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Could Heart Rate Variability Serve as a Prognostic Factor in Patients with Pulmonary Hypertension? A Single-center Pilot Study

Kalp Hızı Değişkenliği, Pulmoner Hipertansiyon Hastalarında Bir Prognostik Gösterge Olarak Kullanılabilir Mi? Tek Merkezli Bir Pilot Çalışma

ABSTRACT

Objective: Heart rate variability (HRV), which is defined as cyclic changes in sinus rate with time, is used as a measure of cardiac autonomic tone. Our aim was to determine the impact of HRV on short-term prognosis in pulmonary hypertension (PH).

Methods: We enrolled 64 PH patients and 69 healthy subjects (control group). Patients were evaluated by Holter-ECG, echocardiography, and laboratory tests. 24-h Holter-ECG monitoring was used for HRV. The development of adverse events (right heart failure, hospitalization, syncope, and death) during the 6-month follow-up was evaluated in PH group.

Results: PH group (39 ± 16 years, 37.5% males) comprised of 16 patients with idiopathic pulmonary arterial hypertension (PAH) (25%), 36 patients with PAH associated with congenital heart disease (56.3%), 3 PAH associated with connective tissue disease (4.7%), 1 with portopulmonary (1.6%), and 8 chronic thromboembolic PH (12.5%). The time-dependent (standard deviation of all NN intervals for a selected time period [SDNN], standard deviation of the 5-min mean R–R intervals tabulated over an entire day [SDANN], SDNN Index, and Triangular Index) and frequency-dependent HRV indices (low frequency, high-frequency power, and total power,) were significantly reduced in those with PH. Functional class was negatively associated with SDNN, SDANN, SDNN Index, and Triangular Index. Adverse events developed in 25% of the patients during the 6-month follow-up period (200 ± 92 days) (7 patients had right-heart failure, 5 syncope, 12 patients were hospitalized, and 9 had died). All the time and frequency-dependent indices significantly associated with adverse events. Mortality correlated with SDNN (rS = −0.354, *P* = 0.005), SDANN (rS = −0.368, *P* = 0.004), SDNN Index (rS = −0.257, *P* = 0.045), Triangular Index (rS = −0.310, *P* = 0.014), and VLF (rS = −0.265, *P* = 0.039).

Conclusion: HRV is significantly depressed in patients with PH and is associated with the clinical status. HRV indices might predict clinical deterioration, adverse events, and mortality for 6 months. Non-invasive assessment of HRV through Holter-ECG may be a valuable and practical tool in risk stratification of patients with PH for short-term outcomes.

Keywords: Adverse events, heart rate variability, Holter ECG, mortality, prognosis, pulmonary hypertension

ÖZET

Amaç: Sinüs hızının zaman içindeki döngüsel değişimleri olarak tanımlanan kalp hızı değişikliği (KHD), kardiyak otonomik tonusun bir ölçüsü ve göstergesi olarak kullanılır. Bu çalışmanın amacı pulmoner hipertansiyonda (PH) KHD'nin prognostik değerini belirlemektir.

Yöntemler: Sinüs ritminde olan 64 PH hastası ve 69 sağlıklı birey kontrol grubu) çalışmaya alındı. Tüm hastalara değerlendirme için EKG, transtorasik-ekokardiyografi ve biyokimya testleri yapıldı. KHD 24 saatlik Holter-EKG monitorizasyonu ile elde edildi. PH grubu 6 aylık takipte yan etki (sağ kalp yetersizliği, senkop, hastaneye yatış ve ölüm) gelişimi açısından değerlendirildi.

Bulgular: PH grubu (39 ± 16 yaş, %37.5 erkek) idiyopatik pulmoner arter hipertansiyonlu (İPAH) 16 hasta (%25), konjenital kalp hastalığı ilişkili PAH olan 36 hasta (%56.3), 3 hasta (%4.7) bağ dokusu hastalığı PAH, 1 hasta (%1.6) porto-pulmoner ve 8 (%12.5) kronik tromboembolik PH hastalarından oluşuyordu. Zamana bağlı KHD parametreleri (SDNN, SDANN, SDNN İndeksi ve Triangular-İndeksi) ve frekansa bağlı parametreler (toplam güç, LF, HF gücü) PH'da anlamlı olarak düşüktü. Fonksiyonel sınıf SDNN, SDANN, SDNN indeksi ve triangular indeksi ile negatif korelasyon gösterdi. Takip süresi boyunca (200 ± 92 gün) hastaların %25'inde advers olay gelişti [7 (%11) sağ kalp yetersizliği, 5 (%8) senkop, 12 (%19) hastane yatışı ve 9 (%14)

ORIGINAL ARTICLE
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ölüm]. Zamana ve frekansa bağlı KHD parametreleri advers olay gelişen veya ölen hastalarda önemli ölçüde düşüktü. Tüm zaman ve frekansa bağlı parametreler olumsuz olaylarla anlamlı şekilde ilişkili bulundu. SDNN (rS = −0.354, *P* = 0.005), SDANN (rS = −0.368, *P* = 0.004), SDNN İndeks (rS = −0.257, *P* = 0.045), Triangular İndeks (rS = −0.310, *P* = 0.014) ve VLF (rS = −0.265, *P* = 0.039).

Sonuç: PH'li hastalarda KHD belirgin şekilde baskılanmıştır ve hastaların klinik durumu ile ilişkilidir. KHD'nin hem zaman, hem de frekansla ilgili parametreleri 6 aylık takipte klinik kötüleşme, advers olaylar ve mortaliteyi tahmin edebilir. Holter-EKG ile KHD'nin non-invazif ölçümü, kısa dönem için PH hastalarının risk sınıflandırmasında yararlı, uygulanabilir bir araç olabilir.

Anahtar Kelimeler: Yan etkiler, kalp hızı değişkenliği, Holter EKG, pulmoner hipertansiyon, mortalite, prognoz

Despite the major treatment advances, pulmonary hypertension (PH) remains a rapidly progressive disorder leading to right ventricular (RV) failure with high mortality.[1,2] As early specific therapy of pulmonary arterial hypertension (PAH) has been shown to be lifesaving,[3] early determination of disease severity, progression, and prognosis is of paramount importance in clinical decision-making. At present, clinical evaluation and risk stratification in PH patients are based on the assessment of right heart functions through hemodynamics, echocardiography, exercise capacity, and/or neurohormonal markers.[4]

Heart rate variability (HRV) is defined as cyclic changes in the sinus rate over time and provides information regarding sympathetic-parasympathetic balance.[5] Therefore, HRV serves as a measure of cardiac autonomic tone. Abnormalities in autonomic tone are potentially linked to worse prognosis including life-threatening ventricular arrhythmias and sudden cardiac death.[6] Decreased HRV, indicating altered autonomic tone, is associated with an impaired prognosis in individuals with left heart failure.[7,8] However, data regarding autonomic dysfunction in RV failure are scarce. Furthermore, autonomic tone alterations have been speculated to contribute to the pathogenesis of PH.[9,10] However, there is little data regarding the involvement of the autonomic nervous system in PH.[10-15] Our aim was to determine clinical significance and associations of HRV with clinical parameters in this patient group.

ABBREVIATIONS

6MWT	6-minute walk test
aPAH	Associated pulmonary arterial hypertension
CHD	Congenital heart disease
CTD	Connective tissue disease
CTEPH	Chronic thromboembolic pulmonary hypertension
FAC	Fractional area change
HF	High frequency
HR	Heart rate
HRV	Heart rate variability
LF	Low frequency
MSNA	Muscle sympathetic nerve activity
NYHA	NewYork Heart Association
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
PNN50	The proportion of differences in successive NN intervals >50 ms
RA	Right atrial
RMSSD	Square root of the mean of the sum of the squares of differences between adjacent R-R intervals
ROC	Receiver operator characteristic
RV	Right ventricular
SDANN	Standard deviation of the 5-min mean R-R intervals tabulated over an entire day
SDNN	Standard deviation of all NN intervals for a selected time period
TAPSE	Tricuspid annular plane systolic excursion
TDI	Tissue Doppler imaging
VLF	Very low frequency

Materials and Methods

We prospectively screened 81 consecutive patients with PAH for this study. All patients were either newly diagnosed or were previously known to have PH (group-1 PH) or chronic thromboembolic PH (CTEPH) (group-IV) and were under outpatient follow-up in the PAH center of the Ege University Medical School.[16] Patients fulfilling the following four criteria were included in this study: (1) Documented diagnosis of PAH confirmed by right heart catheterization,[2] (2) presence of normal sinus rhythm at the time of enrollment, (3) age between 18 and 75 years, and (4) the absence of any cardiac and/or systemic disease and medications that could interfere with the autonomic nervous system. Seventeen patients were excluded for the following reasons: A trial fibrillation (*n* = 9), diabetes mellitus (*n* = 2), hyperthyroidism (*n* = 1), inadequate Holter recordings (*n* = 4), and either unwillingness to provide or with drawal of informed consent (*n* = 1). The remaining 64 patients (40 femalesand 24 males) constituted the patient population. Synchronously screened 69 age and gender-matched asymptomatic healthy individuals (45 females and 24 males) served as the control group for the measurements of HRV. All the control subjects had no history of medical illness, exhibited normal physical examination with sinus rhythm, showed no abnormal laboratory findings, normal echocardiograms with normal pulmonary artery (PA) pressure, and none of them were taking any medication. Study protocol was approved by the Ege University's Review Board (Approval Number: 2010-11/15, Date: 02.11.2010) and written informed consent was obtained from all participants. Complete physical examination and detailed clinical history including duration of PH, symptoms quantified according to the New-York Heart Association (NYHA)/World Health Organization's classification, comorbidities, and the currently used drugs were obtained from all participants. Exercise capacity was assessed using the standard 6-minute walk distance (6MWD).[17] All study subjects underwent 24-h ambulatory Holter monitoring for the evaluation HRV and transthoracic echocardiography. PH patients were also divided into low, intermediate, and high risk, consistent with the ESC/ERS) three-strata risk stratification tool. All PH patients were followed for adverse events for 6 months.

Echocardiographic examinations were performed in accordance with the recommendations of the European Association of Cardiovascular Imaging.[18] All echocardiograms were analyzed offline by two independent blinded physicians (OM and MK).

The standard echocardiographic analysis encompassed M-mode, two-dimensional, Doppler flow assessments, and tissue Doppler imaging (TDI) measurements. In addition to standard left ventricular assessment, we performed a detailed evaluation of right heart dimensions and functions with regard to PH. Standard measures of global RV function included fractional area change (FAC) and the myocardial performance index (Tei index).[19-21] Longitudinal function of the RV was quantified using tricuspid annular plane systolic excursion (TAPSE). Tricuspid annular velocities were recorded with TDI. For the assessment of PH, tricuspid regurgitation velocity and systolic PA pressure were estimated. Right atrial (RA) pressure was estimated (four dichotomized values: 5, 10, 15, and 20 mmHg) based on the inferior vena cava diameter (normal value ≤ 21 mm) and its collapse with sniff (normal value >50%). The presence of indirect findings of PH including right-sided chamber dilatation, RV hypertrophy, paradoxical septal motion, increased pulmonary regurgitation, short acceleration time of the RV into the PA, pericardial effusion, and a dilated PA was also determined.

All participants underwent 24-h ambulatory electrocardiography (ECG) monitoring using 12-channel analog Holter recorders (DMS 300-3A, USA). Medications that could affect heart rate (HR) were discontinued for a period of at least 24–48 h, which aligned with the drugs' 3–5 half-life,before the Holter monitoring. Recordings were analyzed both automatically and manually on using the Holter analysis software of DMS CardioScan II (DMS Inc., USA) with analysis performed by the same cardiologist. Records with <18 h of analyzable ECG data, <100 000 recorded beats, and/or normal heart beats <85% of all the recorded beats were regarded as insufficient to evaluate the parameters of HRV,[5] and these patients were excluded.

The time-domain HRV indices included standard deviation of all NN intervals for a selected time period (SDNN), SD of the 5-min mean R–R intervals tabulated over an entire day (SDANN), SDNN index (the mean of the 5-min standard deviations of NN intervals calculated over 24 h), square root of the mean of the sum of the squares of differences between adjacent R–R intervals (RMSSD), and PNN50 (the proportion of differences in successive NN intervals >50 ms). The triangular index was calculated as the number of all NN intervals divided by the maximum of the density distribution (number of NN intervals in the modal bin).

Power spectral analysis was conductedusing a nonparametric method, the fast Fourier transformation, which is characterized by discrete peaks for several frequency components. Spectral analysis of HRV was obtained by summing the powers of each frequency band: Very low frequency (VLF) <0.04 Hz that is thought to be influenced by the thermoregulation of vasomotor tone; low frequency (LF) 0.04–0.15 Hz that is affected by the baroreceptor reflex and is thought to reflect sympathetic and parasympathetic tone; and high frequency (HF) 0.15–0.40 Hz that is influenced by respiratory frequency and thought to reflect parasympathetic tone. In all subjects, the LF/HF was calculated. LF and HF powers were expressed in normalized values (nu) (LFnu=LF/[Total power–VLF] × 100, HFnu=HF/[Total power–VLF] × 100). The frequency domain parameters were also analyzed for both daytime (from 06:00 to 22:00) and nighttime (from 22:00 to 06:00). In case of a significant change between the day or nighttime, timings were set according to the individual diaries of the participants.

At the end of the 6-month follow-up period (5.9 ± 0.9 months), clinical status was assessed. The evaluated clinical parameters included functional class, exercise capacity assessed by the 6MWD, and adverse events including clinical worsening, syncope, hospitalization for right-sided heart failure, lung transplantation, atrial septostomy, cardiovascular, and all-cause death. Clinical worsening of PH was defined as by the addition of new PAH therapies or dose increases in previously stable PAH therapy. Syncope was defined as a transient loss of consciousness and postural tone characterized by rapid onset, short duration due to an acute fall in cardiac output.

Hospital admission for PH was defined as any admission in which the primary diagnosis was either (1) decompensated right heart failure or (2) PH requiring intensified therapy. Evidence of clinical right heart failure was established ifa patient exhibited any of the following clinical signs: (1) Peripheral edema (≥1+), (2) jugular venous pressure >4 cm above the sternal angle, (3) initiation or increase in a diuretic for heart failure, or (4) development of ascites. Cardiovascular death was accepted if (1) sudden death or (2) death preceded by: (a) cardiogenic shock (hypotension resulting in a failure to maintain normal renal or cerebral function for >15 min before death) or (b) heart failure symptoms or signs requiring intravenous therapy or oxygen in the hospital or confinement to bed, in the absence of underlying causes such as systemic infection or alternative causes of death. Other deaths were considered as non-cardiovascular deaths.

All statistical analysis was performed through SPSS for Windows Version 25.0. Discrete variables are presented as percentages and continuous variables as mean ± SD or median (min-max). Normality of numerical variables was examined by Kolmogorov-Smirnov ($n \geq 50$) test. A $P < 0.05$ (two-sided) was considered as statistically significant. Comparisons between groups were made by t-test or by Mann–Whitney U-test. Discrete variables were compared by Fisher's exact test or by Chi-square analysis, as appropriate. Correlation analyses were performed to identify factors associated with mortality and total adverse events using Pearson correlation testing (or Spearman correlation test when the data were not normally distributed or had ordered categories—coefficient rS). Kruskal–Wallis test is used for the comparison of the numeric variables of the groups; in case of significance, Dunn test with Bonferroni correction is used. The effects of independent variables on mortality and total adverse events were examined by univariate Cox regression. Receiver operator characteristic (ROC) curve analyses were performed to identify the optimal cutoff values of the HRV variables for predicting the development of mortality and total adverse events during follow-up period only in the PH population. The estimated minimal sample size of 64 was necessary for each group to provide a power of 0.8 with a statistical significance level of 0.05.

Results

Of the initially screened 81 consecutive patients, 64 (40 females, aged 39 ± 16 years) were eligible for enrollment. Clinical characteristics of the enrolled study population are summarized in Table 1. Study population consisted of 16 patients with idiopathic

Table 1. Clinical Characteristics of the Patient Population (*n* = 64)	
Age (years)	39 ± 16
Gender (female/male)	40/24
Body mass index (kg/m^2)	25.14 ± 6.29
Subgroups of PH, *n* (%)	
Idiopathic and heritable PAH	16 (25)
PAH associated with congenital heart disease	36 (56.3)
PAH associated with connective tissue disease	3 (4.7)
Portopulmonary PH	1 (1.6)
Chronic thromboembolic PH	8 (12.5)
WHO functional class, *n* (%)	
I	15 (23.4)
II	26 (40.6)
III	16 (25.0)
IV	7 (10.9)
PAH specific treatment, *n* (%)	
Endothelin receptor antagonists	47 (73.4)
Prostacyclin analogues	7 (10.9)
Phosphodiesterase type 5 inhibitors	10 (15.6)
Combination	10 (15.6)
BNP (pg/mL)	262 ± 341
6-minutewalk test	
Distance (m)	327 ± 140
Sa,O_2 rest %	89 ± 9
Sa,O_2 peak exercise %	80 ± 13

Continuous data are expressed as mean ± SD and categorical data as number (percentage). BNP, B-type Natriuretic peptide; NYHA, New York Heart Association; PAH, Pulmonary arterial hypertension; PH, Pulmonary hypertension.

PAH (iPAH), 40 patients with associated PAH (aPAH), and 8 patients with CTEPH. Cases of aPAH included 36 with congenital heart disease, 1 with porto-PH, and 3 with connective tissue disease. Both the incident (*n* = 7) and prevalent PH (*n* = 57) patients were enrolled. Majority of the PH patients were in NYHA functional class II. Majority of the PH patients (*n* = 26-40.6%) were in low risk meanwhile 20 (31.3%) in intermediate and 18 (28.1%) in high risk consistent with the ESC/ERS) three-strata risk stratification. Targeted treatment of PH included endothelin-1 receptor antagonists (*n* = 47), phosphodiesterase type 5 inhibitors (*n* = 10), and prostacyclin agonists (*n* = 7). Sixteen percent of the patients were receiving combination treatment. None of the patients was on parenteral therapy during the baseline evaluation.

Supplementary Table 1 provides a summary of the clinical and echocardiographic assessments of the PH population in comparison to the control subjects. As expected, all echocardiographic parameters related to right heart chambers were severely worsened in patients with PH. Pericardial effusion was present in 13 individuals (20.3%).

HRV variables are presented in Table 2. There were no significant differences regarding mean recording period and mean RR time between the groups. Time domain parameters including SDNN, SDANN, and SDNN index were significantly depressed in PH patients compared to the control group. RMSSD and pNN50 were also decreased in PH patients; however, differences between the groups did not reach statistical significance. Patients with PH exhibited a significant reduction in total power, total LF power, total HF power, and LFnu when compared to healthy controls. However, there were no significant differences between the groups in total VLF power, HFnu, and the LF/HF ratio.

Evaluation of the daytime and nighttime recordings revealed that both time and frequency domain indices were significantly depressed in PH group (Table 2). SDNN was also significantly lower both in daytime and nighttime recordings in PH patients (105 ± 44 vs. 124 ± 36, 0.009 for daytime and 92 ± 44 vs. 132 ± 48, <0.0001 for nighttime). Moreover, SDNN was increased in nighttime recordings compared to daytime values in control group; however, in PH group, nighttime SDNN was significantly decreased compared to daytime SDNN. Daytime and nighttime LF and HF powers were also significantly lower in PH patients than controls. In both groups, LF and HF powers were significantly increased at nighttime recordings; however, these increases were significantly more blunted in the PH patients.

Table 3 presents clinical prognostic parameters as per the current guidelines and HRV variables regarding the patients' functional class. Functional class showed correlations with BNP levels (r = 0.71, *P* = 0.002), 6MWD (r = −0.86, *P* = 0.0001), RV-FAC (r = −0.35, *P* = 0.007), and TAPSE (r = −0.44, *P* = 0.0001). However, there was no correlation between functional class and the RV Tei index. Regarding time-domain HRV indices, all were negatively associated with functional class except RMSSD and PN50 (SDNN [r = −0.51, *P* = 0.0001], SDANN index [r = −0.54, *P* = 0.0001], SDNN index [r = −0.40, *P* = 0.001], and triangular index [r = −0.49, *P* = 0.0001]). For frequency domain variables, functional class was negatively associated with total HF (r = −0.35, *P* = 0.004) and LF (r= −0.43, *P*=0.0001).

A total of 16 patients (25%) experienced adverse events during the follow-up period (220 ± 92 days). Adverse events were clinical worsening due to RV failure in 12 patients of whom 6 eventually died. Syncope was experienced by 5 patients (31.3%). Twelve patients clinically worsened and were hospitalized, and 7 of them were hospitalized more than once. The total number of deaths was 9 (14.1%). Causes of deaths are summarized in Supplementary Table 2. None of the PH patients in the low-risk strata has died, i.e., 22.2% of the deceased were in the moderate-risk category and 77.8% were in the high-risk category.

Table 4 provides a summary of the univariate correlation analysis between adverse events and death with clinical and HRV parameters. All the time and frequency domain HRV indices were negatively associated with adverse events. SDNN, SDANN, SDNN index, triangular index, and total VLF power were negatively correlated with mortality. For daytime and nighttime recordings, all the time and frequency domain indices were negatively associated with the development of all adverse events. Regarding mortality, there was a negative correlation with daytime-recorded SDNN and also nighttime-recorded SDNN, RMSSD, and pNN50 values. Mortality was also negatively associated with nighttime-recorded VLF, LF, and HF, as well as daytime-recorded VLF and LF. The univariate Cox regression analysis showed that not only SDNN (HR: 0.978 [95% CI: 0.960–0996] *P* = 0.016) but also both daytime SDNN (HR: 0.971 [95% CI: 0.950–0.993] *P* = 0.009) and nighttime SDNN (HR: 0.976 [95% CI: 0.955–0.997] *P* = 0.026) were significant predictors of all-cause mortality.

Table 2.Comparison of the Holter electrocardiographic parameters between groups

	PH group (n = 64)	Control group (n = 69)	*P*
Total recorded heart beat in Holter	111,582 ± 16528	110,127 ± 12949	0.572
Mean recording period (hr)	23.13 ± 1.19	23.22 ± 0.98	0.639
Mean RR (msec)	748.1 ± 106.3	749.1 ± 67.4	0.945
Mean heart rate (bpm)	85 ± 16	73 ± 9	**0.001**
Minimum heart rate (bpm)	53.9 ± 13.2	48.0 ± 6.5	**0.002**
Maximum heart rate (bpm)	134 ± 17	140 ± 11	**0.026**
Time-domain analysis			
SDNN (msec)	115 ± 52	149 ± 39	**0.001**
SDANN (msec)	105 ± 48	140 ± 38	**0.001**
SDNN Index (msec)	47 ± 22	58 ± 22	**0.003**
RMSSD (msec)	31 ± 15	36 ± 28	0.229
pNN50 (%)	8.75 ± 9.93	9.75 ± 9.12	0.544
Triangular Index	28 ± 14	40 ± 14	**0.001**
Daytime recordings			
SDNN	105 ± 44	124 ± 36	**0.009**
RMSSD	28 ± 14	31 ± 26	0.468
pNN50	7.48 ± 8.61	6.99 ± 7.83	0.732
Nighttime recordings			
SDNN	92 ± 44	132 ± 48	**0.001**
RMSSD	35 ± 21	44 ± 35	0.100
pNN50	12.7 ± 14.9	16.2 ± 14.5	0.175
Power spectral analysis			
Total power ($msec^2$)	2506 ± 2322	3428 ± 2219	**0.021**
VLF ($msec^2$)	1795 ± 1752	2188 ± 1295	0.142
LF ($msec^2$)	463 ± 433	833 ± 642	**0.001**
HF($msec^2$)	216 ± 247	360 ± 411	**0.017**
LF/HF	3.17 ± 2.31	3.56 ± 2.14	0.319
LFnu (%)	67 ± 13	72 ± 12	**0.015**
HFnu (%)	27.8 ± 11.7	27.0 ± 17.7	0.756
Daytime recordings			
VLF ($msec^2$)	1650 ± 1581	2070 ± 1163	0.083
LF ($msec^2$)	396 ± 376	777 ± 515	**0.001**
HF($msec^2$)	163 ± 179	271 ± 366	**0.037**
Nighttime recordings			
VLF ($msec^2$)	2069 ± 2249	2442 ± 1799	0.293
LF ($msec^2$)	581 ± 591	924.6 ± 923.9	**0.013**
HF($msec^2$)	310 ± 410	490.1 ± 515.6	**0.029**

PH, Pulmonary hypertension; SDNN, Standard deviation of all NN intervals for a selected time period; SDANN, Standard deviation of the 5-min mean R–R intervals tabulated over an entire day; SDNN index: The mean of the 5-min standard deviations of NN intervals calculated over 24 h; RMSSD, Square root of the mean of the sum of the squares of differences between adjacent R-R intervals; PNN50, The proportion of differences in successive NN intervals >50 ms, triangular index: number of all NN intervals divided by the maximum of the density distribution, VLF, Very low frequency; LF, Low frequency; HF, High frequency; LFnu = LF/(Total power–VLF) ×10, HFnu = HF/(Total power–VLF) × 100].Data are expressed as means±SD.

According to the ROC analysis (Figure 1a), the optimum cut-off values for adverse events in PH patients were as follows: 95 msec (sensitivity: 75%, specificity: 72%) for SDNN, 88 msec (sensitivity: 81%, specificity: 71%) for SADNN, 42 msec (sensitivity: 81%, specificity: 65%) for SDNN Index, 24 msec (sensitivity: 75%, specificity: 69%) for triangular index, and 1766 (sensitivity: 81%, specificity: 62%) for total power. ROC analysis also provided cut-off values for predicting mortality risk in PH patients, which were as follows: 90 msec (sensitivity: 78%, specificity: 70%) for SDNN, 77 msec (sensitivity: 78%, specificity: 71%) for SADNN, 39 msec (sensitivity: 67%, specificity: 62%) for SDNN index, and 23 msec (sensitivity: 78%, specificity: 68%) for triangular index (Figure 1b).

Table 3. Comparison of the Prognostic Markers and HRV Parameters with Regard to Functional Class

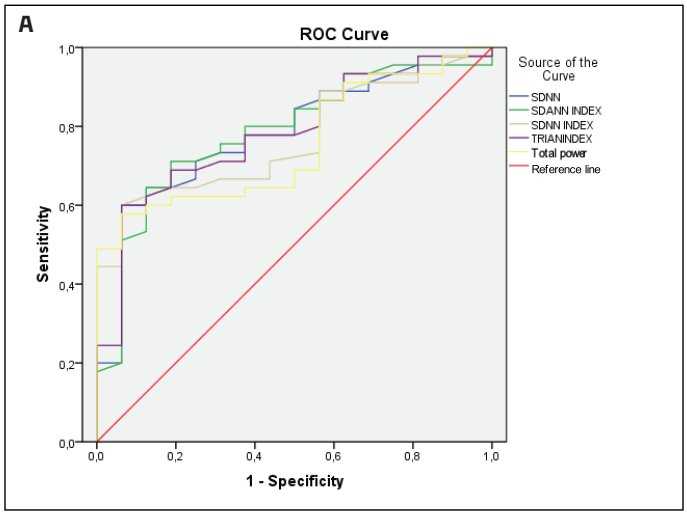
	FC-I	FC-II	FC-III	FC-IV	*P*
n	**15**	**26**	**16**	**7**	
BNP (pg/mL)	44.9 ± 51.6	139.9 ± 263.9	471.5 ± 321.2	703.1 ± 382.5	0.0001
6m-walk distance (m)	485 ± 59	354 ± 68	215 ± 99	114 ± 86	0.0001
TAPSE (mm)	19.7 ± 2.9	18.0 ± 3.5	15.7 ± 3.0	15.9 ± 2.6	0.005
RV-FAC (%)	36.7 ± 15.2	32.2 ± 10.7	24.7 ± 9.5	25.8 ± 7.0	0.00
RA-Area	21 ± 6	21 ± 8	29 ± 11	39 ± 8	0.001
HRV parameters					
SDNN (msn)	141.5 ± 36.9	129.4 ± 51.7	95.5 ± 45.4	52.6 ± 17.3	0.0001
SDANN (msn)	131.5 ± 34.7	118.6 ± 45.0	86.6 ± 43.6	41.3 ± 16.1	0.0001
SDNN İndex (msn)	52.5 ± 17.9	54.9 ± 24.5	36.3 ± 15.1	28.4 ± 13.4	0.005
Triangular Index	35.8 ± 12.6	30.8 ± 14.6	22.5 ± 12.1	13.9 ± 6.8	0.001
Total Power (msn^2)	2906 ± 2023	3450 ± 2830	1385 ± 1057	839 ± 791	0.002
Total VLF (msn^2)	2074 ± 1467	2496 ± 2197	983 ± 690	548 ± 615	0.001
Total LF (msn^2)	538 ± 377	634 ± 522	242 ± 220	195 ± 212	0.003
Total HF (msn^2)	253 ± 258	281 ± 278	139 ± 204	79 ± 66	0.02

FC, Functional class; BNP, B type natriuretic peptide; TAPSE, Tricuspid annular plane systolic excursion; RV, Right ventricular; MPI, Index of myocardial performance; FAC, Fractional area change; SDNN, Standard deviation of all NN intervals for a selected time period; SDANN, Standard deviation of the 5-min mean R-R intervals tabulated over an entire day; SDNN index, The mean of the 5-min standard deviations of NN intervals calculated over 24 h; RMSSD, Square root of the mean of the sum of the squares of differences between adjacent R-R intervals; PNN50, The proportion of differences in successive NN intervals >50 msec, triangular index; Number of all NN intervals divided by the maximum of the density distribution; VLF, Very low frequency; LF, Low frequency; Data are expressed as means ± SD.

Table 4. Relationship between Prognostic Indicators, HRV Indices,and all Events and Death

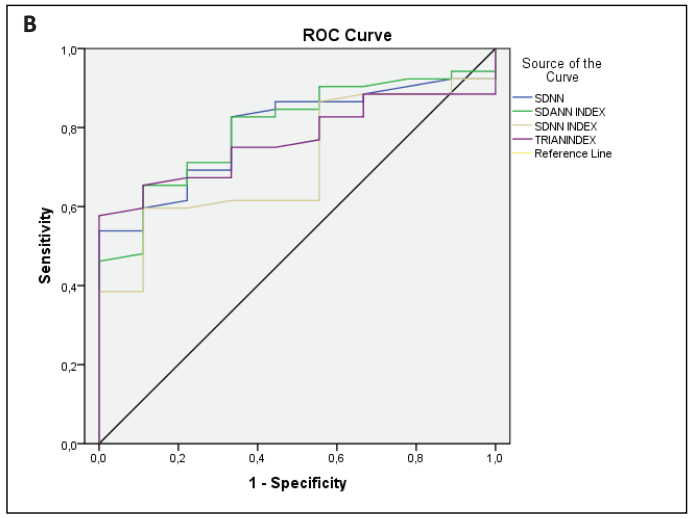
	All Adverse Events		Mortality	
	Rho	*P*	Rho	*P*
TAPSE (mm)	**−0.398**	**0.001**	−0.140	0.277
SPAP (mmHg)	**0.348**	**0.006**	**0.269**	**0.036**
RV MPI (msn)	0.106	0.428	0.043	0.75
RV FAC (%)	**−0.329**	**0.011**	−0.174	0.186
BNP (pg/ml)	**0.573**	**<0.0001**	**0.452**	**<0.0001**
Functional class	**0.641**	**<0.0001**	**0.444**	**<0.0001**
6-minute walking distance (m)	**−0.466**	**<0.0001**	**−0.302**	**0.018**
SDNN (msn)	**−0.419**	**0.001**	**−0.354**	**0.005**
SDANN (msn)	**−0.434**	**<0.0001**	**−0.368**	**0.004**
SDNN index (msn)	**−0.408**	**0.001**	**−0.257**	**0.045**
RMSSD (msn)	**−0.397**	**0.001**	−0.097	0.452
pNN50 (%)	**−0.360**	**0.004**	−0.117	0.366
Triangular index	**−0.409**	**0.001**	**−0.310**	**0.014**
Total power (msn^2)	**−0.387**	**0.002**	−0.247	0.055
Total VLF (msn^2)	**−0.394**	**0.002**	**−0.265**	**0.039**
Total LF (msn^2)	**−0.394**	**0.002**	−0.197	0.128
Total HF (msn^2)	**−0.377**	**0.003**	−0.087	0.507

PH, Pulmonary hypertension; RV, Right ventricular; TAPSE, Tricuspid annular plane systolic excursion;SPAP, Systolic pulmonary arterial pressure; FAC, Fractional area change; MPI, Index of myocardial performance; BNP, B type natriuretic peptide; FC, Functional class; HRV, Heart rate variability; SDNN, Standard deviation of all NN intervals for a selected time period; SDANN, Standard deviation of the 5-min mean R-R intervals tabulated over an entire day, SDNN index, The mean of the 5-min standard deviations of NN intervals calculated over 24 h; RMSSD, Square root of the mean of the sum of the squares of differences between adjacent R-R intervals; PNN50, The proportion of differences in successive NN intervals >50 ms, triangular index: number of all NN intervals divided by the maximum of the density distribution; VLF, Very low frequency; LF, Low frequency; HF, High frequency.



	AUC	P	95% CI
SDNN	0.782	0.001	0.659-0.907
SDANN	0.785	0.001	0.659-0.910
SDNN Index	0.767	0.002	0.649-0.886
Triangular Index	0.783	0.001	0.661-0.905
Total power	0.754	0.003	0.661-0.877

SDNN: standard deviation of all NN intervals for a selected time period, SDANN: standard deviation of the 5-min mean R–R intervals tabulated over an entire day, SDNN index : the mean of the 5-minute standard deviations of NN intervals calculated over 24 hours, triangular index: number of all NN intervals divided by the maximum of the density distribution, AUC, Area under the curve.



	AUC	P	95% CI
SDNN	0.793	0.005	0.670-0.915
SDANN	0.799	0.004	0.673-0.926
SDNN Index	0.709	0.046	0.561-0.858
Triangular Index	0.768	0.011	0.650-0.886

SDNN: standard deviation of all NN intervals for a selected time period, SDANN: standard deviation of the 5-min mean R–R intervals tabulated over an entire day, SDNN index : the mean of the 5-minute standard deviations of NN intervals calculated over 24 hours, triangular index: number of all NN intervals divided by the maximum of the density distribution, AUC, Area under the curve.

Figure 1. (A) ROC curves of heart rate variability indices associated with adverse event development in patients with pulmonary arterial hypertension. (B) ROC curve analysis showing mortality development ROC curves of heart rate variability indices associated with mortality in patients with pulmonary arterial hypertension.

Discussion

The findings from our single-center pilot study demonstrate a significant decrease in HRV among patients with PH and this decrease is associated with the clinical status of these patients. Both the time domain and power spectral indices were notably reduced in our PH patients compared to control subjects. While the exact triggering factor remains unknown, there is mounting evidence supporting the involvement of the autonomic nervous system in the pathogenesis of PAH and PH. Studies using microneurography to assess muscle sympathetic nerve activity (MSNA) have shown increased MSNA in patients with PAH.[12,15] Several studies have examined the role of autonomic system in PAH through assessments ofHRV, baroreflex sensitivity, and/or HR turbulence.[22,23] Nevertheless, there remains a scarcity of both animal and clinical studies that explore changes in HRV as an indicator of sympathovagal balance in PH.[24]

Animal models of PH induced by monocrotaline and hypoxia-induced PH consistently show reduced HRV, suggesting increased sympathetic activity.[11,13] Time domain HRV indices were significantly reduced in a small cohort of PAH patients (*n* = 9) compared to healthy controls (*n* = 20). However, Lammers et al.[25] did not show such a difference in time-domain HRV parameters of 47 retrospectively evaluated children with PAH. Frequency domain HRV evaluated by 9-min ECG recordings was decreased in 9 PAH patients in comparison with 9 healthy subjects. Notably, there was a significant relationship between the decrease in LF power and increase in MSNA with RA pressure, suggesting an increased sympathetic activity and RA tension affecting HRV.[12] In a larger cohort of 48 patients with PAH, the frequency-domain HRV parameters except for LF/HF power ratio were significantly reduced compared to healthy controls (*n* = 41). In addition, the progressive decrease in LF and HF powers significantly correlated with peak O2 consumption, a marker of exercise capacity.[26] Fauchieret al.[14] showed that both time and frequency-dependent HRV indices were low in a small group of 10 patients with isolated RV failure due to PAH compared to 15 healthy subjects. Yi et al.[27] also reported that both the time and frequency-domain HRV parameters were significantly reduced patients with iPAH (*n* = 26) compared to healthy controls (*n* = 51). Similarly, Can et al.[28] identified significantly decreased time and frequency domain indices in a prospective cohort of 38 patients with iPAH compared to controls (*n* = 20).

In our study, which included a larger cohort of 64 patients with PAH and CTEPH, we observed that both time- and power-domain HRV indices were linked to worsening clinical status, as reflected by functional class, in PH patients. Our findings align with the work of Velez-Roa et al.[12] who demonstrated a connection between increased MSNA and functional class in patients with PAH. MSNA was also inversely correlated with HR and prognostic factors such as pericardial effusion, 6MWD, and functional class with oxygen saturation in patients with PAH. Furthermore, increased oxygen saturation was associated with reduced MSNA, suggesting a potential link between sympathetic activity and chemoreflex mechanisms.[15] Lammers et al.[25] reported that functional class III patients had significantly lower values of SDNN, SDANN, and RMSSD compared to functional class

II. Their study also found correlations between HRV and 6MWD and HRV was predictive of transplantation and/or mortality over a 19-month follow-up. However, there was no correlation between RV functions and hemodynamic parameters and HRV indices. In contrast, our 6-month follow-up revealed significant associations between both time and frequency domain HRV indices and all adverse events, as well as mortality. An SDNN value of 95 msec was predictive of adverse event development with a sensitivity of 75% and specificity of 72% (Figure 1).

Given our small sample size, conducting a reliable multivariate analysis to betray collinearity for factors associated with RV failure/functions (such as functional class, BNP, and RA dynamics) was not feasible. Nevertheless, in the multivariate model, we constructed that BNP emerged as the most potent indicator of mortality (HR). It is challenging to ascertain whether reduced HRV in PAH results from isolated RV failure or indicates a causal relationship with autonomic dysfunction, and this lies beyond the scope of our study. It is evident that a single marker cannot fully capture the prognosis in patients with PAH which is why risk classification schemes are utilized. However, these risk scales are not yet entirely robust and may benefit from additional parameters[29] such as HRV. Therefore, future exploration of HRV in larger prospective, long-term studies is warranted to assess its potential value in enhancing these risk schemes.

To the best of knowledge, the results of the present study provided additional information of HRV indices in terms of daytime and nighttime recordings for the first time. All HRV indices measured at daytime or nighttime were significantly depressed in PH group. Moreover, SDNN was increased in nighttime recordings compared to daytime values in control group; however, in PH group, nighttime SDNN was significantly decreased compared to daytime SDNN. In both groups, LF and HF powers were significantly increased at nighttime recordings; however, these increases were significantly more blunted in the PH group. Moreover, all night and daytime recorded HRV indices correlated negatively with all adverse events. Meanwhile, mortality associated negatively with daytime-recorded SDNN and also nighttime-recorded SDNN, RMSSD, and pNN50 values. The suppressed increase of HRV indices at nighttime in the PH group is probably denoting a prominent autonomic dysfunction facing these patients to more adverse events at nighttime. However, daytime SDNN seemed to be more predictive of mortality and adverse events than the nighttime SDNN in the Cox regression analysis.

Besides small sample size, our study harbors the unique limitation of PH studies, consisting of PH patients with various etiologies. Analysis of these subgroups would probably yield different results, however, the number of patients in the subgroups are small to conduct further comparisons. The 6-month follow-up time is also relatively short and the lack of determination of the effect of the treatment, i.e., temporal changes of HRV might also regarded as a limitation. However, this study was not designed to evaluate the effect of treatment including mono or combination therapy on HRV indices. Moreover, this study included both the incident and prevalent PH patients as seen in both PH studies and registries, which is a result of the nature of this rare disease with multiple etiologies. The lack of right heart catheterization synchronously performed with Holter recordings could be considered as a limitation. Especially, the mean PA pressure has been shown to be correlated with autonomic nervous system disturbances in patients with PAH.[30]

Conclusion

Our study demonstrates a significant reduction in HRV in patients with PH indicating autonomic nervous system impairment and increased sympathetic activity. Both the time- and frequency-domain HRV indices serve as predictive factors for adverse events and mortality for 6 months in patients with PH. Therefore, the non-invasive assessment of HRV using Holter ECG may be suggested as a valuable and practical for risk stratification of patients with PH particularly for early outcome prediction. Further studies on larger cohorts are needed to clarify the prognostic value of HRV indices and their potential role in guiding treatment decisions.

Ethics Committee Approval: Ethics committee approval was obtained from Ethics Committee of Ege University (Approval Number: 2010-11/15, Date: 02.11.2010).

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.K., O.M.; Design – O.M., H.K.; Supervision – M.K.; Materials – O.M.; Data Collection and/or Processing – O.M.; Analysis and/or Interpretation – F.İ.; Literature Review – N.M.; Writing – O.M., S.S.; Critical Review – M.K., S.N.

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Supplementary Table 1. Baseline characteristics and echocardiographic findings of the groups

	PH group	Control group	*P*
Number of patients	64	69	
Age (years)	39 ± 16	39 ± 10	0.798
Gender (female/male)	40/24	45/24	0.857
Body mass index (kg/m^2)	25.14 ± 6.29	25.88 ± 4.63	0.446
Echocardiographic findings of the groups			
Interventricular septum (mm)	9.7 ± 1.6	8.7 ± 1.4	0.0001
Posterior wall (mm)	8.0 ± 1.5	7.6 ± 1.2	0.096
LV end-systolic diameter (mm)	24.7 ± 5.2	25.4 ± 4.3	0.377
LV end-diastolic diameter (mm)	40.3 ± 6.4	43.9 ± 4.9	0.0001
PA diameter (mm)	31.4 ± 9.9	18.7 ± 2.8	0.0001
RVend-diastolic volume (ml)	77.6 ± 46.2	32.9 ± 11	0.0001
RVend-systolic volume (ml)	49.3 ± 32.6	14.5 ± 6.2	0.0001
RA volume (ml)	99.5 ± 61.3	40.6 ± 14.9	0.0001
RA area (cm^2)	25.2 ± 10.1	14.8 ± 3.5	0.0001
RV FAC (%)	30.6 ± 11.9	44.2 ± 9.6	0.0001
Systolic PA pressure (mmHg)	83.2 ± 25.1	17.6 ± 3.4	0.0001
TAPSE (mm)	17.6 ± 3.5	25.1 ± 3.0	0.0001
RV MP index	0.60 ± 0.24	0.39 ± 0.08	0.0001
Pericardial effusion (*n*, %)	13 (20.3)	1 (1.4)	0.0001

PH, Pulmonary hypertension; LV, Left ventricular; RV, Right ventricular; RA, Right atrial, PA, Pulmonary artery; MP, Myocardial performance; TAPSE, Tricuspid annular plane systolic excursion; TRV, Tricuspid regurgitation velocity; FAC, Fractional area change, Continuous data are presented as mean ± SD; categorical data as number of patients and percentage of sample. All indices are measured by echocardiography.

Supplementary Table 2. Characteristics of Patients who Died during Follow-up

No.	Age	Gender	Diagnosis	Follow-up* (day)	Causes of death
1.	67	M	IPAH	295	Right heart failure
2.	45	M	CTEPH	113	Right heart failure after PE (day 14)
3.	55	F	CHD (ASD)	226	Sudden death
4.	50	F	CHD (ASD)	260	ARF+RI after hysterectomy (2nd day)
5.	62	F	IPAH	40	Sudden death
6.	24	F	CHD (Comp.)	244	RI +Acute abdomen?
7.	75	F	CTEPH	226	Right heart failure
8.	45	E	CTEPH	112	Right heart failure after PE (day 11)
9.	66	M	IPAH	7	Right heart failure

*, Follow-up after inclusion; F, Female; IPAH, Idiopathic pulmonary arterial hypertension; CHD, Congenital heart disease; CTD, Connective tissue disease; M, Male; PDA, Patent ductus arteriosus; VSD, Ventricular septal defect; PH, Pulmonary hypertension; IPAH, Idiopathic pulmonary arterial hypertension; CHD, Congenital heart disease; CTEPH, Chronic thromboembolic pulmonary hypertension; ASD, Atrial septal defect; Comp-double outlet right ventricle + ventricular septal defect +patent ductus arteriosus + transposition of great arteries, PE, Pulmonary endarterectomy; ARF, Acute renal failure; RI, Respiratory insufficiency.