the lungs fill and empty are determined. These fluctuations in the mean cardiac electrical axis correlate with phasic changes in the respiratory cycle. From these amplitude variations a surrogate ECG-derived respiratory signal (EDR) is obtained. A time series of normal-to-normal sinus (NN) intervals and the time series of the EDR associated with these NN intervals is then extracted from the RR interval time series. Outliers due to false or missed R-wave detections are removed using a sliding window average filter with a window of 41 data points and rejection of central points lying outside 20% of the window average. The resulting NN interval series and its associated EDR are then resampled at 2 Hz using cubic spline interpolation. The cross-spectral power and coherence of these two signals are calculated over a 1024 sample (8.5 min) window using the Fast Fourier Transform applied to the three overlapping 512 sample subwindows within the 1024 coherence window. The 1024 coherence window is then advanced by 256 samples (2.1 min) and the calculation repeated until the entire NN interval/EDR series is analyzed. For each 1024 window, the product of the coherence and cross-spectral power is used to calculate the ratio of coherent cross power in the low-frequency (0.01–0.1 Hz.) band to that in the high-frequency (0.1–0.4 Hz.) band. A preponderance of power in the low-frequency band tends to be associated with periodic sleep behaviors regardless of etiology, while excess power in the high-frequency band is associated with physiologic respiratory sinus arrhythmia and stable/deep sleep. Cardiopulmonary coupling spectrograms reveal that the low- and high-frequency coupling regimes have weak correlations with standard sleep staging but more closely follow CAP scoring [7]. Specifically, low-frequency coupling is generally associated with CAP and high-frequency coupling with non-CAP. It is also observed that the ratio of power in the very low-frequency (0–0.01 Hz) to the combined power in the low- and high-frequency bands may be used to estimate wake/REM, where a preponderance of power in the very low-frequency band is associated with wake/REM periods. Using appropriate thresholds for the power ratios in these bands, sleep demonstrating stability and high-frequency coupling, instability and low-frequency coupling, and wake/REM states can be identified [7].

2.6. Statistical analysis

Baseline characteristics of the study patients were compared using *t*-tests for continuous variables and Fisher's exact test for nominal variables. Two-sample Wilcoxon rank-sum tests adjusted for baseline scores were used to compare the distribution of changes in quality of life scores, 6-min walk distance, serum BNP, and estimated cardiopulmonary coupling after 12 weeks between intervention and control groups. Similar analyses were done for each of the HRV statistics. In addition, we compared within-group pre-post statistics using Wilcoxon rank-sum tests. The Spearman correlation was used to determine the association between high- or low-frequency cardiopulmonary coupling and neurohormonal markers, exercise capacity, and quality of life.

3. Results

3.1. Subject characteristics

The mean age of study patients was 59 ± 14 years. There was an equal gender distribution. The mean left ventricular ejection fraction was $24 \pm 8\%$, and about one-quarter of patients were New York Heart Association Class 3. (Table 1) There were no statistically significant differences between the groups with regard to demographics, clinical factors, and rates of cardiovascular-related disease and other comorbidities. There were no significant differences between this study's subsample and the original study population.

Table 1
Baseline characteristics of the study population

Characteristic	Tai Chi ($N = 8$) N (%)	Control ($N = 10$) N (%)	*P*-value
Demographic factors			
Age (years ± SD)	64.2 ± 16.2	54.7 ± 11.8	0.18
Gender: Men	4 (50%)	5 (50%)	1
Race			0.15
Black	6 (75%)	3 (30%)	
White	2 (25%)	6 (60%)	
Asian	0 (0%)	1 (10%)	
Clinical factors			
Baseline LVEF (% ± SD)	25 ± 6	23 ± 9	0.85
NYHA class			0.55
1	3 (37.5%)	1 (10%)	
2	4 (50%)	6 (60%)	
3	1 (12.5%)	3 (30%)	
Medications			
Angiotensin-converting enzyme inhibitor	7 (87.5%)	9 (90%)	1
Beta-blocker	8 (100%)	10 (100%)	1
Loop diuretic	7 (87.5%)	10 (100%)	0.44
Digoxin	5 (62.5%)	5 (50%)	0.66
Spironolactone	2 (37.5%)	3 (30%)	1
Relevant comorbidities			
Coronary artery disease	0 (0%)	4 (40%)	0.09
Arrhythmia	3 (37.5%)	3 (30%)	1
Valvular disease	1 (12.5%)	2 (20%)	1
Hypertension	5 (62.5%)	6 (60%)	1
Diabetes	1 (12.5%)	3 (30%)	0.59
COPD/asthma	2 (25%)	2 (20%)	1
Anxiety/depression	3 (37.5%)	6 (60%)	0.64

SD, standard deviation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease.

3.2. Sleep spectrograms

Table 2 presents change in mean outcome measures over the 12-week period. In the Tai Chi group, statistically significant improvements were seen, with increases in high-frequency coupling (stable sleep state) and reductions in low-frequency coupling (unstable sleep state), as compared to usual care alone ($p = 0.04$ and $p = < 0.01$, respectively). Figs. 1 and 2 show individual data points from baseline to 12 weeks. Fig. 3 illustrates the effect of Tai Chi on the ECG-derived sleep spectrogram of a single patient, with an increase in high-frequency coupling (stable sleep) following Tai Chi exposure.

3.3. Neurohormones, exercise capacity, and quality of life

Similar to previously published results from the original study, those who participated in Tai Chi ($N = 8$) showed significantly improved 6-min walk distance (76 m ± 52 vs. −33 m ± 85, $p < 0.01$) and quality of life score (−17 ± 14 vs. 7 ± 10, $p < 0.01$), compared to those who received usual care alone ($N = 10$). Non-significant trends were seen in improvement in serum BNP with Tai Chi compared to usual care alone ($p = 0.08$). No changes were seen in peak VO_2 and catecholamine measurements.

3.4. Correlations between sleep stability and neurohormones, exercise capacity, and quality of life

Significant correlations were demonstrated between quality of life and sleep stability measures (Table 3). Increased high-frequency cardiopulmonary coupling was associated with better disease-specific quality of life ($p = 0.01$, lower score on the Minnesota Living with Heart Failure Questionnaire denotes a higher quality of life). Similarly, increased low-frequency coupling was associated with worse quality of life ($p = 0.02$). Increased high-frequency cardiopulmonary coupling was marginally associated ($p = 0.06$) with increased 6-min walk distance. No significant associations were seen with catecholamines, BNP, and peak VO_2.

3.5. Standard heart rate variability measures

There were no statistically significant changes seen in the 24 h heart rate variability analyses. However, the Tai Chi group showed trends toward increased pNN values during sleep that were not seen in the control group. There was a marginally significant increase in pNN30 ($p = 0.049$) with pNN10, pNN20 and pNN40 approaching significance at $p = 0.079$, $p = 0.060$ and $p = 0.054$, respectively. Table 4 present the time and frequency domain measures of heart rate variability during sleep.

4. Discussion

The key finding of our analysis is that a 12-week Tai Chi exercise program improves sleep stability as assessed by a novel, fully automated, ECG-based sleep spectrogram technique. This improvement was found in patients with chronic heart failure already on maximized medical management. Furthermore, an interesting correlation between improved sleep stability and improved quality of life was demonstrated. In the control group, there was a possible worsening of sleep stability measures. With traditional heart rate variability measures, there was a trend towards increased short-term heart rate variability during sleep in the Tai Chi group, suggesting a possible improvement in cardiac vagal modulation. While there were no changes in resting catecholamines, a trend in improvement in serum BNP suggested possible decreases in neurohumoral activation.

An increase in stable sleep may be a robust marker of overall improved sleep quality. For patients with heart failure, unstable sleep may cause excessive hemodynamic stress through respiratory and non-respiratory mechanisms, and may be associated with ventricular arrhythmias [30]. In contrast, stable sleep is associated with stable respiration and hemodynamics and may protect from triggered arrhythmias, thus demonstrating potential restorative effects for the deranged cardiopulmonary physiology of heart failure. Improvements in sleep stability may, therefore, promote acute beneficial changes in hemodynamic indices during sleep, as well as chronic changes in the overall

Table 2
Comparison of Tai Chi intervention vs. control in mean change in ECG-derived sleep stability measures from baseline to 12 weeks

Outcome measure	Tai Chi ($N = 8$)			Control ($N = 10$)			P-value[b]
	Baseline (± SD)	Mean change (± SD)	P-value[a]	Baseline (± SD)	Mean change (± SD)	P-value[a]	
High-frequency coupling (stable sleep)	0.30 (0.19)	0.05 (0.1)	0.27	0.29 (0.22)	−0.06 (0.09)	0.07	0.04
Low-frequency coupling (unstable sleep)	0.42 (0.2)	−0.09 (0.09)	0.04	0.38 (0.17)	0.13 (0.13)	0.02	<0.01
Estimated wake/REM	0.25 (0.12)	0.02 (0.08)	0.57	0.29 (0.1)	−0.07 (0.13)	0.14	0.08

[a] Comparison of within-group pre-post change.
[b] Comparison of mean change between groups.

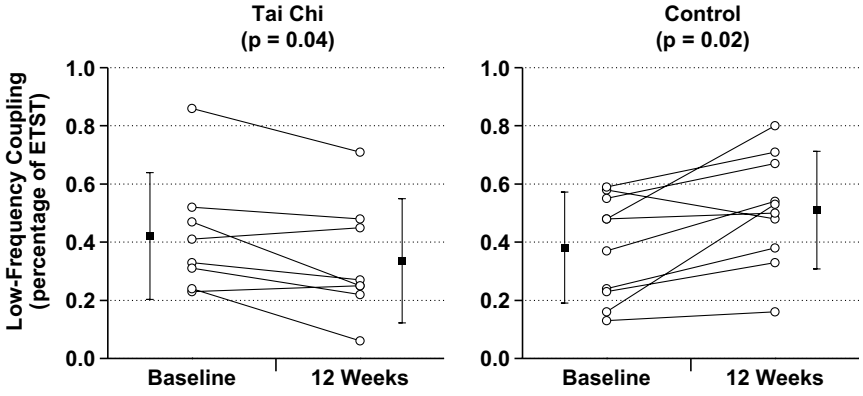

Fig. 1. Change in low-frequency (unstable) cardiopulmonary coupling. Individual measures of ECG-derived low-frequency cardiopulmonary coupling (as a percentage of estimated total sleep time [ETST] with cyclic alternating pattern) are shown at baseline and 12 weeks. The means (±standard deviation) are shown in bold. At 12 weeks, patients in the Tai Chi group showed significantly decreased time in unstable sleep compared to the usual care group ($p < 0.01$).

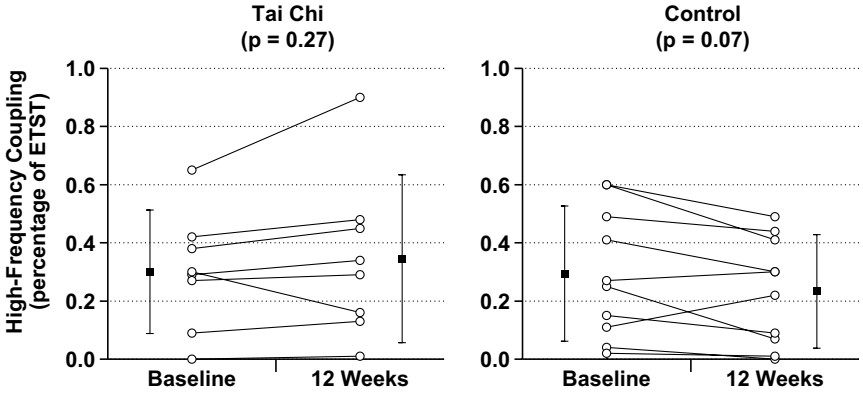

Fig. 2. Change in high-frequency (stable) cardiopulmonary coupling. Individual sleep stability measures of ECG-derived high-frequency cardiopulmonary coupling (as a percentage of estimated total sleep time [ETST] with non-cyclic alternating pattern) are shown at baseline and 12 weeks. The means (±standard deviation) are shown in bold. At 12 weeks, patients in the Tai Chi group showed significantly increased time in stable sleep as compared to the usual care group ($p = 0.04$).

hemodynamic profile. This study suggests that Tai Chi may be a potential adjunctive therapeutic option for patients with heart failure that can improve sleep stability. Sleep stability, as reflected in CAP/non-CAP sleep, has not previously been described with Tai Chi, although one prior clinical trial has reported improvements in sleep quality after 24 weeks of Tai Chi as compared to conventional low-impact exercise. Improvements were seen in self-reported sleep quality (Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale), as well as decreased sleep latency and increased sleep duration [15]. Changes in sleep quality have also been demonstrated with other meditative practices, such as mindfulness-based stress reduction and yoga [31,32].

Mechanisms of improvement in sleep stability with Tai Chi are speculative but biologically plausible. Certainly, exercise has been shown to improve sleep quality. In both humans and animal models, regular physical activity increased EEG delta power during stage 3/4 NREM sleep and improved overall sleep quality [33]. Exercise has also been shown to affect the neurohormonal axis, which could contribute to improved stable sleep state. Increased physical activity has also been shown to improve sleep hygiene [33–37]. In addition, the meditative practice inherent in Tai Chi may also contribute to increased sleep stability. Reduced respiratory chemoreflex sensitivity [38–41] and increases in baroreflex sensitivity have been described in practitioners of yoga and meditation [42,43]. These improvements in respiratory control could lead to improvements in sleep-disordered breathing. Furthermore, Tai Chi includes a component of respiratory rhythm training with slow, deep, diaphragmatic breathing, which could play a role in retraining breathing patterns during sleep. Finally, the Tai Chi exercise program may have indirectly promoted better sleep hygiene, improved mental health (e.g., decreased anxiety/depression), and provided a social group for participants, which each may have

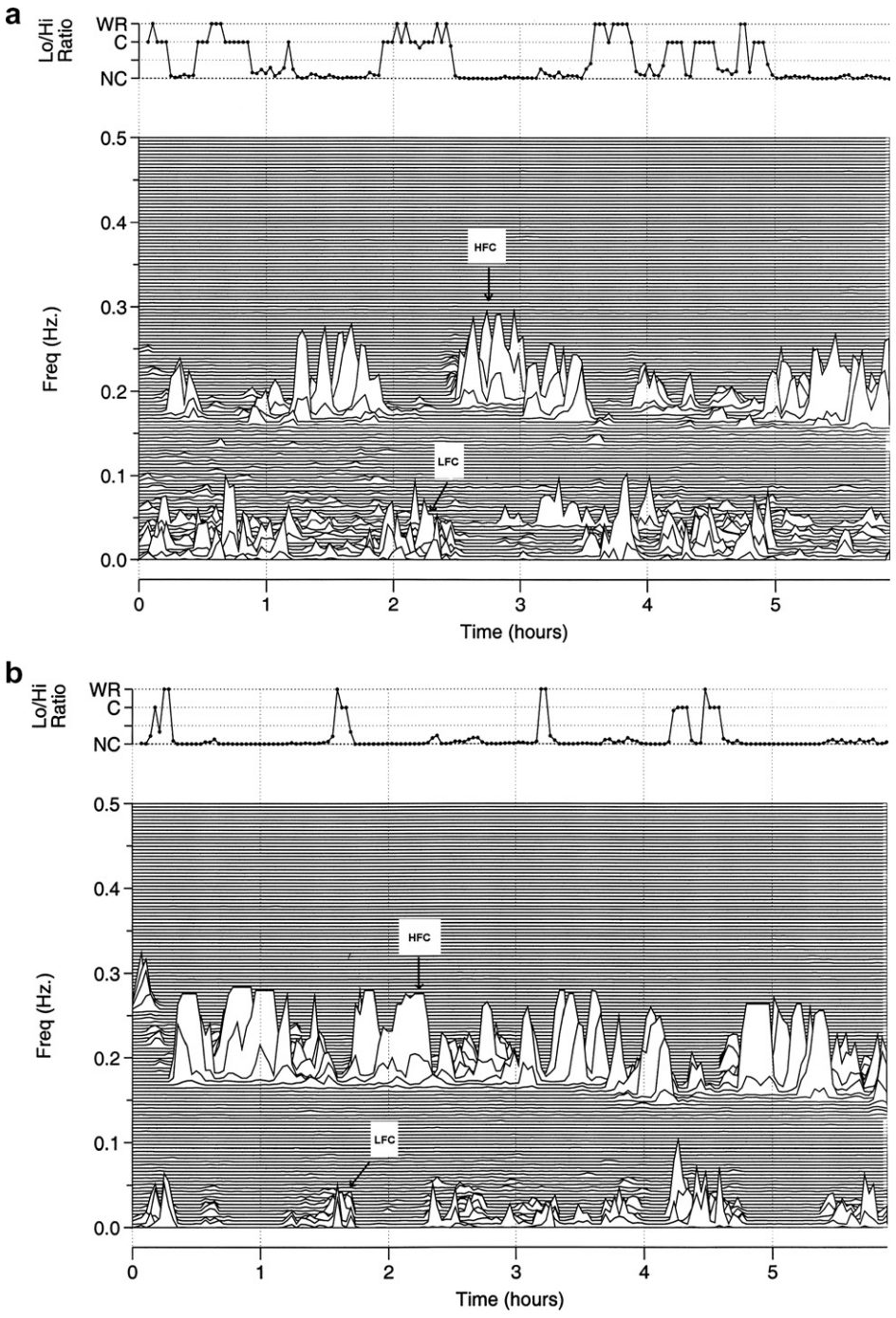

Fig. 3. Effect of Tai Chi on the sleep spectrogram. The upper panel of the figure (a) shows the ECG-derived sleep spectrogram at baseline for a single patient. Note high-frequency (stable sleep state) and low-frequency (unstable sleep state) cardiopulmonary coupling and spontaneous switching between states. The lower panel (b) demonstrates an increase in high-frequency coupling following the Tai Chi exposure. This change is evident across the night, and is thus distinctly different from the type of information that can be obtained from standard sleep scoring approaches. Specifically, slow-wave (delta) sleep is an increasingly small percentage of total sleep time in older adults and would thus be less useful in this assessment. In each figure, C, cyclic alternating pattern; LFC, low-frequency coupling; NC, non-cyclic alternating pattern; HFC, high-frequency coupling; W/R, wake or REM sleep, all derived from a single channel of ECG [5]. As polysomnographic data were not available, the sleep period was defined as the 6 nighttime hours of the 24 h period with the lowest mean heart rate.

contributed to improved sleep quality and increased spectrographic sleep stability. Of note, we also observed a possible deterioration of spectrographic sleep stability in the control group. Possible explanations include natural progression of disease, night-to-night variability in sleep quality, sleep stability, and disordered breathing, and group variability in sleep hygiene.

Table 3
Correlations between ECG-derived sleep stability measures and neurohormones, exercise capacity, and quality of life from baseline to 12 weeks

Relationship	Spearman ρ correlation coefficient	*P*-value
HFC[a]–Norepinephrine	−0.08	0.50
HFC–Epinephrine	0.05	0.64
HFC–Dopamine	0.16	0.73
HFC–BNP[c]	−0.12	0.30
HFC–Peak VO_2[d]	0.31	0.10
HFC–6 min walk	0.32	0.06
HFC–QOL[e]	−0.39	**0.01**
LFC[b]–Norepinephrine	0.05	0.46
LFC–Epinephrine	0.10	0.18
LFC–Dopamine	−0.06	0.87
LFC–BNP	0.11	0.62
LFC–Peak VO_2	−0.11	0.59
LFC–6 min walk	−0.17	0.23
LFC–QOL	0.35	**0.02**

[a] HFC, High-frequency coupling (stable sleep).
[b] LFC, Low-frequency coupling (unstable sleep).
[c] BNP, B-type natriuretic peptide.
[d] Peak VO_2, Peak oxygen uptake on bicycle stress test.
[e] QOL, Disease-specific quality of life score (Minnesota living with heart failure questionnaire. *Note:* A lower score represents better quality of life.).

There may be an association between sleep stability and quality of life, with stable sleep (high-frequency cardiopulmonary coupling) correlating with better quality of life, and unstable sleep (low-frequency cardiopulmonary coupling) correlating with worse quality of life. Interestingly, unstable EEG sleep is seen in several chronic disease states, including depression, fibromyalgia, primary insomnia, sleep apnea and epilepsy [44–47]. This disrupted sleep is typically associated with a worse perceived quality of life [48]. The preliminary findings here suggest that Tai Chi-related improvements in patients may, in part, be mediated by effects on sleep.

We recognize several inherent study limitations. First, this was a retrospective analysis of existing data and polysomnographic evaluation of patients was not done in the original study. Thus, changes in conventional sleep stages, especially slow-wave sleep, and the exact reasons for sleep disruption in the study subjects are not known. In addition, the sample size is small and likely underpowered to detect relationships between change in sleep stability measures and markers of neurohormonal activation, or to detect changes in standard HRV measures or in serum BNP. For example, in the original cohort of 30 patients,[21] we reported a significant improvement in BNP in the Tai Chi versus control group ($p = 0.03$). With the subset of 18 patients in this analysis, trends toward improvement in BNP still exist ($p = 0.08$); however, power becomes limited. As with the original study, we also cannot determine what component of Tai Chi is responsible for the observed benefits. Physical activity may have important effects, and it is unclear what added role meditation and relaxation may play. Finally, we have no data on direct hemody-

Table 4
Comparison of Tai Chi intervention vs. control in mean change in selected heart rate variability (HRV) measures from baseline to 12 weeks

	Tai Chi	*P*-value[a]	Control	*P*-value[a]	*P*-value[b]
Mean change (±SD) in 24-h HRV					
AVNN[c]	16.3 ± 37.7	0.26	3.2 ± 67.3	0.88	0.68
SDNN[d]	8.8 ± 21.6	0.29	−7.4 ± 23.6	0.35	0.14
RMSSD[e]	4.2 ± 8.8	0.22	−3.3 ± 12.1	0.41	0.39
PNN30[f]	2.3 ± 6.9	0.37	−3.4 ± 13.7	0.45	0.56
LF[g]	57.6 ± 308.5	0.61	20.4 ± 370.9	0.87	0.68
HF[h]	188.6 ± 709.7	0.48	10.1 ± 318.1	0.92	0.82
LF/HF	−0.5 ± 1.2	0.24	0.2 ± 0.6	0.41	0.30
Mean change (±SD) in HRV during sleep					
AVNN	31.4 ± 87.2	0.34	−1.5 ± 86.9	0.96	0.39
SDNN	−9.7 ± 20.7	0.23	0.4 ± 37.2	0.97	0.50
RMSSD	7.9 ± 13.7	0.15	−1.4 ± 90.9	0.84	0.68
PNN30	10.2 ± 12.1	**0.05**	0.3 ± 20.1	0.97	0.50
LF	−209.5 ± 344.6	0.13	135.1 ± 875.0	0.64	0.35
HF	878.3 ± 2539.4	0.36	8.7 ± 595.0	0.96	0.96
LF/HF	−0.7 ± 1.2	0.16	0.2 ± 1.6	0.73	0.45

HRV, heart rate variability.
[a] Comparison of within group pre-post mean change.
[b] Comparison of mean change between groups.
[c] AVNN, Average of all normal sinus to normal sinus (NN) intervals.
[d] SDNN, Standard deviation of all NN intervals.
[e] RMSSD, Square root of the mean of the squares of differences between adjacent NN intervals.
[f] PNN30, Percentage of differences between adjacent NN intervals that are >30 ms.
[g] LF, Low frequency power (between 0.04 and 0.15 Hz).
[h] HF, High frequency power (between 0.15 and 0.4 Hz).

namic effects during sleep or respiratory chemoreflexes, so that possible mechanistic effects remain speculative. Despite these limitations, the data presented provide valuable preliminary information for generating testable hypotheses on the potential effects on sleep of Tai Chi exercise in patients with heart failure.

In conclusion, we report preliminary findings suggesting that a 12-week Tai Chi exercise program may improve sleep stability in patients with heart failure on maximal medical therapy. As stable sleep has the potential to improve the sleep-related hemodynamic profile in heart failure and have at least theoretical cardioprotective effects, further evaluation of this safe approach seems justified. Further research should include polysomnographic testing to document sleep stages and patterns of sleep disruption, active controls (e.g., conventional exercise) in order to better understand component effects of meditative exercise, and outcomes directly assessing cardiac function and hemodynamic changes during sleep. In addition, further characterization of the study population, such as heart failure with and without Cheyne-Stokes respiration and central sleep apnea, may provide insights into the mechanisms of the effects of Tai Chi on sleep.

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