

Heart rate recovery is an important predictor of outcomes in patients with connective tissue disease–associated pulmonary hypertension

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Abstract: Reduced heart rate recovery (HRR) after exercise is associated with increased mortality in cardiac and pulmonary diseases. We sought to evaluate the association between HRR after the 6-minute walk test (6MWT) and outcomes in patients with connective tissue disease–associated pulmonary hypertension (CTD-PH). Data were obtained by review of the medical records. HRR was defined as the difference in heart rate at the end of the 6MWT and after 1 minute (HRR1), 2 minutes (HRR2), and 3 minutes (HRR3) of rest. All patients with pulmonary hypertension and a diagnosis of systemic sclerosis, systemic lupus erythematosus, or mixed connective tissue disease who underwent the 6MWT between August 1, 2009, and October 30, 2011, were included ($n = 66$). By Kaplan-Meier analysis, HRR1, HRR2, and HRR3 at different cutoff points were all good predictors, with HRR1 of <16 being the best predictor of time to clinical worsening (log-rank $P < 0.0001$), hospitalization (log-rank $P = 0.0001$), and survival (log-rank $P < 0.003$). By proportional hazards regression, patients with HRR1 of <16 were at increased risk of clinical worsening (hazard ratio [HR]: 6.4 [95% confidence interval (CI): 2.6–19.2]; $P < 0.0001$), hospitalization (HR: 6.6 [95% CI: 2.4–23]; $P < 0.0001$), and death (HR: 4.5 [95% CI: 1.6–15.7]; $P = 0.003$). Patients in the highest tercile (HRR1 of ≥ 19) were unlikely to have a clinical worsening event (HR: 0.1 [95% CI: 0.04–0.5]; $P = 0.001$), to be hospitalized (HR: 0.1 [95% CI: 0.02–0.5]; $P = 0.001$), or to die (HR: 0.3 [95% CI: 0.07–0.9]; $P = 0.04$). In conclusion, in patients with CTD-PH, abnormal HRR1 (defined as HRR1 of <16) after the 6MWT is a strong predictor of clinical worsening, time to clinical worsening, survival, and hospitalization.

Keywords: scleroderma, pulmonary hypertension, heart rate, 6-minute walk test, survival.

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Pulmonary arterial hypertension (PAH) is a disease that can result from diverse etiologies, including connective tissue diseases (CTD-PH). Despite recent advances in its management, PAH remains a progressive disease that results in death.¹ Historically, 6-minute walk distance (6MWD) has been used as a predictor of prognosis in these patients;^{2,3} however, it is felt to suffer from a “ceiling effect” that can limit its utility in patients with limited functional capacity.^{4,5} These concerns are felt to be even more important among patients with CTD-PH.^{6–8} To identify groups of patients that may be at an increased risk and may benefit from more aggressive therapy, several studies have attempted to establish predictors of poor prognosis in a more comprehensive manner using several variables.^{9,10} Although these are of value, their ease of use in everyday practice in the community setting is unclear.

Investigators have attempted to augment the ability of the 6-minute walk test (6MWT) to predict future clinical outcomes by using ancillary data, including the need for oxygen.⁹ Recent publications have reported on the presence of autonomic dysfunction and

its possible association with survival in patients with PAH.^{11–13} Heart rate recovery (HRR) refers to the reduction in heart rate with rest after graded exercise.¹⁴ We have previously reported that HRR at 1 minute after a 6MWT was the best predictor of clinical worsening, time to clinical worsening (TtCW), hospitalization, and survival in a cohort of patients with idiopathic PAH (IPAH).^{15,16} HRR is attractive as a biomarker because it is potentially generalizable, since it is simple to perform and does not incur a significant cost burden.

The main objective of our study was to determine whether HRR after a 6MWT can predict clinical worsening, TtCW, survival, and hospitalization for worsening pulmonary hypertension (PH) among a cohort of patients with CTD-PH. Some of these data have been presented previously in abstract form and as an oral presentation.¹⁷

METHODS

The study was approved by our Institutional Review Board (IRB 10-048 and 10-055). Patients with CTD-PH who completed a 6MWT

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Table 1. Clinical characteristics of the study population by heart rate recovery after 1 minute of rest (HRR1)

Factor	Overall (<i>n</i> = 66)	HRR1 of ≥ 16 (<i>n</i> = 28; 42%)	HRR1 of < 16 (<i>n</i> = 38; 58%)	<i>P</i>
Age, years	56 \pm 15	52 \pm 16	58 \pm 14	0.09
Female, no. (%)	56 (85)	27 (96)	29 (76)	0.03
WHO FC, no. (%)				0.002 ^a
I	4 (6)	4 (14)	0 (0)	
II	32 (48)	17 (61)	15 (39)	
III	25 (38)	7 (25)	18 (47)	
IV	5 (8)	0 (0)	5 (13)	
BUN, mg/dL	20 \pm 15	15.5 \pm 10	23.5 \pm 17	0.02
Creatinine, mg/dL	0.96 \pm 0.4	0.8 \pm 0.3	1.1 \pm 0.5	0.004
Sodium, mmol/L	139 \pm 4	140 \pm 3	138 \pm 4	0.04
PFT parameters, % predicted				
FVC	71 \pm 22	76 \pm 24	67.5 \pm 19	0.1
DLCO	40 \pm 18	45 \pm 19	36 \pm 17	0.1
6MWT				
6MWD, m	316 \pm 109	372 \pm 102	274 \pm 95	<0.001
6MWD, % predicted	61 \pm 25	68 \pm 21	56 \pm 26	0.04
Baseline heart rate, beats/min	87 \pm 19	85 \pm 18	89 \pm 19	0.4
6M heart rate, beats/min	123 \pm 22	129 \pm 22	119 \pm 21	0.05
Delta heart rate, beats/min	36 \pm 18	44 \pm 17	30 \pm 16	<0.001
HRR1, beats/min	16 \pm 13	27 \pm 11	8 \pm 6	<0.001
HRR2, beats/min	26 \pm 13	36 \pm 11	18 \pm 10	<0.001
HRR3, beats/min	32 \pm 13	39 \pm 12	27 \pm 12	<0.001
Supplemental O ₂ (yes), no. (%)	33 (50)	9 (32)	24 (63)	0.01
BNP, pg/mL	267 \pm 368	109 \pm 218	390 \pm 414	0.002
DE parameters				
RA enlargement, no. (%)	30 (45)	6 (22)	24 (63)	0.009 ^a
RVSP, mmHg	63 \pm 25	55 \pm 22	68 \pm 25	0.03
RV dysfunction (moderate or severe), no. (%)	27 (41)	13 (46)	27 (71)	0.004
Pericardial effusion present, no. (%)	22 (33)	6 (22)	16 (43)	0.1
Baseline hemodynamics				
mRAP, mmHg	9 \pm 5	9 \pm 5	10 \pm 4	0.4
mPAP, mmHg	43 \pm 10	41 \pm 12	44 \pm 9	0.1
CI (Fick), mL/min/m ²	2.7 \pm 0.7	2.9 \pm 0.9	2.5 \pm 0.6	0.1
SvO ₂ , %	65 \pm 9	71 \pm 7	62 \pm 8	0.005
TPG, mmHg	29 \pm 12	23 \pm 12	32 \pm 10	0.005
PVR, Wood units	6.9 \pm 3.6	5 \pm 3	8 \pm 4	0.007
PH medications at time of 6MWT, no. (%)				0.2 ^a
None	16 (24)	7 (25)	9 (24)	
Parenteral prostanoids alone	3 (5)	1 (4)	2 (5)	
Single oral	21 (32)	13 (46)	8 (21)	
Combination (oral and parenteral)	6 (9)	1 (4)	5 (13)	
Combination (other)	20 (30)	6 (21)	14 (37)	
Clinical worsening (yes), no. (%)	29 (44)	7 (25)	22 (58)	0.008

Table 1 (Continued)

Factor	Overall (<i>n</i> = 66)	HRR1 of ≥ 16 (<i>n</i> = 28; 42%)	HRR1 of < 16 (<i>n</i> = 38; 58%)	<i>P</i>
Hospitalization (yes), no. (%)	22 (33)	4 (14)	18 (47)	0.005
Dead, no. (%)	20 (30)	4 (14)	16 (42)	0.01

Note: Except where otherwise noted, data are mean \pm standard deviation. Percentages are by column group. All comparisons are by the Student two-sample *t* test unless otherwise specified. 6M heart rate: heart rate at the end of the 6MWT; 6MWD: 6-minute walk distance; 6MWT: 6-minute walk test; BMI: body mass index; BNP: B-type natriuretic peptide; BUN: blood urea nitrogen; CI: cardiac index; DE: Doppler echocardiography; delta heart rate: 6M heart rate minus baseline heart rate; DLCO: diffusion capacity for carbon monoxide; dPAP: diastolic pulmonary arterial pressure; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; HRR2: heart rate recovery after 2 minutes of rest; HRR3: heart rate recovery after 3 minutes of rest; mPAP: mean pulmonary arterial pressure; mRAP: mean right atrial pressure; SvO₂: mixed venous oxygen saturation; PH: pulmonary hypertension; PFT: pulmonary function test; PVR: pulmonary vascular resistance; RA: right atrium; RV: right ventricle; RVSP: right ventricular systolic pressure; sPAP: systolic pulmonary arterial pressure; supplemental O₂: patients using supplemental oxygen during the 6MWT; TPG: transpulmonary gradient; WHO FC: World Health Organization functional class.

^a Fisher exact test.

between August 1, 2009, and October 31, 2011, were included in the analysis.

At our center, the 6MWT is performed according to American Thoracic Society/European Respiratory Society criteria (in terms of instructions to patients);¹⁸ however, the test was modified by recording heart rate at the end of the 6MWT and at 1, 2, and 3 minutes after completion of the test with the patient seated. The 6MWT is begun after the patient has been seated for 10 minutes. Pulse oximeters (Ohmeda Biox 3740 or Ohmeda 3900; Datex-Ohmeda, Laurel, MD) with finger probes were used. Forehead probes were used where finger probes were not felt to be adequate. These oximeters display heart rate and SpO₂. Supplemental oxygen flow rates were used according to the subjects' current oxygen prescriptions.

Assessment of HRR, echocardiographic parameters, and B-type natriuretic peptide (BNP) were performed on the same day, and no changes were made between these measurements. Baseline right heart catheterization values were used for all patients. HRR was defined as the difference between a subject's heart rate at the sixth minute of the 6MWT and at 1 minute (HRR1), 2 minutes (HRR2), and 3 minutes (HRR3) after completion of the 6MWT. Mortality data were collected by search of the electronic medical record as well as the Social Security Death Index, and all-cause mortality was included. Only hospitalizations due to worsening PH or right ventricular failure were included in the analysis. Doppler echocardiographic measurements and adjudication of cause of PH hospitalization were performed blindly by physicians unaware of individual

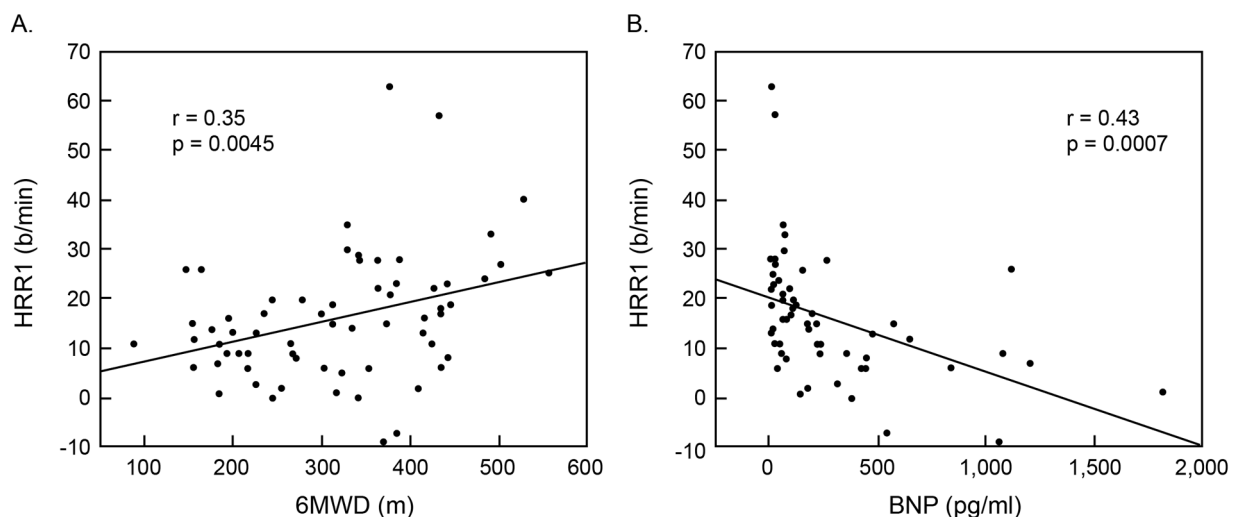


Figure 1. Correlation between heart rate recovery after 1 minute of rest (HRR1) and 6-minute walk distance (6MWD; A) and between HRR1 and B-type natriuretic peptide (BNP; B) in the overall cohort.

Table 2. Clinical characteristics of the study population by clinical worsening (CW) event status

Factor	CW (<i>n</i> = 29; 44%)	No CW (<i>n</i> = 37; 56%)	<i>P</i>
Age, years	57 ± 14	54 ± 17	0.3
Female, no. (%)	23 (79)	33 (89)	0.3
WHO FC, no. (%)			0.001 ^a
I	0 (0)	4 (11)	
II	9 (31)	23 (62)	
III	15 (52)	10 (27)	
IV	5 (17)	0 (0)	
BUN, mg/dL	24 ± 19.5	17 ± 9	0.06
Creatinine, mg/dL	1 ± 0.5	0.9 ± 0.3	0.2
Sodium, mmol/L	138 ± 4	139 ± 4	0.2
PFT parameters, % predicted			
FVC	68 ± 22	73 ± 21	0.3
DLCO	35 ± 19.5	43 ± 17	0.1
6MWT			
6MWD, m	266 ± 91	354 ± 107	<0.001
6MWD, % predicted	50 ± 18	71 ± 25	<0.001
Baseline heart rate, beats/min	89.5 ± 21	86 ± 17	0.2
6M heart rate, beats/min	119 ± 21	126 ± 22	0.1
Delta heart rate, beats/min	30 ± 15	41 ± 18	0.009
HRR1, beats/min	11 ± 8	20 ± 14	0.003
HRR2, beats/min	20 ± 9	30 ± 15	0.001
HRR3, beats/min	27 ± 10	36 ± 15	0.004
Supplemental O ₂ (yes), no. (%)	20 (69)	13 (35)	0.006
BNP, pg/mL	457 ± 474	138 ± 192	0.005
DE parameters			
RA enlargement, no. (%)	20 (69)	10 (18)	<0.001
RVSP, mmHg	72 ± 25	56 ± 23	0.01
RV dysfunction (moderate or severe), no. (%)	17 (59)	10 (27)	0.002
Pericardial effusion present, no. (%)	11 (38)	11 (31)	0.8
Baseline hemodynamics			
mRAP, mmHg	10 ± 5	8 ± 4	0.1
mPAP, mmHg	45 ± 9	41 ± 11	0.1
CI (Fick), mL/min/m ²	2.6 ± 0.8	2.7 ± 0.7	0.4
SvO ₂ , %	62 ± 9	68 ± 7	0.02
TPG, mmHg	31 ± 11	26 ± 12	0.1
PVR, Wood units	8 ± 4	6 ± 3	0.1
PH medications at time of 6MWT, no. (%)			0.1
None	9 (31)	7 (19)	
Parenteral prostanoids alone	2 (7)	1 (3.5)	

Table 2 (Continued)

Factor	CW (<i>n</i> = 29; 44%)	No CW (<i>n</i> = 37; 56%)	<i>P</i>
Single oral	4 (14)	17 (46)	
Combination (oral and parenteral)	3 (10)	3 (8)	
Combination (other)	11 (38)	9 (24)	

Note: Except where otherwise noted, data are mean ± standard deviation. Percentages are by column group. All comparisons are by the Student two-sample *t* test unless otherwise specified. 6M heart rate: heart rate at the end of the 6MWT; 6MWD: 6-minute walk distance; 6MWT: 6-minute walk test; BNP: B-type natriuretic peptide; BUN: blood urea nitrogen; CI: cardiac index; DE: Doppler echocardiography; delta heart rate: 6M heart rate minus baseline heart rate; DLCO: diffusion capacity for carbon monoxide; FVC: forced vital capacity; HRR1: heart rate recovery after 1 minute of rest; HRR2: heart rate recovery after 2 minutes of rest; HRR3: heart rate recovery after 3 minutes of rest; mPAP: mean pulmonary arterial pressure; mRAP: mean right atrial pressure; PH: pulmonary hypertension; PFT: pulmonary function test; PVR: pulmonary vascular resistance; RA: right atrium; RV: right ventricle; RVSP: right ventricular systolic pressure; supplemental O₂: patients using supplemental oxygen during the 6MWT; SvO₂: mixed venous oxygen saturation; TPG: transpulmonary gradient; WHO FC: World Health Organization functional class.

^a Fisher exact test.

results of the 6MWT and HRR. Clinical worsening was defined as death, lung transplantation, or hospitalization due to PH worsening, and TtCW was defined as time to the first worsening event in an individual patient.

We have previously described that HRR1 of <16 was the best predictor of clinical worsening and TtCW in patients with IPAH;¹⁵ therefore, for the purposes of this analysis, HRR1 of <16 was used as the HRR1 cutpoint. As described elsewhere,¹⁵ we also determined the value for abnormal HRR2 and HRR3 by finding the maximum value of the log-rank χ^2 statistics for every 5th-percentile increase of the cutoff points for abnormal HRR between the 10th and 90th percentiles in the study sample for TtCW as HRR2 of <24 and HRR3 of <32 (Fig. S1, available online). These analyses showed that HRR1 of <16 was the best determinant of clinical worsening and TtCW, and the rest of the analysis focused on HRR1. To study the true association between HRR1 and outcomes, analysis of association between HRR1 and clinical worsening, survival, and hospitalization was also performed by dividing the study population into terciles of HRR1.

Continuous measures were described as means, standard deviations, and percentiles, and categorical measures were summarized using frequencies and percentages. The two-sample *t* test or the Wilcoxon rank sum test was used to evaluate the association between HRR1 (binary) and continuous measures, and the Pearson χ^2 test or the Fisher exact test was used to assess the association between

HRR1 (binary) and categorical measures. The Pearson correlation coefficient was used to assess the correlation between HRR1 (continuous) and continuous measures. For the multivariable analysis, risk factors with a P value of <0.05 by univariable analysis that were felt to be clinically relevant were considered as candidates in the final model. Proportional hazard regression analyses with backward elimination were performed to evaluate the multivariable association between TtCW, time to death, time to hospitalization for worsening PH, and the risk factors. All tests were performed at a significance level of 0.05. SAS software (ver. 9.2; SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Overall characteristics of the study population

Between August 1, 2009, and October 31, 2011, 71 patients with CTD-PH underwent a 6MWT. Of these, 5 patients were taking β -blockers and were excluded from the analysis. The remainder ($n = 66$) included 53 patients with systemic sclerosis (limited: 48; diffuse: 5), 5 patients with mixed connective tissue disease, and 8 patients with systemic lupus erythematosus, and this group formed the study cohort.

Patients were followed up for a median of 17.8 months (interquartile range: 8.9–29.7 months). Table 1 outlines the clinical and hemodynamic characteristics of the study population as well as baseline characteristics. Patients were mostly white women in World Health Organization functional class (WHO FC) II or III. HRR1 had a strong correlation with 6MWD and BNP (Fig. 1).

Relationship between HRR1 and clinical worsening in CTD-PH

During the study period, 29 patients had clinical worsening events (Table 2). Those with clinical worsening had worse WHO FC ($P = 0.001$), shorter 6MWD ($P < 0.001$), higher delta heart rate ($P = 0.009$), reduced HRR1 ($P = 0.003$), reduced HRR2 ($P = 0.001$), reduced HRR3 ($P = 0.004$), and higher BNP ($P = 0.005$) and were more likely to require oxygen supplementation during the 6MWT ($P = 0.006$), to have right atrial enlargement ($P < 0.001$), and to have moderate or severe right ventricular dysfunction ($P = 0.002$). As described above, HRR1, HRR2, and HRR3 were all predictors of clinical worsening and TtCW (Figs. 2, S1), with HRR1 of <16 being the best predictor (log-rank $P < 0.0001$). Patients with HRR1 of <16 were much more likely to have clinical worsening than patients with

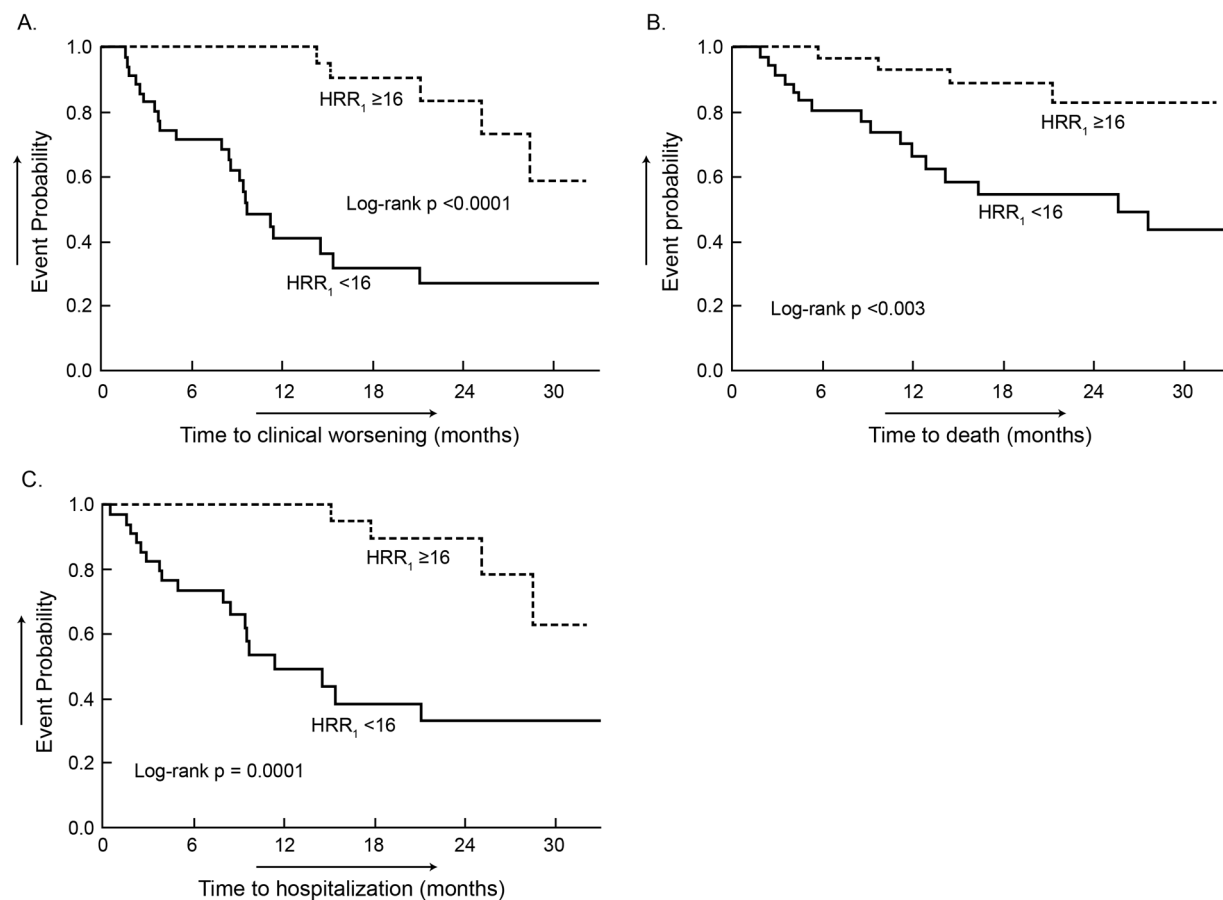


Figure 2. Kaplan-Meier analysis for time to clinical worsening (A), survival (B), and time to first hospitalization for worsening pulmonary hypertension (PH; C), showing that patients with heart rate recovery after 1 minute of rest (HRR1) of <16 had more rapid clinical worsening, reduced survival, and shorter time to first hospitalization for worsening PH than patients with HRR1 of ≥ 16 .

Table 3. Clinical characteristics of the study population by tercile of heart rate recovery after 1 minute of rest (HRR1)

Factor	Tercile 1: HRR1 of <10 (<i>n</i> = 22; 33.3%)	Tercile 2: HRR1 of 10–19 (<i>n</i> = 22; 33.3%)	Tercile 3: HRR1 of >19 (<i>n</i> = 22; 33.3%)	<i>P</i>
Age, years	58.5 ± 11	59 ± 18	49 ± 15	0.7
Female, no. (%)	18 (82)	17 (77)	21 (95)	0.06
WHO FC, no. (%)				0.1
I	0 (0)	0 (0)	4 (18)	
II	7 (32)	12 (55)	13 (59)	
III	12 (54)	8 (36)	5 (23)	
IV	3 (14)	2 (9)	0 (0)	
BUN, mg/dL	24 ± 18	22 ± 16	14 ± 8	0.07
Creatinine, mg/dL	1.1 ± 0.4	1 ± 0.4	0.8 ± 0.2	0.02
Sodium, mmol/L	139 ± 4	139 ± 4	139 ± 3	0.6
PFT parameters, % predicted				
FVC	64.5 ± 16	74 ± 28	75 ± 18	0.2
DLCO	35 ± 16	39 ± 18	45 ± 20	0.3
6MWT				
6MWD, m	285 ± 87	286 ± 110	376 ± 106	0.005
6MWD, % predicted	59 ± 29	58 ± 26	67 ± 19	0.4
Baseline heart rate, beats/min	90 ± 17	89 ± 21	83 ± 19	0.3
6M heart rate, beats/min	119 ± 21	122 ± 20	130 ± 23	0.2
Delta heart rate, beats/min	29 ± 17	32 ± 14	47 ± 17	0.001
Supplemental O ₂ (yes), no. (%)	12 (55)	15 (68)	6 (27)	0.09
BNP, pg/mL	531 ± 480	181 ± 187	110 ± 244	0.0001
DE parameters				
RA enlargement, no. (%)	17 (77)	8 (36)	5 (23)	0.1
RVSP, mmHg	77 ± 24	54 ± 19	58 ± 25	0.004
RV dysfunction (moderate or severe), no. (%)	14 (64)	7 (32)	6 (27)	0.1
Pericardial effusion present, no. (%)	10 (45)	7 (32)	5 (23)	0.06
PH medications at time of 6MWT, no. (%)				0.05
None	5 (23)	6 (27)	5 (23)	
Parenteral prostanoids	1 (5)	1 (5)	1 (5)	
Single oral	5 (23)	6 (27)	10 (45)	
Combination (oral and parenteral)	4 (18)	1 (5)	1 (5)	
Combination (other)	7 (32)	8 (36)	5 (23)	
Clinical worsening (yes), no. (%)	13 (59)	12 (55)	4 (18)	0.01
Hospitalization (yes), no. (%)	11 (50)	9 (41)	2 (9)	0.01
Status, no. (%)				0.07
Alive	12 (55)	15 (68)	19 (86)	
Dead	10 (46)	7 (32)	3 (14)	

Note: Except where otherwise noted, data are mean ± standard deviation. Percentages are by column group. All comparisons are by the Student two-sample *t* test. 6M heart rate: heart rate at the end of the 6MWT; 6MWD: 6-minute walk distance; 6MWT: 6-minute walk test; BNP: B-type natriuretic peptide; BUN: blood urea nitrogen; DE: Doppler echocardiography; delta heart rate: 6M heart rate minus baseline heart rate; DLCO: diffusion capacity for carbon monoxide; FVC: forced vital capacity; PH: pulmonary hypertension; PFT: pulmonary function test; RA: right atrium; RV: right ventricle; RVSP: right ventricular systolic pressure; supplemental O₂: patients using supplemental oxygen during the 6MWT; WHO FC: World Health Organization functional class.

Table 4. Cox regression analysis for heart rate recovery after 1 minute of rest (HRR1) and clinical outcomes in the study population

	Clinical worsening		Hospitalization		Death	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
HRR1 of <16 vs. ≥16	6.4 (2.6–19.2)	<0.001	6.6 (2.4–23)	<0.0001	4.5 (1.6–15.7)	0.003
Highest tercile (HRR1 of >19 vs. ≤19)	0.1 (0.04–0.5)	<0.001	0.1 (0.02–0.5)	0.001	0.3 (0.07–0.9)	0.04

Note: Cox regression analysis adjusted for World Health Organization functional class, B-type natriuretic peptide, 6-minute walk distance, and creatinine. CI: confidence interval; HR: hazard ratio by Cox regression analysis.

HRR1 of ≥16, and patients in the highest tercile were unlikely to have a clinical worsening event (Tables 3, 4; Figs. 3, 4).

Using the entire study sample, HRR1 of <16 was the strongest predictor of clinical worsening by univariable ($P < 0.0001$) and multivariable ($P = 0.0009$) analysis (Table 5). WHO FC III or IV was also predictive of clinical worsening in multivariable analysis ($P = 0.04$).

Relationship between HRR1 and hospitalization for worsening PH in patients with PH

During the study period, 22 (33%) patients were hospitalized for worsening PH (Table S1; Tables S1, S2 are available online). Those who were hospitalized had worse WHO FC ($P = 0.003$), 6MWD ($P = 0.04$), BNP ($P = 0.02$), HRR1 ($P = 0.002$), HRR2 ($P < 0.001$), and HRR3 ($P = 0.01$). These patients were also more likely to have

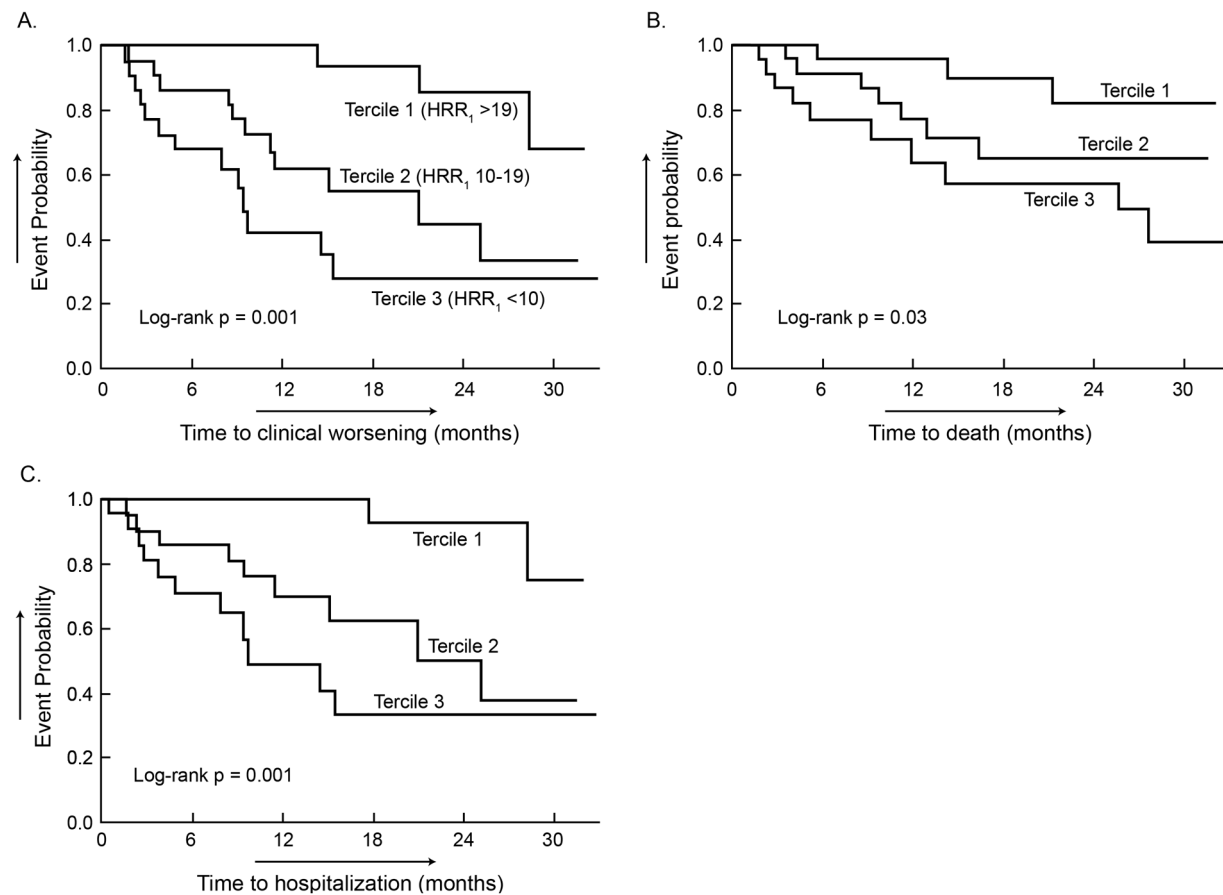


Figure 3. Kaplan-Meier analysis of heart rate recovery after 1 minute of rest (HRR1) by tercile, showing that patients in the lowest tercile had the shortest time to clinical worsening (A), the lowest survival (B), and the shortest time to first hospitalization for worsening pulmonary hypertension (PH; C) and that patients in the highest tercile had the longest time to clinical worsening, the highest survival, and the longest time to first hospitalization for worsening PH.

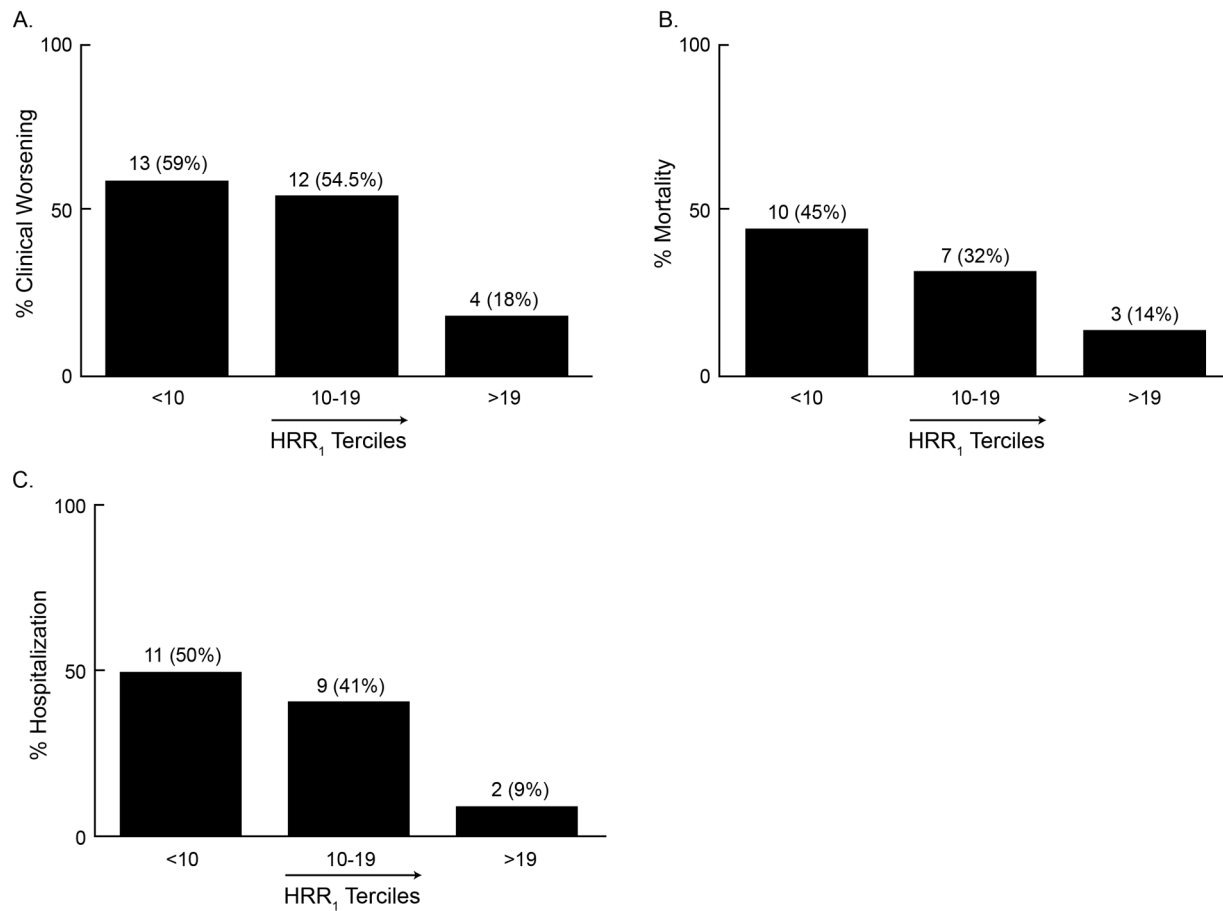


Figure 4. Bar graph of event rate in the study population across terciles for heart rate recovery after 1 minute of rest (HRR₁), showing that patients in the highest tercile had the lowest event rate for clinical worsening, survival, and hospitalization for worsening PH over the study period. Values above bars indicate the number of patients with the event and the percentage in their respective tercile group.

moderate or severe right ventricular dysfunction ($P = 0.005$) and to die ($P < 0.001$). As described above, HRR₁, HRR₂, and HRR₃ were all predictors of time to hospitalization for PH worsening, with HRR₁ of <16 being the best predictor (log-rank $P = 0.0001$; Fig. 2). Patients with HRR₁ of <16 were much more likely to be hospital-

ized for PH worsening than patients with HRR₁ of ≥ 16 , and patients in the highest tercile were unlikely to be hospitalized (Tables 3, 4; Figs. 3, 4).

Using the entire study sample, HRR₁ of <16 was the strongest predictor of the need for hospitalization for PH worsening by uni-

Table 5. Univariable and multivariable Cox regression analysis for predictors of clinical worsening, hospitalization, and death in the study population

Variable	Clinical worsening		Hospitalization		Death	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
HRR1 of <16	<0.0001	0.0009	0.0002	0.002	0.003	...
WHO FC I + II vs. III + IV	0.0008	0.04	0.005	0.1	<0.0001	0.002
BNP	0.01	...	0.008	...	0.009	...
6MWD	0.0003	...	0.003	...	0.0001	0.02
Creatinine	0.04	...	0.1	...	0.07	...

Note: 6MWD: 6-minute walk distance; BNP: B-type natriuretic peptide; HRR₁: heart rate recovery after 1 minute of rest; WHO FC: World Health Organization functional class.

variable ($P = 0.0002$) and multivariable ($P = 0.002$) analysis (Table 5).

Relationship between HRR1 and mortality in patients with CTD-PH

During the study period, 20 (30%) patients died (Table S2). Those who died had worse WHO FC ($P < 0.001$), 6MWD ($P < 0.001$), BNP ($P = 0.005$), HRR1 ($P = 0.007$), HRR2 ($P = 0.004$), and HRR3 ($P = 0.003$). Patients who died were more likely to require oxygen supplementation during the 6MWT ($P < 0.001$), to have right atrial enlargement ($P < 0.001$), and to have moderate or severe right ventricular dysfunction ($P < 0.001$) by Doppler echocardiography. Patients who died were also more likely to have been hospitalized for worsening PH ($P < 0.001$). As described above, HRR1, HRR2, and HRR3 were all predictors of survival, with HRR1 of <16 being the best predictor (log-rank $P < 0.003$; Fig. 2). Patients with HRR1 of <16 were much more likely to die than patients with HRR1 of ≥ 16 , and patients in the highest tercile were unlikely to die (Tables 3, 4; Figs. 3, 4).

Using the entire study sample, the strongest predictor of death by univariable analysis were WHO FC III or IV ($P < 0.0001$), 6MWD ($P = 0.0001$), and HRR1 of <16 ($P = 0.003$; Table 5). The best predictors by multivariable analysis were WHO FC III or IV ($P = 0.002$) and 6MWD ($P = 0.02$).

Patients with HRR1 of <16 were more likely to have worse WHO FC, higher BNP, and shorter 6MWD (Table 1; Fig. 5). Comparing the performance of HRR1 and BNP (Fig. 6), we found that, as expected, most patients with poor clinical outcomes had HRR1 of <16 and BNP above the median value of 106 pg/mL. It was noticeable that very few patients with HRR1 of ≥ 16 and especially those with HRR1 of ≥ 16 and BNP of <106 pg/mL (bottom-right quadrant) had clinical worsening events during the study period.

DISCUSSION

We report that HRR is an easily measured biomarker that is highly predictive of clinical worsening, TtCW, survival, and hospitalization for PH worsening among patients with CTD-PH. In addition, our results show that HRR1 was a better discriminator of future clinical events than HRR2 and HRR3. We also found that, similar to patients with IPAH, HRR1 of <16 can be used as a cutoff to predict future clinical events in patients with CTD-PH. Last, we found that patients with HRR1 of >19 (highest tercile) had a very low likelihood of being hospitalized or dying during the study period.

We have previously reported that HRR1 after a 6MWT was the best predictor of clinical worsening and TtCW in a cohort of patients with IPAH.¹⁵ We now report that HRR is also an important predictor of clinical worsening and TtCW among patients with CTD-PH. This is especially important given that the 6MWT is felt to suffer from several limitations and is not currently accepted as a validated predictor of long-term outcomes in this group.^{8,19,20} Several attempts have been made to predict “harder” outcomes, such as survival and hospitalizations among PAH patients. Such attempts have included single variables as well as composite prediction equations.^{2,9,10} We have previously shown that HRR1 could accurately predict hospitali-

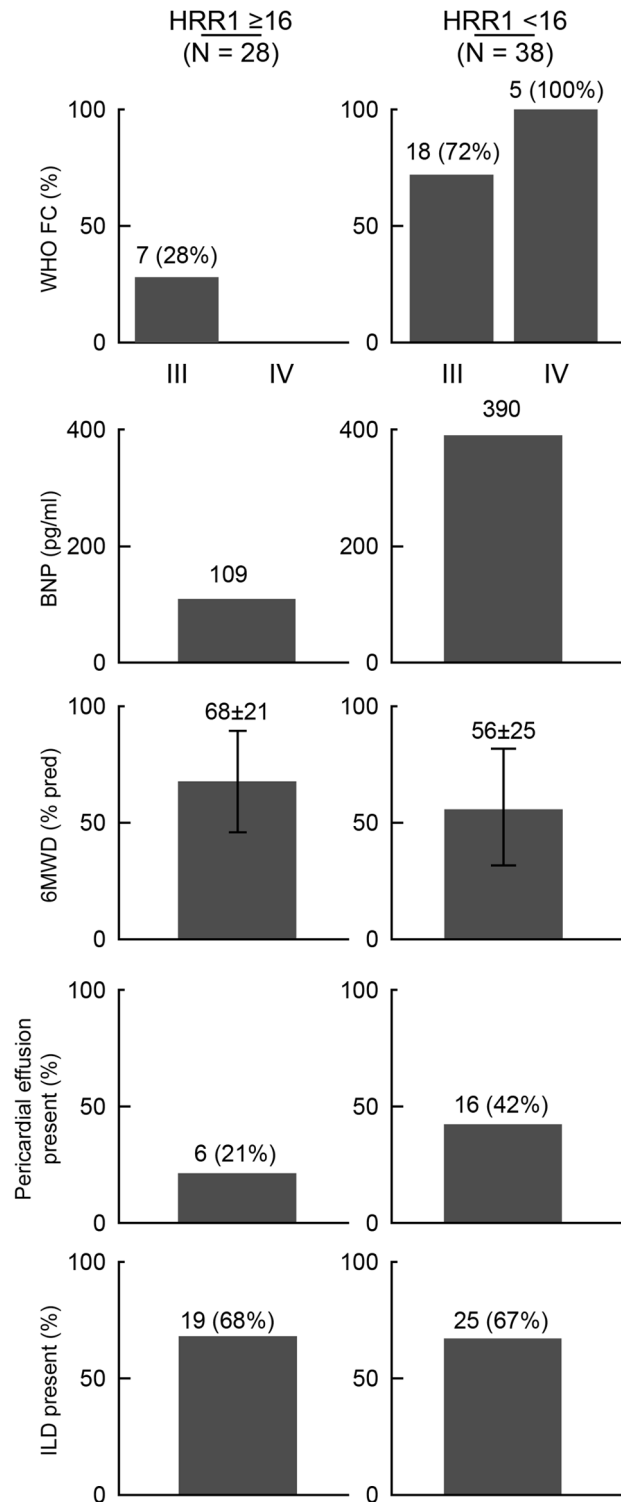


Figure 5. Patients with heart rate recovery after 1 minute of rest (HRR1) of <16 had worse World Health Organization functional class (WHO FC), higher B-type natriuretic peptide (BNP), and shorter 6-minute walk distance (6MWD) and were more likely to have a pericardial effusion on Doppler echocardiography. There was no difference with respect to the presence of interstitial lung disease (ILD) on thoracic imaging.

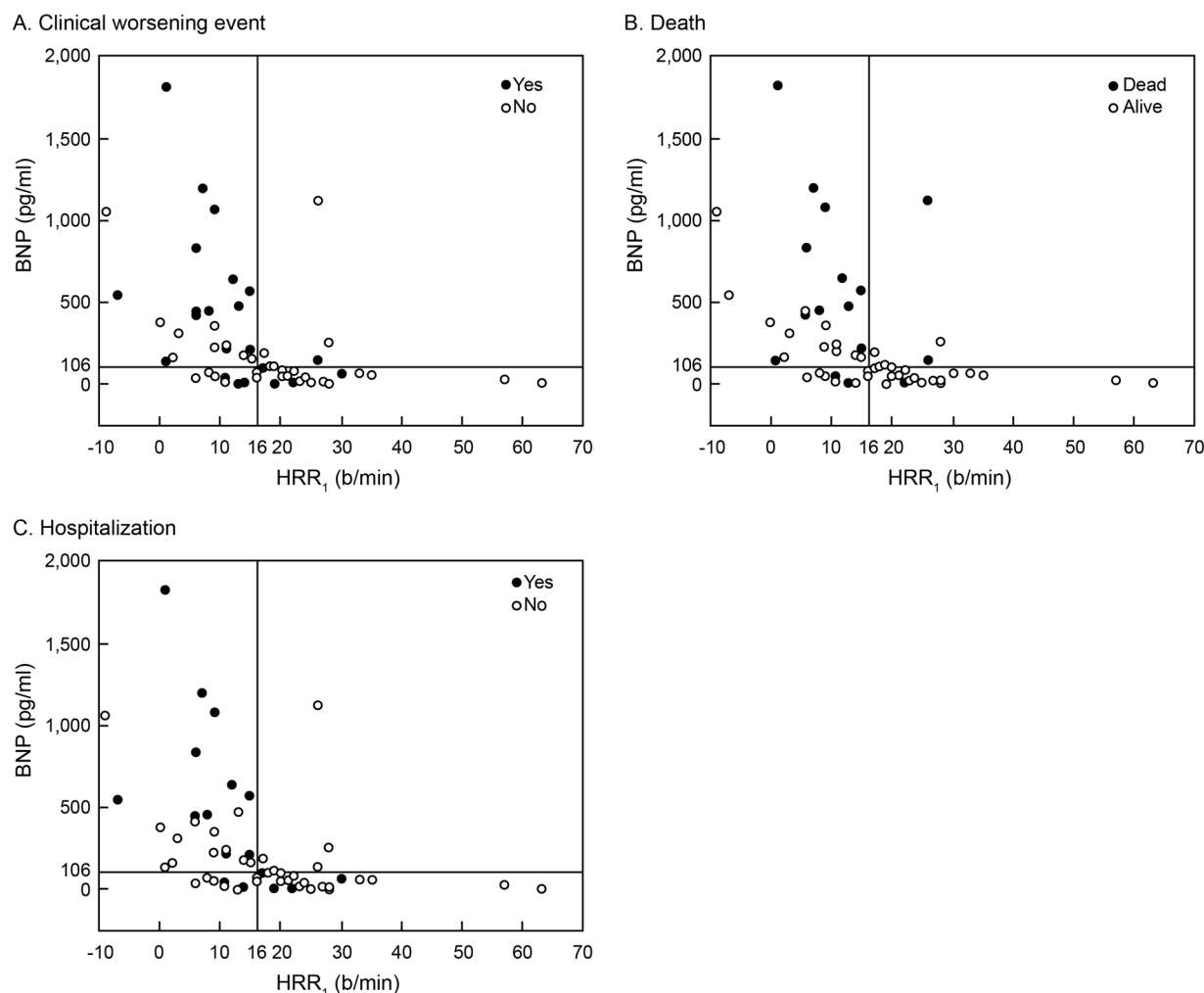


Figure 6. B-type natriuretic peptide (BNP) compared with heart rate recovery after 1 minute of rest (HRR₁) as predictors of clinical worsening (A), survival (B), and hospitalization (C) in the study population. Each circle denotes 1 study subject with connective tissue disease–associated pulmonary hypertension. The vertical line for HRR₁ is drawn at 16 beats/min (X-axis), and the horizontal line represents the median value for BNP (106 pg/mL; Y-axis).

zation and survival in patients with IPAH.¹⁶ Among patients with CTD-PH, scleroderma has received the most attention, and both measures of functional capacity as well as pulmonary hemodynamics have been shown to be important predictors of clinical outcomes.^{19,21} Measures of functional capacity such as the WHO FC and the 6MWT are felt to be subjective and suffer from a ceiling effect,^{5–8,19} whereas pulmonary hemodynamics require an invasive procedure. Attention has also focused on prediction equations, which, although accurate, are less generalizable and not easy to use.¹⁰

More recently, it has been postulated that a composite end point focused on clinical worsening events may be a more reliable reflection of outcome.²⁰ Even though clinical worsening may be a useful end point in clinical trials, the inherent fallacy in using clinical worsening in clinical practice is that, by definition, we are waiting for an adverse event to occur rather than trying to prevent the event from occurring. Such a strategy would be especially unfortunate in a progressive disease, where these events portend a poor outcome.²² Our own study showed that patients who eventually died were much

more likely to have been hospitalized during the follow-up period. Thus, there is a continuing effort to find an easy-to-measure biomarker that can accurately predict outcomes in these patients so that these outcomes may be prevented. This is the first study to report that HRR can not only predict clinical worsening and TtCW but is an important predictor of survival and hospitalization for worsening PH in a cohort of patients with CTD-PH.

Our findings tie in nicely with recent studies that have found evidence of autonomic dysfunction and sympathetic overactivation in patients with PAH^{11,23} and the fact that sympathetic overactivity has been associated with clinical deterioration in these patients.^{12,13} In the presence of impaired ventricular contraction, sympathetic discharge increases to maintain cardiac output by increasing the heart rate. The increase in heart rate with exercise is a function of both sympathetic activation and parasympathetic withdrawal. Recovery of heart rate during the initial resting period, however, is predominantly a function of parasympathetic reactivation.^{24–26} It is well known that increased parasympathetic activity is protective against

ischemia-related arrhythmias and also reduces heart rate and blood pressure.²⁷ The poor HRR may be a function of continued sympathetic activation and a lack of the normal parasympathetic reactivation at the end of the 6MWT.²⁴⁻²⁶ This may be a result of reduced tonic vagal activity similar to that in patients with chronic heart failure.^{28,29} In heart failure, decreased parasympathetic and increased sympathetic tone increase the risk of arrhythmic events and sudden cardiac death. Schwartz et al.³⁰ reported that increased parasympathetic activity had been associated with a decrease in the risk of death by protecting the heart against arrhythmias. It has also been reported that HRR may be linked to endothelial dysfunction among patients with heart disease.³¹ Our study reinforces the notion that autonomic dysfunction, as evidenced by reduced HRR, is predictive of both reduced survival and an increased likelihood of hospitalization for worsening PH in patients with CTD-PH.

We also found that patients in the highest tercile of HRR1 (HRR1 of >19) were at a very low risk of dying or being hospitalized during the study period. Thus, patients with HRR1 of >19 may be considered in a “safe zone,” with a reduced likelihood of the occurrence of these events. The same may be said of patients with HRR1 of ≥ 16 and BNP of <106 pg/mL. These findings are even more noteworthy because this was largely a prevalent cohort of patients with PAH, already receiving PH-specific therapy.

Abnormal HRR1 had a strong association with several indicators of poor prognosis that are well established in the PH literature. These include TtCW, hospitalization for PH worsening, death, reduced 6MWD, the need for oxygen with exertion, poor WHO FC, increased BNP, serum sodium of ≤ 136 mmol/L, right ventricular systolic dysfunction, and presence of pericardial effusion.^{1,3,4,9,10}

Similar to findings in our IPAH cohort,¹⁵ there was a strong correlation between HRR1 and 6MWD as well as heart rate at the end of the 6MWT and delta heart rate among patients with CTD-PH. We also found an association between 6MWD and delta heart rate among patients with CTD-PH—that is, the farther a patient walked, the greater the change in heart rate from baseline. We believe that patients with better cardiovascular function were able to walk farther, increase their heart rate appropriately with exercise, and have a better HRR1 than patients with more significant cardiovascular limitation. Similar findings have been reported by other investigators evaluating patients with heart failure undergoing cardiopulmonary exercise testing, and it has been shown that the prognostic significance of HRR is not dependent on maximal effort³² and may be a reflection of autonomic dysfunction and cardiovascular reserve.

Even though much of the HRR literature is based on patients undergoing cardiopulmonary exercise testing, there is a good correlation between HRR derived from cardiopulmonary exercise testing and a submaximal exercise test, such as the 6MWT.³³ There is also a growing body of evidence that autonomic dysfunction is present in patients with various cardiac and pulmonary disorders and that HRR after a 6MWT is a good reflection of its presence and is an accurate predictor of long-term outcomes.^{15,16,34,35}

In summary, our study shows that HRR1 is an easily measured biomarker that is highly predictive of clinical worsening, TtCW, survival, and hospitalization for PH worsening among patients with

CTD-PH. We also found that, similar to patients with IPAH, HRR1 of <16 can be used as a cutoff to predict future clinical events and that patients with HRR1 of >19 (highest tercile) had a very low likelihood of being hospitalized or dying during the study period. Further investigations are needed to better characterize the utility of this biomarker in prospective studies and larger populations. Studies are also needed to define its clinical utility in other forms of PAH.

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