ORIGINAL ARTICLE

Severity of Arterial and Chronic Thromboembolic Pulmonary Hypertension is Associated with Impairment of Heart Rate Turbulence

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Background: Heart rate turbulence (HRT) impairment is a validated and an independent indicator of cardiovascular death. There are limited data on HRT in pulmonary hypertension (PH), so we assessed potential HRT alterations in PH, especially in relation to its severity.

Methods: Thirty-three out of 41 patients were enrolled in the study aged 49.7 ± 15.9 years (22 with arterial, 11 with chronic thromboembolic PH). Routine evaluations, right heart catheterization, and 24-hour Holter monitoring with heart rate variability and HRT assessment were performed.

Results: HRT was significantly impaired in PH patients, as compared to 25 healthy controls: mean turbulence onset (TO) was -0.27% versus -2.60% ($P < 0.0001$), and median turbulence slope (TS) was 3.13 versus 13.5 msRR ($P < 0.0001$). Abnormal HRT ($TO \geq 0.0\%$ and/or $TS \leq 2.5$ ms/RR) was found in 63.3% of PH patients. Patients with PH and abnormal HRT presented more compromised functional, biochemical, and hemodynamic status than PH patients with normal TO and TS values. Multivariate stepwise regression analysis showed that TO value was related to oxygen desaturation $<90\%$ in 6-minute walking test (6-MWT; OR 0.41, $P < 0.001$) and was related to N-Terminal pro-B type Natriuretic Peptide concentration (OR 0.40, $P < 0.001$); TS was related to 6-MWT distance (OR 0.53, $P < 0.0001$).

Conclusions: Patients with arterial or chronic thromboembolic PH are characterized by significant impairment of HRT which is related to the disease severity. We hypothesize that patients with abnormal HRT could be considered as subjects with an increased risk of cardiovascular death, however, it needs further investigation.

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pulmonary hypertension; heart rate turbulence; heart rate variability; sudden cardiac death; risk stratification

Pulmonary arterial and chronic thromboembolic pulmonary hypertension (PH) are characterized by an obliterative pulmonary vasculopathy leading

to a progressive increase in pulmonary vascular resistance, chronic right heart dysfunction or failure, and finally to death. The main reasons

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of death in PH patients are right ventricular failure, sudden cardiac death (including arrhythmogenic death), and respiratory insufficiency. Some patients also die due to main pulmonary artery dilatation (rupture or dissection with cardiac tamponade).¹⁻⁴

Heart rate turbulence (HRT) is an electrocardiogram-derived autonomic marker and describes the baroreflex-mediated oscillation of cardiac cycle length after spontaneous ventricular premature complexes (VPCs). HRT is described by two parameters, i.e., turbulence onset (TO) and turbulence slope (TS). According to proposed criteria by International Society for Holter and Noninvasive Electrocardiology, HRT is normal when TO <0.0% and TS >2.5 ms/RR (ms/RR interval) and such cut-off values were used in most clinical studies.⁵ Many studies of patients after myocardial infarction or with congestive left ventricular heart failure proved that cardiac autonomic disbalance manifested by impaired HRT and also diminished heart rate variability (HRV), is a risk factor for malignant ventricular arrhythmia, sudden cardiac death, and cardiovascular mortality.⁵⁻⁸ However, there are limited data on HRV and no data on HRT in arterial and chronic thromboembolic PH, also at risk of sudden cardiac death. Therefore, except time-domain HRV, we also calculated HRT parameters in 24-hour Holter monitoring in PH patients and in healthy control group. We also examined the relationships between results of HRT and various clinical features and others parameters in PH patients.

MATERIAL AND METHODS

Study Population

Forty-one consecutive adult patients with PH diagnosed on right heart catheterization (RHC) or echocardiography and 34 healthy subjects with similar mean age and similar sex distribution were examined before including in the study. All examined persons underwent: clinical evaluation, 24-hour Holter monitoring, standard electrocardiography, transthoracic echocardiography, and routine laboratory tests. Most of the PH patients also underwent 6-minute walking test (6-MWT) with pulseoximetry, spirometry, and RHC. The 6-

MWT was performed on a level hallway surface in accordance with the American Thoracic Society Guidelines.⁹

Subjects with echocardiographic signs of left ventricle dysfunction, moderate-to-severe left heart valvular abnormalities, and atrial fibrillation or flutter were not included in the study. Patients with significant pulmonary function abnormalities (defined by forced vital capacity or forced expiratory volume in 1 second <70% of predicted) were not included either. Diabetes mellitus, impaired renal function defined by a serum creatinine concentration $\geq 132 \mu\text{mol/l}$, hepatic or thyroid dysfunction were also exclusion criteria. Serum N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP) concentration exceeding 125 pg/ml and cardiac high-sensitive troponin T exceeding 0.01 ng/ml were regarded abnormal as indicated by the producer (Roche Diagnostics, Rotkreuz, Switzerland).

All 41 patients and 34 control subjects expressed their written informed consent to take part in the study. This study was conducted in accordance with the amended Declaration of Helsinki. The protocol of the study was accepted by the local institutional review board (Bioethics Committee in Medical University of Warsaw, Poland; KB/201/2012)

The 24-Hour Holter Monitoring

All studied subjects underwent an ambulatory 24-hour Holter monitoring performed on a three-channel digitized recordings (Lifecard CF, Space-labs Healthcare, Snoqualmie, WA, USA). An evaluation of heart rate, presence of ventricular and supraventricular arrhythmias, and time-domain HRV analysis were performed (Sentinel Impresario, Spacelabs Healthcare, Snoqualmie, WA, USA). Two numerical HRT parameters after VPCs were calculated using custom-designed software based on Schmidt et al. described methodology. First, TO reflecting the initial phase of sinus rhythm acceleration and second, TS describing following deceleration phase. TO was defined as a percentage difference between the mean of first two sinus RR intervals after VPC and the last two RR intervals before VPC. TS was described as a maximum positive slope of a regression line assessed over five consecutive RR intervals within the first 15 sinus RR interval after

Table 1. Characteristics of Studied Population

Characteristics	PH Patients (n = 33)	Controls (n = 25)	P Value
Clinical Data			
Age (years)	49.7 ± 15.9	48.3 ± 9.9	0.70
Female/male gender (no.)	25/8	20/5	0.51
Body mass index (kg/m ²)	24.0 ± 5.2	24.0 ± 3.0	0.97
Body surface area (m ²)	1.72 ± 0.19	1.74 ± 0.14	0.65
Some Biochemical Evaluation			
NT-proBNP (pg/ml) ^a	2047.1 ± 2238.5 ^a 1055.0 (68–8700)	48.6 ± 33.8 ^a 35.4 (5–119)	<0.0001
Cardiac troponin T > 0.01 ng/ml (no., pts%)	8 (24.2%)	–	–
Echocardiography			
Right ventricle (mm)	38 ± 9	22 ± 2	<0.0001
Tricuspid regurgitation pressure gradient (mmHg)	85 ± 27	19 ± 4	<0.0001
Tricuspid annular peak systolic excursion (mm) ^a	17.0 ± 4.1 ^a 18.0 (9.0–23.0)	24.1 ± 2.4 ^a 24 (21.0–30.)	<0.0001
Left ventricle (mm)	38 ± 8	44 ± 3	0.0006
6-Minute Walking Test			
Distance (m) ^a	n = 29 381 ± 139 ^a 370 (116–643)	618 ± 41 ^a 620 (516–572)	<0.0001
Oxygen saturation at rest (%) ^a	91 ± 6 ^a 93 (77–99)	98 ± 1 ^a 98 (96–100)	<0.0001
Oxygen saturation during test (%) ^a	84 ± 13 ^a 91 (51–97)	97 ± 1 ^a 98 (95–99)	<0.0001

^aValue not demonstrated normal distribution, additionally expressed as a median (range).
NT-proBNP = N-terminal pro-B-type natriuretic peptide.

VPC. TO was calculated for all VPCs separately and then averaged. TS was calculated based on an averaged local tachogram. Careful manual review and special filtering algorithm were used to eliminate inappropriate electrocardiographic strips. TO and TS were calculated, if at least two suitable VPCs for HRT analysis were detected in Holter ECG. According to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, typical indexes of time-domain HRV were measured (names and its abbreviations are in Table 3).¹⁰

Transthoracic Echocardiography and Right Heart Catheterization

Echocardiographic examination was performed with Acuson Sequoia (Siemens AG, Erlangen, Germany) with 2.5–3.5 MHz transducers. Typical dimensions in typical views were measured. After recording of the tricuspid valve peak systolic velocity with continuous-wave Doppler echocardiography, the tricuspid regurgitation peak gradient (TRPG) was calculated.

PH was considered likely according to European Society of Cardiology criteria when TRPG >46 mmHg (tricuspid regurgitate velocity >3.4 m/s).¹¹ In order to assess the right ventricular function using the one-dimensional M-mode echocardiography, tricuspid annular peak systolic excursion (TAPSE) was measured. In concordance to American Society of Echocardiography, TAPSE <16 mm was regarded abnormal.¹² Left ventricular ejection fraction in PH was not reported because this measurement in patients with signs of severe right ventricular overload is not reliable.

Patients in whom PH was likely were referred to the RHC. The Swan-Ganz catheter was passed under fluoroscopic guidance to the pulmonary artery and typical variables were recorded and calculated. Cardiac output was determined by thermodilution injecting cooled saline until a variability of <10% was achieved in three consecutive measurements. Mixed venous oxygen saturation was assessed in blood sampled from pulmonary artery. Pulmonary hypertension was diagnosed when mean pulmonary artery pressure was >25 mmHg.¹¹

Table 2. Pulmonary Hypertension Characteristics and Clinical Data

Characteristics	
Pulmonary Hypertension Etiology (No., Pts%)	
Pulmonary arterial hypertension (no., pts%)	22 (66.7%)
–Idiopathic (no., pts%)	12 (36.4%)
–Hereditary (no., pts%)	1 (3.0%)
–Associated with connective tissue diseases (no., pts%)	4 (12.1%)
–Associated with congenital heart diseases (no., pts%)	4 (12.1%)
–Associated with cirrhosis hepatitis (no., pts%)	1 (3.0%)
Chronic thromboembolic pulmonary hypertension (no., pts%)	11 (33.3%)
Medical History and Coexisting Diseases (No., Pts%)	
Syncope and presyncope in medical history	7 (21.2%)
Cigarette smoking	6 (18.2%)
Arterial hypertension (no., pts%)	8 (24.2%)
Coronary artery disease (no., pts%)	1 (3%)
Therapy (No., Pts%)	
Calcium channel blockers	12 (36.4%)
Endothelin antagonist	7 (21.2%)
Prostacyclin analogs	10 (30.3%)
Phosphodiesterase type 5 inhibitor	8 (24.2%)
Digitalis	1 (3.0%)
Diuretics	21 (63.6%)
Balloon atrial septostomy in medical history	1 (3.0%)
Right Heart Catheterization (n = 28)	
Right atrial pressure (mmHg)	8.4 ± 4.5
Diastolic pulmonary arterial pressure (mmHg)	40.3 ± 13.5
Mean pulmonary arterial pressure (mmHg)	59.0 ± 16.6
Systolic pulmonary arterial pressure (mmHg)	86.6 ± 24.3
Postcapillary wedge pressure (mmHg)	9.0 ± 2.0
Pulmonary vascular resistance (Wood's units)	11.8 ± 6.7
Cardiac index (l/min/m ²)	2.7 ± 0.7
Mixed venous oxygen saturation (%)	64.9 ± 8.5

Statistical Analysis

Patients with PHs and controls were compared by either Student's *t* test or the Wilcoxon test, depending on the parameter distribution assessed by the Kolmogorov–Smirnov test. Variables with a normal distribution are presented as mean ± standard deviation. Variables not showing a normal distribution are presented as median with range and additionally as mean ± standard deviation. Deletions of outliers' data were not performed. For categorical variables, the differences between groups were compared by Fisher's exact test. All tests were double-sided. Correlations were evaluated by Spearman correlation coefficients.

Regression analysis was performed to examine the influence of confounding factors on value of TO and TS. Univariate and stepwise multivariate analyses were performed, and multiple models were examined. Model selection was based on fit measurement by chi-square test for inclusion ($P <$

0.05) and Wald test for exclusion ($P > 0.15$). The influence of measured parameters was expressed as an odds ratio (OR). Values of $P < 0.05$ were considered statistically significant. Analyses were performed using a statistical software package (STATISTICA 10, StatSoft Inc., Tulsa, OK, USA).

RESULTS

Clinical Characteristics of Study Population

Thirty-three out of 41 PH patients were enrolled in this study. Mean disease duration of PH patients was 4.85 ± 4.72 years (median 3, range 1–19 years). Remaining eight patients were not included due to persistent atrial fibrillation (1 pt), diabetes mellitus (1 pt), and lack of VPCs suitable for HRT calculating (6 pts). Control group eventually consisted of 25 healthy persons, because 9 subjects showed no VPCs suitable for HRT analysis.

Table 3. Comparison of 24-Hour Holter Monitoring Findings, Heart Rate Turbulence, and Time-Domain Heart Rate Variability Parameters in Pulmonary Hypertension Patients and Control Group

Characteristics	PH Patients (N = 33)	Controls (N = 25)	P Value
24-Hour Holter Monitoring Findings			
Recording duration (h:min)	23:27	23:35	0.73
Maximal heart rate (1/min)	114 ± 18	140 ± 13	<0.0001
Minimal heart rate (1/min)	59 ± 8	48 ± 5	<0.0001
Mean heart rate (1/min)	77 ± 9	75 ± 6	0.38
VPCs/24 h (no.) ^a	895 ± 2798	113 ± 325	0.17
	^a 14 (2–11601)	^a 3 (2–1302)	
SupraVPCs/24 h (no.) ^a	151 ± 343	58 ± 182	0.22
	^a 21 (0–1694)	^a 11 (1–910)	
Heart Rate Turbulence Parameters			
Turbulence onset (%)	–0.27 ± 2.30	–2.60 ± 1.43	<0.0001
	–0.52 (–4.86–3.97)	–2.69 (–5.6– –0.4)	
Turbulence slope (ms/RR) ^a	4.06 ± 4.78	19.96 ± 13.61	<0.0001
	^a 3.13 (–1.56–22.67)	^a 13.5 (3.9–47.9)	
Time-Domain Heart Rate Variability Parameters^b			
SDNN (ms)	104.4 ± 37.7	152.1 ± 33.7	<0.0001
RMSSD (ms)	28.3 ± 11.5	29.0 ± 8.1	0.79
pNN50 (%) ^a	6.3 ± 6.2	7.8 ± 6.0	0.34
	^a 3.5 (0.1–20.0)	^a 5.3 (1.3–23.0)	
SDNN-I (ms)	31.8 ± 14.2	59.3 ± 11.7	<0.0001
SDANN (ms)	98.0 ± 34.2	138.8 ± 32.7	<0.0001

^aValue not demonstrated normal distribution, additionally expressed as a median (range).

^bNN = normal-to-normal; pNN50 = number of pairs of adjacent N-N differing by more than 50 ms in the entire recording divided by the total number of all N-N; RMSSD = the square root of the mean of the sum of the squares of differences between adjacent N-N; SDANN = the standard deviation of the average of N-N in all 5-minute periods of the entire recording; SDNN = the standard deviation of N-N interval; SDNN-I (index) = mean of the standard deviations of all N-N for all 5-minute periods of the entire recording; VPC = ventricular premature contraction.

In 22 (66.66%) patients arterial and in 11 (33.33%) patients chronic thromboembolic PH was diagnosed. Eleven PH patients were in I–II and 22 others were in III–IV World Health Organization Functional Class (WHO-FC). The general characteristics of study population, the main clinical, biochemical, echocardiographic findings, 6-MWT and RHC results, and also administered drugs are shown in Tables 1 and 2. In five patients, RHC was not performed—in one patient with arterial PH and in four patients with chronic thromboembolic PH (in two due to very early stage of vitamin K antagonist treatment, and in subsequent two cases due to peripheral organizing thrombi in earlier performed computed tomography pulmonary angiography, so these patients would not be considered for pulmonary thromboendarterectomy). In four PH patients, 6-MWT test was not performed due to inadequate physical abilities. All patients and healthy subjects had sinus rhythm in standard electrocardiography. In 12 (36.4%) PH patients, TAPSE in echocardiography was abnormal, i.e., <16 mm.

Holter Monitoring, Heart Rate Turbulence and Variability Data

Basic Holter data, HRT, and HRV parameters in study populations of the entire recording period are presented in Table 3. It is worth noting that mean values of TO and TS and most of the HRV parameters were impaired in PH patients, as compared to controls. HRV was performed for entire day and night period and the shortest electrocardiographic recording lasted 20 hours and 46 minutes.

HRT-1 group (impairment of TO or TS) consisted of 13 (39.4%) patients and HRT-2 group (pathological TO and TS) consisted of 8 (24.2%) patients. Twenty-one PH subjects (63.6%) belonging to HRT-1 and HRT-2 groups were combined into one group—PH patients with abnormal HRT. As expected, abnormal HRT (TO ≥ 0% and/or TS ≤ 2.5 ms/RR) was not found in controls. Characteristics in PH patients with abnormal and normal HRT parameters are presented in Table 4. In general, PH patients with abnormal HRT had impaired most of

Table 4. Comparison of Various Characteristics in Pulmonary Hypertension Patients with Abnormal and Normal Heart Rate Turbulence Parameters

Characteristics	PH Patients with Abnormal HRT (N = 21)	PH Patients with Normal HRT (N = 12)	P Value
Age (years)	54.6 ± 16.9	41.2 ± 9.5	0.02
PAH (pts no, % pts)	12 (57.1%)	9 (75.0%)	0.25
WHO-FC III-IV (pts no, % pts)	17 (80.1%)	5 (41.7%)	0.055
NT-proBNP (pg/ml)	2518.9 ± 2384.1 ^a 1803.0 (89–8700)	1146.2 ± 1674.8 ^a 424.4 (68–4523)	0.10
Tricuspid annular peak systolic excursion in echocardiography (mm)	15.8 ± 4.1	19.3 ± 3.2	0.018
6-MWT (n = 29)	^a 15.0 (9.0–22.0) (n = 17)	^a 21.0 (12.0–23.0) (n = 12)	
Distance (m) ^a	339 ± 137 ^a 306 (116–576)	439 ± 124 ^a 440 (206–643)	0.054
Oxygen saturation at rest (%) ^a	89 ± 6 ^a 90 (75–98)	94 ± 4 ^a 94 (85–99)	0.045
Oxygen saturation after test (%) ^a	80 ± 13 ^a 82 (53–94)	88 ± 13 ^a 92 (51–97)	0.11
Desaturation <90% during test (pts no, %PH pts)	12 (70.6%)	2 (16.7%)	0.013
24-Hour Holter Monitoring Findings			
Maximal heart rate (1/min)	112 ± 21	118 ± 14	0.45
Minimal heart rate (1/min)	61 ± 8	56 ± 6	0.08
Mean heart rate (1/min)	77 ± 9	75 ± 8	0.56
VPCs/24 h (no.)	842 ± 2525 ^a 17 (2–11,109)	989 ± 3342 ^a 14 (2–11,601)	0.89
SupraVPCs/24 h (no.)	192 ± 405 ^a 24 (1–1694)	81 ± 188 ^a 8 (0–659)	0.38
Nonsustained ventricular tachycardia (no., pts%)	4 (19.0%)	2 (16.7%)	0.76
Nonsustained supraventricular tachycardia (no., pts%)	10 (47.6%)	2 (16.7%)	0.16
Time-Domain Heart Rate Variability Parameters^b			
SDNN (ms)	93.6 ± 37.0	123.3 ± 32.0	0.03
RMSSD (ms)	28.6 ± 11.2	27.7 ± 12.6	0.84
pNN50 (%) ^a	6.0 ± 5.2 ^a 4.1 (0.3–17.8)	6.7 ± 7.7 ^a 2.8 (0.1–20.0)	0.76
SDNN-I (ms)	29.8 ± 13.4	35.4 ± 15.4	0.28
SDANN (ms)	87.5 ± 3.7 (n = 17)	116.5 ± 29.5 (n = 11)	0.02
Right Heart Catheterization (n = 28)			
Right atrial pressure (mmHg)	9.6 ± 4.9	6.5 ± 3.4	0.08
Diastolic pulmonary arterial pressure (mmHg)	44.3 ± 14.5	34.0 ± 9.2	0.046
Mean pulmonary arterial pressure (mmHg)	63.7 ± 16.6	51.7 ± 14.2	0.06
Systolic pulmonary arterial pressure (mmHg)	92.1 ± 25.3	78.2 ± 21.0	0.14
Postcapillary wedge pressure (mmHg)	9.1 ± 2.2	8.9 ± 1.7	0.78
Pulmonary vascular resistance (Wood's units)	13.5 ± 7.7	9.4 ± 4.0	0.12
Cardiac index (l/min/m ²)	2.6 ± 0.7	2.8 ± 0.7	0.52
Mixed venous oxygen saturation (%)	62.6 ± 8.9	68.2 ± 6.7	0.09

^aValue not demonstrated normal distribution and additionally expressed as a median (range).^bFor abbreviations of time-domain heart rate variability parameters—see Table 3.

NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAH = pulmonary arterial hypertension; VPC = ventricular premature contraction; WHO-FC = World Health Organization–Functional Class.

the measurements of 6-MWT and RHC. Significant lower values of two HRV parameters were also revealed in patients with diminished HRT.

In all PH patients, TO significantly correlated with oxygen saturation at rest ($r = -0.390$, $P = 0.036$), and with RHC parameters: mixed venous oxygen saturation ($r = -0.459$, $P = 0.02$), cardiac output ($r = -0.465$, $P = 0.013$), and cardiac index ($r = -0.470$, $P = 0.012$) and also with older age ($r = 0.472$, $P = 0.006$). TS nearly significantly correlated with diastolic pulmonary artery pressure ($r = -0.353$, $P = 0.066$) and with pulmonary vascular resistance ($r = -0.374$, $P = 0.054$).

Univariate and Multivariate Stepwise Regression Analysis

Univariate and multivariate stepwise regression analysis was performed to detect potential predictors influencing TO and TS values. Univariate analysis results are presented in Tables 5 and 6. In multivariate analysis, higher TO value was significantly influenced by higher NT-proBNP concentration and oxygen desaturation <90% during 6-MWT, while lower TS value was significantly influenced by shorter 6-MWT distance only (full results in Tables 5 and 6).

DISCUSSION

Patients with arterial and chronic thromboembolic PH are characterized with a poor prognosis, even though specific drugs have improved these patients' outcomes in recent years. Progressive right ventricular failure still remains the most frequent reported cause of death of patients with PH (in about 36%). Arrhythmogenic sudden death is also common in these patients and was reported in approximately 28% fatalities.^{2,13,14} The main cause of sudden cardiac death in arterial PH is not ventricular tachycardia or ventricular fibrillation, but severe bradycardia (in 45%), electromechanical dissociation (in 28%) and asystole (in 15% of patients).^{13,14} Among the most important prognostic factors influencing PH patients' survival are not any established electrocardiographic signs as yet.¹¹ However, significant changes occur in a variety of electrocardiographic parameters between the time of the initial arterial PH diagnosis and close to death.¹⁵ Holter-derived cardiac autonomic dysfunction has been proved as a useful and noninvasive predictor of cardiovascular mortality

in many studies so far.^{16–18} Currently, American and European experts still recommend HRT and HRV as potentially useful tools in the improvement of risk stratification of patients at risk of life-threatening ventricular arrhythmias.^{19,20} Relationship between PH and the function of cardiac autonomic nervous system is not well elucidated. There are only a few studies reporting impairment of HRV in time and frequency domain in PH.^{21–24} For instance, in study of Lammers et al., HRV parameters predicted death or lung transplantation in 47 children with arterial PH.²² A prognostic value of observed HRV in adults with PH has not been examined yet. As an issue of HRV in PH patients is described comprehensively in referenced papers, we focused on HRT only. Our results of HRV confirm autonomic imbalance in PH subjects and authenticate HRT measurements.

In our previous study, we showed that abnormal HRT is present more frequent in systemic sclerosis patients with echocardiographically recognized PH.²⁵ In our current study of 33 patients with PH, we observed significant higher values of TO and lower values of TS when compared to healthy controls. Abnormal values of TO and/or TS were observed in 21 (63.3%) out of all patients with PH. Moreover, in our study three time-domain HRV parameters, which mainly reflect chronic sympathetic stimulation (SDNN, SDNN-I, SDANN), were significantly lower than in healthy controls. And, two others mainly reflecting vagal activity (RMSSD, pNN50) were not. Such results of time-domain heart rate variability are in line of a study of Folino et al.²¹ Sympathetic activation in PH patients should not be surprising, and it was also confirmed by other studies.^{24,26}

A literature review and our results suggest that a possible explanation of diminished HRT (similarly as HRV) in patients with PH may be sympathetic nervous system activation mainly resulting from heart failure and hypoxia. Our results confirm that HRT is associated with oxygen saturation and various parameters of heart failure assessment, too. Nevertheless, it is still not known whether autonomic imbalance in PH patients may promote life-threatening arrhythmias or is associated with cardiovascular mortality. Both HRT characteristics are powerful predictors in patients with post-myocardial infarction heart failure, but have a moderate role in predicting outcome in patients with nonischemic left ventricular heart failure.⁵ However, in our opinion data on neurohormonal

Table 5. Stepwise Regression Analysis Predictors of Turbulence Onset Increase of 1% in Pulmonary Hypertension Patients

Parameter	Univariate Analysis		Multivariate Analysis ⁱ	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Age ^a	0.36 (0.11–0.61)	0.006	-	-
WHO-FC ^b	0.44 (0.11–0.77)	0.01	-	-
NT-proBNP (pg/ml) ^c	0.55 (0.32–0.77)	<0.0001	0.40 (0.18–0.63)	<0.001
TAPSE <16 mm ^d	0.31 (–0.06–0.67)	0.09	-	-
6-MWT Distance (m) ^e	–0.53 (–0.77– –0.30)	<0.0001	-	-
Oxygen saturation at rest (%) ^f	–0.55 (–0.78– –0.31)	<0.0001	-	-
Oxygen desaturation <90% during 6-MWT	0.55 (0.32–0.78)	<0.0001	0.41 (0.18–0.63)	<0.001
Mean pulmonary artery pressure (mmHg) ^g	0.14 (–0.26–0.54)	0.47	-	-
Pulmonary vascular resistance (Wood's units) ^h	0.26 (–0.13–0.66)	0.18	-	-

^aOdds ratio (OR) and 95% confidence interval (CI) corrected for increase of 1 year.

^bOR and 95%CI corrected for higher WHO-FC Class = World Health Organization-Functional Class.

^cOR and 95%CI corrected for increase of 100 pg/ml; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

^dTricuspid annular peak systolic excursion in echocardiography.

^eOR and 95%CI corrected for decrease of 10 m; 6-MWT = 6-minute walking test.

^fOR and 95%CI corrected for decrease of 1%.

^gOR and 95%CI corrected for increase of 1 mmHg.

^hOR and 95%CI corrected for increase of 1 Wood's units.

ⁱResults of multivariate analysis shown only for statistically significant parameters.

activation and cardiac autonomic imbalance in PH patients seem to be potentially useful in context of planned studies on beta-blockers treatment in this disease.²⁷ Maybe, patients with PH and diminished cardiac autonomic tone (expressed by HRT or HRV) will benefit from such treatment—similar to patients with left ventricular congestive heart failure. Maybe, HRT and HRV will be helpful to monitoring response to beta-blocker treatment. Till now, no large trials of prophylactic antiarrhythmic therapy have been conducted in patients with PH and there is even a recommendation against such treatment.²⁰

Currently, we may only conclude that HRT impairment is associated with the severity of PH. However, as an interpretation of HRT parameters is much simpler than HRV, we hope that our study will not be sole on this issue and we will know more soon.

Our study has several limitations. It is based on two-center observational data only. As PH is a rare disease, our study also involves a relatively low number of included cases. Additionally, women constitute the majority of the studied group, which is caused by a preponderance of females in pulmonary arterial hypertension.²⁸ A further potential limitation of our study is the obligatory

presence of VPCs suitable for HRT analysis. Due to this requirement, six PH patients were not included in our study. However, patients with no VPCs are usually classified as low-risk patients and considered as a part of normal HRT group (especially in risk stratification trials). Another limitation of our study is that in 11 PH patients and 18 healthy subjects a number of VPCs suitable for HRT analysis was ≥ 2 and < 5 . Standards of International Society for Holter and Noninvasive Electrocardiology suggest use of at least five VPCs for HRT assessment, especially for TS.⁵ This restriction is usually needed in large risk stratification trials and is difficult to fulfil in studies concerning rare diseases (like PH) or healthy volunteers. In our study, two patients with PH were also excluded due to coexisting disorders. However, designed restrictions for inclusion in the study were necessary to avoid any known conditions influencing autonomic nervous system function. Results of our study cannot be generalized to patients with other types of PH. One of the potential limitations of our study is also the lack of invasive verification of all patients with PH. However, tricuspid regurgitation pressure gradient indicated very high pressure in main pulmonary artery in our patients. It seems unlikely for a

Table 6. Stepwise Regression Analysis Predictors of Turbulence Slope Decrease of 1 ms/RR in Pulmonary Hypertension Patients

Parameter	Univariate Analysis		Multivariate Analysis ⁱ	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Age ^a	-0.22 (-0.49–0.03)	0.09	-	-
WHO-FC ^b	-0.40 (-0.74– -0.07)	0.02	-	-
NT-proBNP (pg/ml) ^c	-0.42 (-0.67– -0.18)	0.001	-	-
TAPSE <16 mm ^d	-0.35 (-0.71–0.0001)	0.05	-	-
6-MWT Distance (m) ^e	0.53 (0.29–0.77)	<0.0001	0.53 (0.29–0.77)	<0.0001
Oxygen saturation at rest (%) ^f	0.45 (0.20–0.70)	<0.001	-	-
Oxygen desaturation <90% during 6-MWT	-0.41 (-0.66– -0.15)	0.002	-	-
Mean pulmonary artery pressure (mmHg) ^g	-0.32 (-0.70–0.06)	0.1	-	-
Pulmonary vascular resistance (Wood's units) ^h	-0.37 (-0.76–0.01)	0.05	-	-

^aOdds ratio (OR) and 95% confidence interval (CI) corrected for increase of 1 year.

^bOR and 95%CI corrected for higher WHO-FC Class = World Health Organization-Functional Class.

^cOR and 95%CI corrected for increase of 100 pg/ml; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

^dTricuspid annular peak systolic excursion in echocardiography.

^eOR and 95%CI corrected for decrease of 10 m; 6-MWT = 6 minute walking test.

^fOR and 95%CI corrected for decrease of 1%.

^gOR and 95%CI corrected for increase of 1 mmHg.

^hOR and 95%CI corrected for increase of 1 Wood's units.

ⁱResults of multivariate analysis shown only for statistically significant parameters.

false recognition of PH in these patients using transthoracic Doppler echocardiography, which is a very sensitive and specific method for PH diagnosis.¹¹

CONCLUSIONS

Patients with pulmonary arterial and chronic thromboembolic PH are characterized by cardiac autonomic dysfunction revealed by significant impairment of HRT and HRV. Diminished HRT parameters in these patients are especially associated with higher NT-proBNP concentration, oxygen desaturation <90% during 6-MWT and shorter 6-MWT distance. Similar to studies in other populations at risk of sudden cardiovascular death, our results indicate a potential future use of measurement of HRT in risk stratification in PH patients. However, it should be emphasized that our findings need to be validated in other trials before HRT assessment in PH patients could be regarded as a reliable and helpful prediction method.

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