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SCIENTIFIC INVESTIGATIONS

Day–night patterns in heart rate variability and complexity: differences with age and cardiopulmonary disease

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Study Objectives: Heart rate variability (HRV) measures provide valuable insights into physiology; however, gaps remain in understanding circadian patterns in heart rate dynamics. We aimed to explore day–night differences in heart rate dynamics in patients with chronic cardiopulmonary disease compared with healthy controls.

Methods: Using 24-hour heart rate data from patients with chronic obstructive pulmonary disease (COPD) and/or heart failure (n = 16) and healthy adult controls (older group: ≥50 years, n = 42; younger group: 20–49 years, n = 136), we compared day–night differences in conventional time and frequency domain HRV indices and a multiscale-entropy–based complexity index (CI_{1-20}) of HRV among the 3 groups.

Results: Twenty-four-hour HRV showed significant day–night differences (marked with "△") among younger healthy (mean age: 34.5 years), older healthy (mean age: 61.6 years), and cardiopulmonary patients (mean age: 68.4 years), including change in percentage of adjacent intervals that differ > 50 ms (△pNN50), high frequency (△HF), normalized low frequency (△nLF), ratio (△LF/HF), and $\triangle CI_{1-20}$. Among these, △LF/HF (2.13 ± 2.35 vs 1.1 ± 2.47 vs –0.35 ± 1.25; $P < .001$) and $\triangle CI_{1-20}$ (0.15 ± 0.24 vs 0.02 ± 0.28 vs –0.21 ± 0.27; $P < .001$) were significant in each pairwise comparison following analysis of variance tests. Average CI_{1-20} was highest in younger healthy individuals and lowest in cardiopulmonary patients (1.37 ± 0.12 vs 1.01 ± 0.27; $P < .001$). Younger healthy patients showed a heart rate complexity dipping pattern (night < day), older healthy patients showed nondipping, and cardiopulmonary patients showed reverse dipping (night > day).

Conclusions: As measures of 24-hour variability, traditional and complexity-based metrics of HRV exhibit large day–night differences in healthy individuals; these differences are blunted, or even reversed, in individuals with cardiopulmonary pathology. Measures of diurnal dynamics may be useful indices of reduced adaptive capacity in patients with cardiopulmonary conditions.

Keywords: 24-hour rhythm, sleep, complexity, heart rate, heart rate variability, dynamics, COPD, heart failure

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Lower heart rate variability and reduction in complexity metrics of heart rate dynamics have been reported in disease states, but circadian and or sleep-wake patterns contributing to diurnal variation in these metrics are not understood. Further characterization of day–night patterns in heart rate dynamics may greatly inform our understanding of physiological changes affected by age and disease.

Study Impact: Complexity-based heart rate dynamics may be especially informative to the understanding of pathological alterations compared with convention linear indices, and thus serve as a complementary metric to traditional heart rate variability measures for distinguishing heart rate dynamics among diseased and healthy populations. Measures of diurnal dynamics may serve as more sensitive indices of reduced adaptive capacity to physiological stress or changes in patients with cardiopulmonary conditions. Future study is encouraged to use a circadian protocol to further investigate sleep-induced changes and understand how activity influences patterns and day–night differences.

INTRODUCTION

Circadian rhythms, the endogenously generated rhythms with a period close to 24 hours, are part of the body's internal clock and are critical to carrying out essential functions. Such rhythms are driven by a circadian clock composed of 2 distinct components: the central clock, located in the suprachiasmatic nucleus within the hypothalamus, and the peripheral clocks, located in almost all tissues and organ systems in the body.[1]

Cardiovascular variables, including heart rate (HR), electrocardiogram (ECG) waveforms, and blood pressure (BP), all demonstrate a robust circadian rhythm. For example, BP varies in a diurnal manner throughout a 24-hour period, being higher during the day and lower at night. Healthy individuals have a dipping BP pattern characterized by a nighttime BP that is 10–20% lower than their daytime BP.[2,3] A nondipping pattern (nocturnal decrease in BP < 10%) and reverse dipping pattern (nocturnal BP higher than daytime BP) are both associated with deterioration in heart function.[4,5] Similar patterns are observed in heart rate.[6] During the night, RR intervals increase, corresponding to slower heart rates. A lengthening of the PR interval, QRS duration, and both uncorrected and corrected QT intervals can also be observed.[7,8] Regulation of circadian rhythm in HR is not well understood, but it is commonly believed that the

suprachiasmatic nucleus clock controls the circadian rhythm through varying autonomic tone to the sinus node—that is, circadian sympathovagal balance due to an increase in vagal tone at night[9] or diurnal fluctuations in sympathetic tone.[10]

The most commonly used measurement for autonomic regulation is HR variability (HRV). The oscillation of HR varies at different time scales. While it has been suggested that HRV also exhibits a circadian pattern, this has been poorly studied. Only ECG or HR recordings of at least 24 hours can contribute to the understanding of circadian rhythms in HR dynamics. Unfortunately, most studies report only simple HR data, or short-term HRV. In those that do include 24-hour recordings, day–night subsets of data are typically not examined. Studies with circadian protocols (eg, constant routine) to distinguish between activity-sleep–induced changes are even more rare. Thus, the day–night differences in HRV and their clinical implications are not well characterized. While it has been well established that HRV decreases with age and is lower in patients with chronic disease compared with healthy controls, the possibility of circadian patterns and day–night difference in these profiles has not been clearly addressed.

There are very few studies that provide information on circadian HRV or have described the 24-hour patterns of dynamic HRV. For example, in 1 study of healthy volunteers, aging was reported to be associated with a constant decline in cardiac vagal modulation due to a significant decrease in nocturnal parasympathetic activity.[11] Another small study in 8 healthy young males showed that endogenous circadian rhythmicity influences autonomic control of HR and that the timing of these endogenous rhythms can be altered by extended sleep/rest episodes and associated changes in photoperiod as well as by melatonin treatment.[12] Existing studies related to circadian HRV mainly studied a single group of individuals and a limited number of selected HRV measures. There are clear gaps in knowledge with respect to day–night differences and circadian patterns. It is not clear whether the patterns are different among different populations, what HRV measures are more sensitive to day–night variations, and whether the 24-hour pattern of HR dynamics may be useful clinically or have implications for future research.

Similarly, circadian or diurnal patterns of HR complexity are unknown. Physiological outputs from cardiovascular regulation are complex and chaotic.[13–15] That is, HR oscillations are not linear combinations of arbitrary frequency components, and the frequency components actually change in amplitude or shape as time evolves, which is the property known as "nonlinearity" and "nonstationarity."[16] Because of this property, HRV analysis using nonlinear dynamical techniques (eg, entropy, a measure for the complexity of physiological time series) has become an important area of research. Paralleling findings with time and frequency domain metrics of HRV, research supports that aging and pathological conditions degrade a system's complexity (indicated by lower entropy).[13,14,17,18] An increasing number of studies have used complexity-based measures in clinical trials to show physiological improvement after interventions. Among them, multiscale entropy (MSE) is a widely used measurement for characterizing the degree of complexity of HR dynamics.[13,14,16–23] However, as with HRV research, day–night variation or differences in complexity have not been studied, and the available literature on HR complexity has largely focused on daytime wakeful HR dynamics.

Within this context, we aimed to explore the 24-hour patterns of HR dynamics, and to understand the day–night differences in populations with chronic disease compared with healthy controls. Given that functions of the heart and the lung also display clear circadian variation,[24] and that some studies have suggested altered HR dynamics in populations with chronic cardiopulmonary disease,[25–27] we focused our analysis on patients with chronic obstructive pulmonary disease (COPD) and heart failure. In this context, we examine 24-hour ECG data from patients with COPD and/or heart failure compared with both young and older healthy adult controls to characterize profiles and explore 24-hour patterns of HR dynamics, including both conventional time and frequency domain, as well as complexity-based HRV measures.

METHODS

Data from patients with COPD and/or heart failure

ECG data were collected as part of a collaborative project between Beth Israel Deaconess Medical Center and the University of Michigan. In the original randomized controlled trial, patients with a diagnosis of COPD and/or heart failure were asked to participate in a study examining a Web-based physical activity intervention compared with usual care.[28] We only included baseline 24-hour ECG data from participants with valid ECG recordings before randomization and preintervention. Inclusion criteria included the following: male and female patients > 40 years of age; clinical diagnosis of COPD (defined as either a ratio of forced expiratory volume in 1 second [FEV_1] to forced vital capacity < 0.70, or chest computed tomography evidence of emphysema) or clinical diagnosis of heart failure syndrome (with left ventricular systolic dysfunction or preserved ejection fraction, and New York Heart Association class 1–3); medical clearance from provider to participate in an exercise program; and having an active email account and access to appropriate computer technology. Exclusion criteria included COPD or heart failure exacerbation in the previous 2 weeks; inability to ambulate that would preclude a 6-minute walk test (6MWT) during baseline testing; clinical signs of unstable cardiovascular disease; hypoxemia during 6MWT, ie, oxygen saturation < 85% using supplemental oxygen; inability to collect at least 7 of 14 days of baseline step counts; and current participation in a cardiac or pulmonary rehabilitation program.

Recruitment included on-site screening of patients using the electronic medical records, direct referral from clinic physicians, targeted mailings, and visits to cardiopulmonary rehabilitation programs. Detailed demographic data were available, including age, sex, height, weight, medical history, smoking, drinking, educational level, marital status, etc.[28]

All participants at baseline were asked to wear a portable ECG device to continuously collect 24 hours of ECG data (time stamped) with a sampling rate of 256 Hz. Participants were asked to refrain from alcohol or caffeine during this time. Heartbeat intervals were extracted from the 24-hour ECG recordings

by a MATLAB (MathWorks, Natick, MA) program and were verified by visual inspections. Patients who were unable to complete baseline tests and ECG recordings with low data quality were excluded from this analysis.

This study was approved by the ethics committee of Beth Israel Deaconess Medical Center, and we confirm that all experiments were performed in accordance with relevant guidelines and regulations. All participants provided written informed consent prior to participating in the study.

Data from healthy participants

HR data for young healthy controls were obtained from an open dataset, which consists of 202 healthy individuals from the Intercity Digital Electrocardiogram Alliance (IDEAL) database.[29] Twenty-four-hour Holter recordings were acquired using the SpaceLab-Burdick digital Holter recorder (SpaceLab-Burdick, Inc., Deerfield, WI). In the original study, healthy individuals were eligible for enrollment based on the following inclusion criteria: (1) normal physical examination, (2) no medication use, (3) sinus rhythm in 12-lead ECG without any suspicious abnormalities (eg, signs of ventricular hypertrophy, inverted T-wave, intraventricular conduction disturbances), and (3) normal echo and normal ECG exercise testing in the presence of suspicious ECG changes. Exclusion criteria included (1) cardiovascular disease, history of cardiovascular disorders (including stroke, transient ischemic attack, peripherical vascular disease), or cardiovascular-related syndrome (chest pain, palpitation, syncope); (2) history of high BP; (3) other chronic illness (eg, diabetes, asthma, COPD, etc.); and (4) pregnancy. We categorized all participants aged 50 years and over into the older healthy control group to be consistent with the age range in the COPD/heart failure cohort. Other participants aged 20 to 49 years were categorized into the younger healthy control group. We excluded 2 individuals due to their use of a beta-blocker medication and 22 individuals under 20 years of age. The sampling rate of this dataset was 200 Hz. The dataset was in the Telemetric and Holter ECG Warehouse, hosted by University of Rochester Medical Center.[29] The use of this dataset was for a secondary analysis with only publicly available de-identified data. It did not involve a research protocol requiring approval by an institutional review board or ethics committee.

Heart rate variability

In the time domain, mean of NN intervals (mean NN), standard deviation (SD) of NN (SDNN), the root mean square of successive differences between normal heartbeats (RMSSD), SD of successive differences (SDSD), and percentage of adjacent NN intervals that differ from each other by > 20 ms (pNN20) and > 50 ms (pNN50) were included. In the frequency domain, NN intervals were interpolated and resampled to 4 Hz for HRV frequency domain analysis. The Welch protocol (with a Hamming window applied to each 5-minute segment and moving window approach with 50% overlap) was used for spectral analysis. Frequency domain indices included total power (TP), very low frequency (VLF), low frequency (LF), and high frequency (HF). HRV power spectrum measurements were also log-transformed to normalize their distribution for analysis (LnLF and LnHF). Normalized percentage of LF and HF was defined as nLF = LF/(LF + HF) and nHF = HF/(LF + HF), respectively. LF/HF was defined as the ratio of LF over HF.

Multiscale entropy of HR dynamics

Multiscale entropy (MSE) is an increasingly used, entropy-based nonlinear measurement for the complexity of HR dynamics.[13,16–23] MSE applies Sample Entropy (SampEn) analysis to measure the degree of irregularity of the time series, and SampEn requires the time series being studied to be stationary.[13,14,16] Therefore, we applied MSE analyses using 2 approaches. First, we applied a moving window technique to the un-detrended raw data using 2-hour windows with 10-minute steps.[17] Then, the data were detrended using a commonly used technique, Empirical Mode Decomposition (EMD),[30] to remove the long-term overall trend and improve the stationarity of the time series and the accuracy of entropy calculation.[17] In this study, MSE analysis included 20 scales, and the mean of entropies on all 20 scales was calculated as a complexity index ($CI_{1\text{-}20}$).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corporation, Armonk, NY, USA). Available demographic characteristics from both datasets were limited to age, sex, height, and weight. Body mass index (BMI) was calculated for each participant. Categorical variables were tested using chi-square test. Continuous variables with normal distributions are reported as mean ± SD in tables and presented as mean ± standard error in figures. Group differences were tested by analysis of variance (ANOVA). If significant differences were found among groups, post hoc pairwise tests using least significant difference (LSD) were performed. Variables with nonnormal distributions are reported as medians with first and third quartiles (Q_1, Q_3), and group differences were tested by Kruskal-Wallis test.

To illustrate the day–night patterns in cardiopulmonary patients and healthy controls, we present the averaged results on a 24-hour scale from main indices in each domain (eg, HR, SDNN, TP, VLF, LF, HF, LF/HF; 12 data points in each hour) and original complexity index ($CI_{1\text{-}20}$; 6 data points in each hour). To compare the HR dynamic differences between day and night, we took two 8-hour windows as daytime (9 AM–5 PM) and nighttime (11 PM–7 AM), respectively. With the concept of 24-hour patterns commonly used in BP, we described the 24-hour patterns of HR outcomes as a dipping pattern (night < day), a nondipping pattern (no obvious decrease during the night), and a reverse dipping pattern (night > day). Day–night difference (marked with a "△") was defined as a daytime index minus the respective nighttime index. Both overall averaged 24-hour long-term HRV and day–night differences in HRV were compared on all time and frequency domain indices, as well as complexity indices ($CI_{1\text{-}20}$). We created regression models to understand day–night differences in the 2 most discriminative measures, LF/HF ratio and complexity index, and the impact of age, sex, and cardiopulmonary conditions (patients with COPD/heart failure vs healthy controls). P values < .05 indicate a significant difference.

RESULTS

Demographic characteristics

We included 16 patients with COPD and/or heart failure and 178 healthy control participants (n = 136 in the young group and n = 42 in the old group). By design, significant differences were expected in some demographic characteristics including age, BMI, BP, and medical history (**Table 1**). Among the 16 cardiopulmonary patients, 9 (56.3%) had COPD, 9 (56.3%) had heart failure, 2 (12.5%) had both COPD and heart failure, 13 (81.3%) had hypertension, 5 (31.3%) had diabetes, and 8 (50%) reported obstructive sleep apnea.

Twenty-four-hour HRV and overall complexity index

When comparing the 3 groups, significant differences were found in all long-term (overall, averaged 24-hour) HRV indices in time and frequency domains (**Table 2**), as well as complexity measured by both the original $CI_{1\text{-}20}$ and detrended $CI_{1\text{-}20}$ ($P < .001$). Post hoc comparisons revealed that young healthy controls had the highest variability and complexity levels while cardiopulmonary patients showed the lowest.

Day–night patterns of HR dynamics

The HRs from the 3 groups showed the same visual 24-hour patterns (dipping at night; **Figure 1A**), but the differences in △HR were not significant (**Table 3**). For LF/HF (**Figure 1G**), healthy controls had a significantly higher LF/HF ratio during the day compared with cardiopulmonary patients, but had a significant decrease during the night, and reached the lowest after midnight. LF/HF ratio was lower in the patient group during the day but started to increase in the early evening and remained higher than their daytime baseline during most of the night. Other HRV time and frequency domain measures also showed variable fluctuations. A significant increase in HF was observed in the younger healthy group but not in the other 2 groups (**Figure 1F**).

Interestingly, for complexity measures, the day–night patterns showed 3 distinct trends (**Figure 1H**). In the young healthy participants, complexity was high during the day and decreased during the night (dipping pattern). In older healthy participants, the 24-hour complexity curve remained relatively flat, showing no decrease during the night (nondipping pattern), and was overall lower than in the younger healthy group. The complexity was the lowest in cardiopulmonary patients compared with the healthy control groups, and there was an increase during the night compared with the day (reverse dipping pattern; **Figure 1H**).

Day–night differences in traditional and complexity-based metrics of HRV

When comparing the 3 groups, significant differences were observed in multiple conventional measures related to HRV including △RMSSD ($P = .005$), △SDSD ($P = .005$), and pNN50 ($P = .004$) in the time domain, and △HF ($P = .002$), △nLF ($P < .001$), △nHF ($P = .003$), and △LF/HF ($P < .001$) in the frequency domain (**Table 3**). For these indices where the 3-way comparison was significant, post hoc comparisons reveal significant differences between healthy younger participants vs healthy older participants, and between healthy younger participants vs cardiopulmonary patients. The differences between older healthy particpants vs older cardiopulmonary patients were only significant on △LF/HF (**Figure 2**). The regression

Table 1—Demographic characteristics.

	Younger Healthy (20–49 y, n = 136)	Older Healthy (≥ 50 y, n = 42)	Cardiopulmonary Patients (≥ 50 y, n = 16)	*P*
Age, y	34.5 ± 8.9	61.6 ± 9.1	68.4 ± 8.9	—
Male, n (%)	74 (54.4%)	16 (38.1%)	6 (37.5%)	.110
Race, White, n (%)	129 (94.9%)	37 (88.1%)	13 (81.3%)	.081
Height, cm	170.8 ± 10.5	166.1 ± 9	167 ± 9.7	.020
Weight, kg	70.6 ± 15.2	72.8 ± 15.3	90.8 ± 24.3	< .001
BMI, kg/m^2	24.1 ± 4.2	26.3 ± 5.1	32.4 ± 7.9	< .001
SBP, mmHg	114.7 ± 10.2	127.1 ± 14.8	132.3 ± 18.3	< .001
DBP, mmHg	74.8 ± 7.8	78.1 ± 5.9	71.2 ± 9	.006
COPD, n (%)	0	0	9 (56.3%)	—
Asthma, n (%)	0	0	7 (43.8%)	—
Heart failure, n (%)	0	0	9 (56.3%)	—
Hypertension, n (%)	0	0	12 (75.0%)	—
Diabetes, n (%)	0	0	5 (31.3%)	—
Depression, n (%)	0	0	5 (31.3%)	—
OSA, n (%)	NC	NC	8 (50%)	—

Values are mean ± SD unless otherwise indicated. The em dash "—" indicates that the variable was expected to be significantly different between groups by study design. BMI = body mass index, COPD = chronic obstructive pulmonary disease, DBP = diastolic blood pressure, NC = not clear, OSA = obstructive sleep apnea, SBP = systolic blood pressure.

Table 2—Twenty-four-hour HRV and complexity.

	Younger Healthy (20–49 y, n = 136)	Older Healthy (≥ 50 y, n = 42)	Cardiopulmonary Patients (≥ 50 y, n = 16)	*P*
Time domain				
NN (ms)	769.37 ± 67.00	786.78 ± 78.28	825.55 ± 118.14	.013
HR (beats/min)	80.91 ± 8.28	78.62 ± 8.54	75.34 ± 10.99	.027
SDNN (ms)	62.91 ± 15.57	45.53 ± 13.81	33.53 ± 13.88	< .001
RMSSD (ms)	30.94 ± 9.82	22.51 ± 9.96	22.74 ± 13.80	< .001
SDSD (ms)	30.98 ± 9.83	22.54 ± 9.97	22.77 ± 13.81	< .001
pNN20 (%)	27.29 (22.20, 30.76)	20.93 (17.84, 26.76)	19.47 (12.20, 28.17)	< .001
pNN50 (%)	9.84 (6.21, 14.14)	4.18 (2.97, 10.72)	5.05 (1.33, 11.91)	< .001
Frequency domain				
TP (ms^2)	6,176.5 (4,155.01, 8,136.64)	2,418.63 (1,558.46, 3,832.53)	1,834.87 (579.33, 2,663.3)	< .001
VLF (ms^2)	2,599.38 (1,718.85, 3,574.31)	1,305.49 (812.36, 2,026.56)	759.62 (359.7, 1349.18)	< .001
LF (ms^2)	2,467.87 (1,631.96, 3,369.00)	784.7 (449.39, 1,351.20)	510.64 (123.81, 631.80)	< .001
HF (ms^2)	876.92 (494.70, 1389.61)	303.93 (151.08, 506.52)	330.93 (114.16, 542.27)	< .001
nLF (nu)	74.76 (67.73, 80.60)	73.35 (62.59, 78.78)	56.92 (44.50, 60.57)	< .001
nHF (nu)	25.24 (19.40, 32.27)	26.65 (21.22, 37.41)	43.08 (39.43, 55.50)	< .001
LnLF (ms^2)	7.56 (7.18, 7.90)	6.4 (5.87, 6.90)	5.8 (4.40, 6.12)	< .001
LnHF (ms^2)	6.40 (5.75, 6.89)	5.52 (4.86, 5.89)	5.42 (4.44, 5.87)	< .001
LF/HF (nu)	4.15 (3.00, 5.82)	3.54 (2.53, 4.93)	1.93 (0.96, 2.25)	< .001
Complexity-based nonlinear analysis				
$CI_{1\text{-}20\text{-}original}$	1.37 ± 0.12	1.24 ± 0.12	1.01 ± 0.27	< .001
$CI_{1\text{-}20\text{-}detrended}$	1.46 ± 0.10	1.35 ± 0.11	1.12 ± 0.27	< .001

Values are mean ± SD unless otherwise indicated. $CI_{1\text{-}20}$ = complexity index calculated by multiscale entropy using 20 scales, HF = high frequency, HR = heart rate, HRV = heart rate variability, LF = low frequency, LF/HF = ratio of low-frequency and high-frequency power, LnHF = log-normal high frequency, LnLF = log-normal low frequency, nHF = normalized high frequency, nLF = normalized low frequency, NN = normal-to-normal heartbeat intervals, pNN20 = percentage of adjacent intervals that differ > 20 ms, pNN50 = percentage of adjacent intervals that differ > 50 ms, RMSSD = root mean square of successive differences between normal heartbeats, SDNN = standard deviation of NN intervals, TP = total power, VLF = very low frequency.

model showed that age (β = –0.033, 95% confidence interval [CI]: –0.057, –0.009; *P* = .008) was significantly correlated with △LF/HF but not the cardiopulmonary condition (patients with COPD/heart failure vs healthy controls: β = –1.371; 95% CI: –2.796, 0.054; *P* = .059). When sex was included in the regression model, age remained a significant modifier to △LF/HF (β = –0.032; 95% CI: –0.056, –0.007; *P* = .011), but not sex or cardiopulmonary condition. Inclusion of BMI in our models had a very small and statistically nonsignificant impact on △LF/HF (β = 0.028, *P* = .433, without sex in the model, or β = 0.026, *P* = .476, with sex in the model).

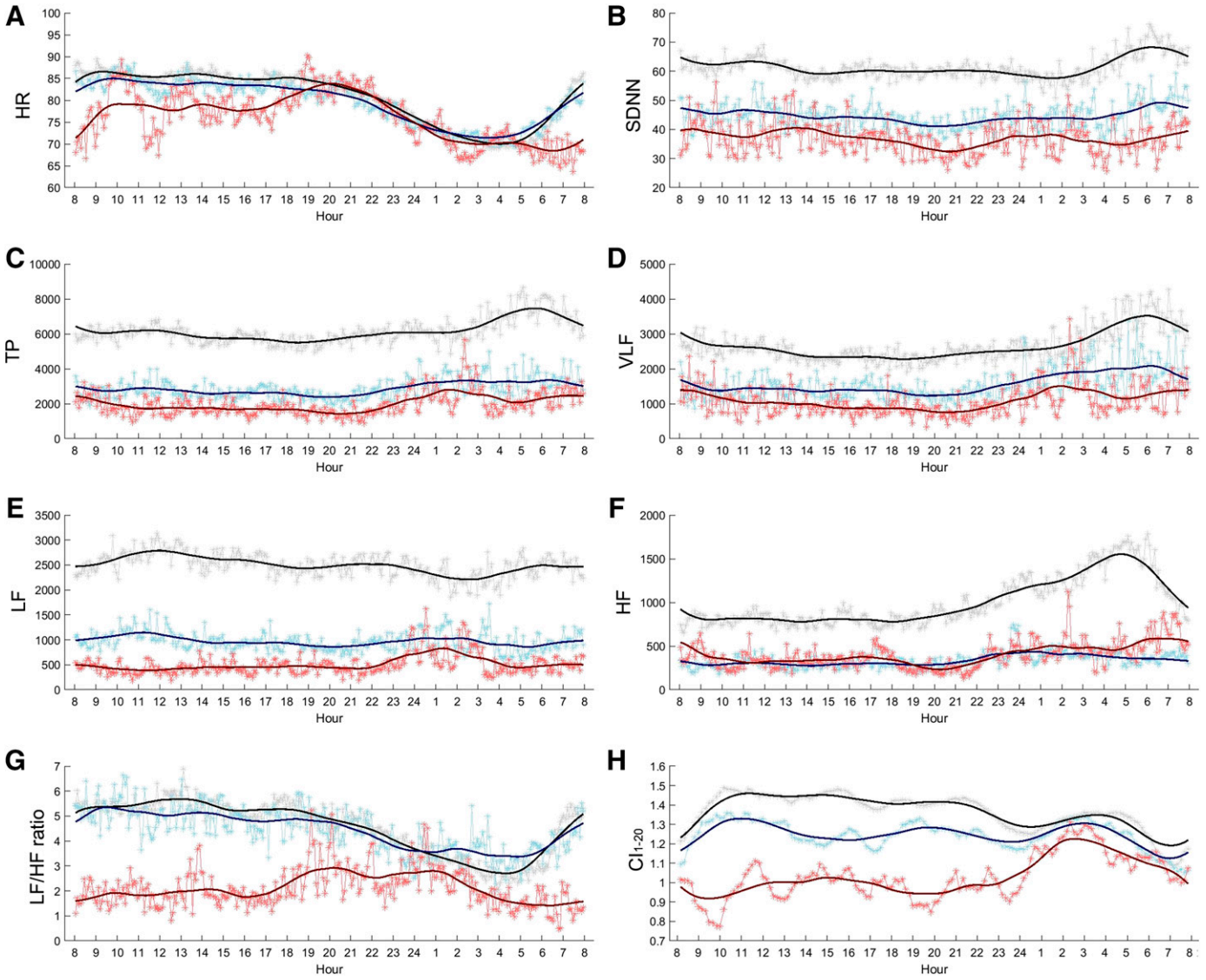
For complexity-based measures of HRV, both original $CI_{1\text{-}20}$ and detrended $CI_{1\text{-}20}$ showed significant differences among the 3 groups (*P* < .001), with younger healthy controls showing positive $\triangle CI_{1\text{-}20}$ on ($CI_{day} > CI_{night}$) and older healthy controls showing a smaller positive $\triangle CI_{1\text{-}20}$ ($CI_{day} > CI_{night}$). Cardiopulmonary patients exhibited a negative $\triangle CI_{1\text{-}20}$, indicating a significant increase in complexity during the night ($CI_{day} < CI_{night}$). Post hoc comparisons also reveal significant differences on each pairwise comparison of $\triangle CI_{1\text{-}20}$, including the differences between older healthy participants vs older cardiopulmonary patients (**Figure 2**).

The regression model showed that age (β = –0.006; 95% CI: –0.008, –0.003; *P* < .001) and cardiopulmonary condition (patients with COPD/heart failure vs healthy controls: β = –0.183; 95% CI: –0.328, –0.038; *P* = .014) were significantly correlated with day–night differences in complexity index. When sex was included in the model, the effects of age (β = –0.005; 95% CI: –0.008, –0.003; *P* < .001) and cardiopulmonary condition (β = –0.182; 95% CI: –0.327, –0.037; *P* = .014) on $\triangle CI_{1\text{-}20}$ remained relatively unchanged. Although BMI had some effect on $\triangle CI_{1\text{-}20}$ (β = –0.008, *P* = .040, without sex in the model, or β = –0.008, *P* = .026, with sex in the model), inclusion of BMI did not show effects on complexity index estimates (eg, the estimate of age remained the same and the estimate of cardiopulmonary condition was changed < 3.8%).

DISCUSSION

By examining the profiles of HR dynamics, we found significant differences among the 3 groups (patients with COPD and/or heart failure, healthy younger and healthy older controls)

Figure 1—(A–H) Twenty-four-hour rhythm of HR dynamics.



In each panel, the x-axis shows the natural clock time of a 24-hour cycle. Each dot represents the mean of the measure in each group at each time point. HRV time and frequency domain analyses were based on 5-minute windows (12 data points presented in each hour). Complexity index was calculated by moving 2-hour windows with 10-minute steps (6 data points presented in each hour). Black: younger healthy adults; blue: older healthy adults; red: older cardiopulmonary patients. The 3 curves represent the diurnal patterns of each group by illustrating the overall trends of oscillations (curve fitting was done using local averages by moving windows). $CI_{1\text{-}20}$ = complexity index calculated by multiscale entropy using 20 scales, HF = high frequency, HR = heart rate, HRV = heart rate variability, LF = low frequency, LF/HF = ratio of low-frequency and high-frequency power, NN = normal-to-normal heartbeat intervals, SDNN = standard deviation of NN intervals, TP = total power, VLF = very low frequency.

in 24-hour long-term HRV indices as objective measures of diurnal rhythm. Our results suggest not only decreased HRV in aging patients and those with COPD/heart failure, which is in line with previous studies using averaged 24-hour HRV,[31,32] but also newly document decreased day–night differences in many of the HRV measures in these population groups, including complexity-based metrics. In addition, we report novel patterns of diurnal variations in HR dynamics in these populations.

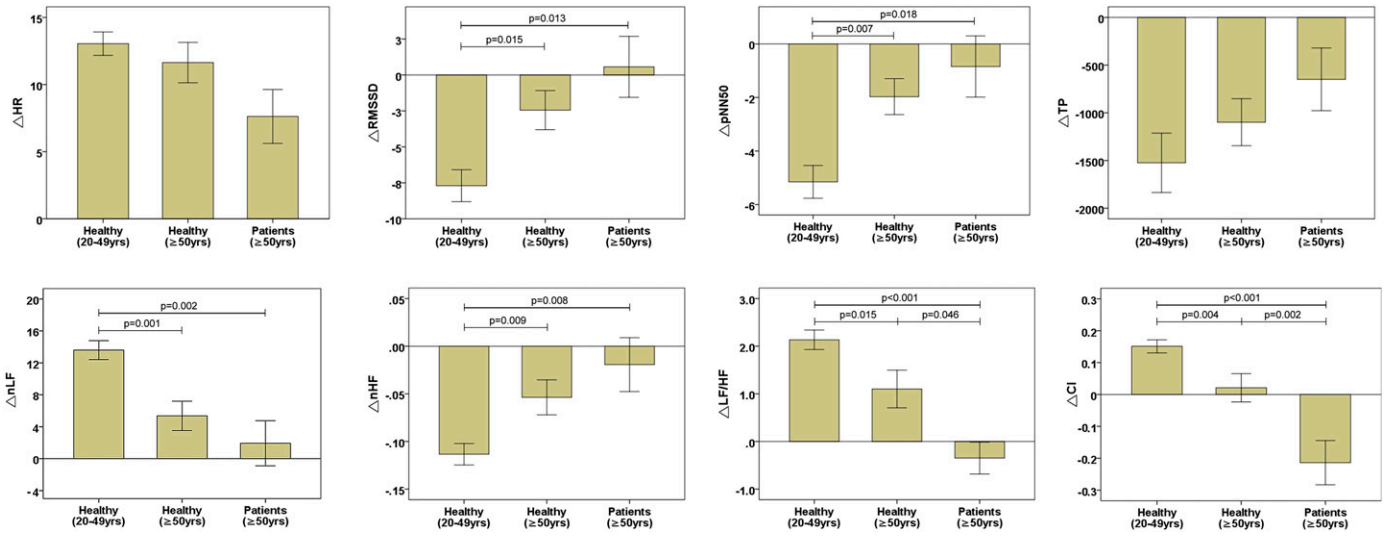
In COPD, there is a described time-of-day variation in symptoms, airway physiology, and airway inflammation,[33] which is worse in the night and early morning.[34] Patients with severe COPD exacerbations presenting to emergency departments between midnight to early morning are 3-fold more likely to necessitate intubation, a surrogate measure of case severity, than those presenting at other times.[35] Chronic heart failure and COPD frequently coexist, significantly reducing the patient's quality of life and increasing morbidity, disability, and mortality.[36–38] Patients with heart failure may experience orthopnea at night, and nocturnal symptoms and symptomatic sleep disturbance are common in these patients.[24] Despite this, the day–night differences in symptoms and severity may often go unnoticed in clinical management.[24,39,40] In fact, there is

Table 3—Day−night differences in HRV and complexity.

	Younger Healthy (20–49 y, n = 136)	Older Healthy (≥ 50 y, n = 42)	Cardiopulmonary Patients (≥ 50 y, n = 16)	*P*
Time domain				
△NN (ms)	−104.26 ± 171.78	−113.89 ± 82.09	−77.4 ± 70.69	.743
△HR (beats/min)	13.04 ± 9.99	11.64 ± 9.39	7.62 ± 7.52	.125
△SDNN (ms)	−5.52 ± 21.03	−5.82 ± 12.34	0.45 ± 9.22	.515
△RMSSD (ms)	−7.7 ± 12.82	−2.44 ± 8.49	0.56 ± 7.93	.005
△SDSD (ms)	−7.72 ± 12.84	−2.45 ± 8.5	0.56 ± 7.94	.005
△pNN20 (%)	−5.59 ± 8.63	−4.23 ± 4.47	−1.36 ± 6.91	.128
△pNN50 (%)	−5.15 ± 7.06	−1.97 ± 4.20	−0.84 ± 4.28	.004
Frequency domain				
△TP (ms^2)	−1,523.99 ± 3,586.23	−1,098.6 ± 1,538.59	−649.33 ± 1,230.91	.511
△VLF (ms^2)	−868.3 ± 1,778.85	−848.14 ± 990.22	−397.23 ± 650.44	.571
△LF (ms^2)	−36.79 ± 1,332.65	−123.45 ± 632.72	−141.45 ± 510.86	.891
△HF (ms^2)	−618.9 ± 1,002.32	−127.01 ± 217.76	−110.64 ± 282.06	.002
△nLF (nu)	13.60 ± 13.64	5.37 ± 11.46	1.93 ± 10.58	< .001
△nHF (nu)	−11.34 ± 12.95	−5.37 ± 11.46	−1.93 ± 10.58	.003
△LnLF (ms^2)	0.2 ± 1.28	−0.1 ± 0.51	−0.09 ± 0.65	.281
△LnHF (ms^2)	−0.46 ± 1.36	−0.39 ± 0.57	−0.15 ± 0.68	.638
△LF/HF (nu)	2.13 ± 2.35	1.1 ± 2.47	−0.35 ± 1.25	< .001
Complexity-based nonlinear analysis				
$CI_{1\text{-}20\text{-}original}$	0.15 ± 0.24	0.02 ± 0.28	−0.21 ± 0.27	< .001
$CI_{1\text{-}20\text{-}detrended}$	0.14 ± 0.21	0.02 ± 0.24	−0.16 ± 0.29	< .001

Values are mean ± SD unless otherwise indicated. $CI_{1\text{-}20}$ = complexity index calculated by multiscale entropy using 20 scales, HF = high frequency, HR = heart rate, HRV = heart rate variability, LF = low frequency, LF/HF = ratio of low-frequency and high-frequency power, LnHF = log-normal high frequency, LnLF = log-normal low frequency, nHF = normalized high frequency, nLF = normalized low frequency, NN = normal-to-normal heartbeat intervals, pNN20 = percentage of adjacent intervals that differ > 20 ms, pNN50 = percentage of adjacent intervals that differ > 50 ms, RMSSD = root mean square of successive differences between normal heartbeats, SDNN = standard deviation of NN intervals, TP = total power, VLF = very low frequency.

Figure 2—Day–night differences in HR dynamics.



Bar graphs present means and standard error of the mean. Pairwise comparisons were based on post hoc test using LSD test. CI = complexity index, HR = heart rate, LF/HF = ratio of low frequency and high frequency power, LSD = least significant difference, pNN50 = proportion of consecutive RR intervals that differ by > 50 ms, nHF = normalized high frequency, nLF = normalized low frequency, RMSSD = root mean square of successive differences between normal heartbeats, TP = total power.

empirical evidence that impaired circadian rhythm is one of the major influencing factors on autonomic function in individuals with COPD and heart failure.[41] In addition, abnormal sleep dynamics in patients with heart failure is 1 mechanism for the relative predominance of central sympathetic outflow over parasympathetic tone.[42] Patients with COPD and obstructive sleep apnea syndrome also present with marked sympathetic activation, and the presence of obstructive sleep apnea syndrome in patients with COPD has a negative impact on functional capacity, regardless of the severity of lung disease.[43]

Recent studies have also added to our knowledge on rhythms of the heart. Circadian, autonomic, and behavioral inputs interact to determine the temporal dynamics of cardiac electrophysiology and time-of-day susceptibility to arrhythmia.[44] Heart cells regulate their circadian rhythms through daily changes in the levels of ions inside the cell, which vary according to the daily demands of our lives, allowing the heart to better accommodate and sustain increased HR when we are active.[45]

Although HRV analysis has been widely applied in research, for both clinical and nonclinical purposes, long-term ECG recordings are not typically conducted in cardiopulmonary patients. Some existing studies have shown the value of 24-hour ECG monitoring in such patients that suggest potential applications of HRV measures, but there are very few data on the implications of day–night or circadian differences. For example, some studies have reported that HRV indices may have prognostic value in patients with acute exacerbation of COPD, and increase in normalized HF or decrease in LF/HF ratio can be used to support hospital admission despite 24-hours of treatment in the emergency department.[46] In 1 study, patients with COPD with arrhythmia were shown to exhibit circadian HRV disturbances, such as unchanged nighttime parasympathetic tone and disturbed sympathovagal balance in favor of the sympathetic system during the day, which may explain the increased frequency of arrhythmia.[47] In patients with heart failure, depressed HRV on 24-hour ambulatory ECG monitoring has been shown to be an independent risk factor for a poor prognosis.[48] Decreased VLF power of nighttime HRV below 0.04 Hz, high pulmonary wedge pressure, and low left ventricular ejection fraction are independently related to death in progressive pump failure, while the reduction in LF power and increased left ventricular end-systolic diameter have been linked to sudden mortality.[49]

In addition to the value of 24-hour averaged measures of HRV, our results showed altered diurnal variations in the HR dynamics in the cardiopulmonary patient group compared with the healthy controls. The differences between older healthy controls and cardiopulmonary patients were most pronounced in $\triangle CI_{1\text{-}20}$, suggesting that the MSE complexity index we used may be especially informative, and thus serve as a complementary metric to traditional HRV measures for distinguishing HR dynamics among diseased and healthy populations. Compared with conventional time and frequency domain HRV measures, nonlinear analysis including complexity index derived from MSE has been previously reported to be more sensitive in distinguishing autonomic abnormalities caused by metabolic syndrome.[17] Entropy-based measures are particularly well suited for characterizing complex nonlinear cardiovascular accommodative responses. The MSE-based complexity index has also been shown to be more informative than traditional HRV metrics in characterizing long-term response to exercise.[18] In our analysis, HR complexity was the highest in the young healthy group and lowest in the older cardiopulmonary patient group. Compared with younger and older healthy participants who showed a dipping pattern and a nondipping (or reduced, less apparent dipping) pattern of HR dynamics, respectively, cardiopulmonary patients had a reverse dipping pattern, which suggests abnormal exertion in the cardiopulmonary system during the night.

Since the early papers where MSE was first proposed as a metric for cardiorespiratory health, the notion that decreased complexity is associated with aging or pathological conditions has become well accepted.[13–15,17,19] However, we propose that this characterization is likely to be too simplified and incomplete. In fact, the current study has demonstrated that complexity level fluctuates throughout the day and there are large day–night differences in healthy individuals, which are blunted in individuals with cardiopulmonary pathology. This loss of differentiation in the complexity of sleep/wake dynamics in cardiopulmonary patients may be a useful new index of reduced adaptive capacity.[14]

Limitations and future research

There are limitations to the current study. First, it represents a secondary analysis using existing datasets that were limited by available data (ie, disease populations to study, small and unequal sample sizes, differential age groups, limited information on daily activity and specific sleep times). Given the characteristics of our groups, and the cross-sectional, observational nature of our data, there may be other explanations beyond the healthy/disease or young/old between-group differences we describe. Future studies might consider a larger spectrum of patient populations, such as patients with sleep disorders due to known altered autonomic activity at night. The 24-hour rhythm is thought to be driven by the sleep-wake/rest-activity cycle as well as by endogenous circadian rhythmicity.[12] Future studies in individuals with different levels of daytime activity, daytime stress levels, and sleep-wake cycles are also encouraged. Studies targeting the underlying mechanisms are also encouraged. Second, we are aware of the impact of respiration on HRV indices and we believe that the incorporation of respiration data, particularly in cardiopulmonary patients, would have informed our findings. Nonetheless, the differences in respiration rates are minimized among the groups with long-term 24-hour data and spontaneous breathing; thus, our analyses are still valid. In order to further inform neurophysiological mechanisms, future analyses should also consider changes in brain dynamics (eg, quantitative electroencephalogram analyses, electroencephalogram patterns during presleep wakefulness stage using spectral analysis or complexity analysis) or other physiological signals that may inform sleep quality/patterns or the role of sleep in HR oscillations. Our results (eg, **Figure 1H**) also suggest that potential short-term (< 24-hour) periodical oscillations, or ultradian rhythms, may be a worthy area of future research. Since ambulatory ECG devices and HR monitors are readily available

and feasible for home settings even during sleep, we would encourage further study using wearable sensors to collect long-term HR data and including complexity measures in addition to conventional HRV indices.

To our knowledge, this is the first study to compare 24-hour patterns of complete HRV measures among different group of individuals, and to use day–night differences as outcomes to compare groups with different age and health conditions. Although our analyses have some important limitations, this exploratory analysis may inform and inspire future investigation. Future studies are encouraged to better understand the circadian and/or sleep-wake patterns contributing to 24-hour variation in complexity metrics—for example, studies with a circadian protocol (eg, constant routine) to distinguish between activity-sleep–induced changes. In addition, future studies are encouraged to collect comprehensive information, such as exercise/physical activity and screen for diseases including sleep disorders, history/severity/treatment of sleep apnea, recent travel or shift work, meal schedule, and sleep times of each individual.

CONCLUSIONS

Heart rate dynamics in cardiopulmonary patients with COPD and heart failure not only exhibit decreased HRV but also show day–night differences and altered patterns in the diurnal rhythm not previously described. In addition to the notion that complexity decreases with aging and pathological conditions, the patterns of day–night differences in complexity also decreased, or even reversed, with aging and pathological cardiopulmonary conditions. Specifically, in our analysis, the day–night differences were significantly visible in younger healthy adults, decreased in older healthy adults, and reversed in older patients. Measures of 24-hour HR dynamics may be useful indices of reduced adaptive capacity in cardiopulmonary patients. Further research is needed to better understand the circadian profiles of traditional HRV as well as nonlinear complexity measures among patients with worsened physiological symptoms during sleep, and to explore clinical/research applications of these patterns in other chronic disease populations.

ABBREVIATIONS

BMI, body mass index
BP, blood pressure
CI, confidence interval
$CI_{1\text{-}20}$, complexity index calculated by multiscale entropy using 20 scales
COPD, chronic obstructive pulmonary disease
ECG, electrocardiogram
HF, high frequency
HR, heart rate
HRV, heart rate variability
LF, low frequency
LF/HF, ratio of low frequency and high frequency power
MSE, multiscale entropy
nHF, normalized high frequency
nLF, normalized low frequency
NN, normal-to-normal heartbeat intervals
RMSSD, root mean square of successive differences between normal heartbeats
SD, standard deviation
SDNN, the standard deviation of NN intervals
TP, total power
VLF, very low frequency

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