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Heart Rate Variability in Pulmonary Arterial Hypertension

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ABSTRACT

Resting heart rate has been incorporated in REVEAL risk assessment. Rest and sleep heart rate variability (HRV) measured in the home setting could provide early insight into worsening physiology in patients with pulmonary arterial hypertension (PAH). We hypothesized continuous HRV monitoring in the home setting for 7 days would be a treatment responsive measure and be associated with outcomes in PAH. This was a prospective observational study completed at the University of Rochester. We recruited two groups, one with stable background therapy and another with therapy intensification during the study. MC10 Biostamp (continuous electrocardiogram heart rate monitoring) was worn for 7 days at baseline and follow up; stable patients completed monitoring twice within 4 weeks while treatment intensification patients were assessed 3 months later. HRV was calculated using MC10 proprietary algorithm. Baseline, follow up, and changes in heart rate and HRV (rest and sleep) were compared between the groups and correlated to clinical outcomes at 2 years. Periods of activity were excluded from analysis. Non-parametric testing was performed. Twenty-four (10 stable and 14 treatment intensification) PAH patients had paired monitoring sessions during sleep and rest. There were no statistical differences in heart rate or HRV values at baseline or follow-up within either stable PAH patients or those requiring treatment escalation. Additionally, the change in heart rate from baseline to follow-up did not differ significantly between the two groups. There was no difference in HRV between patients who had clinical worsening (parenteral therapy, hospitalization, or death) within 2 years, while elevated rest and sleep heart rate did predict clinical worsening at 2 years. Unlike left ventricular systolic failure, continuous HRV for 7 days in the home setting does not appear to improve assessment in PAH, and functional testing appears to be a better way to assess treatment response and risk for clinical worsening.

1 | Introduction

Pulmonary arterial hypertension (PAH) is a progressive vasculopathy leading to increased pulmonary vascular afterload and right heart failure [1]. Risk assessments are a proactive, objective way to identify patients with increased likelihood for mortality and clinical worsening [2, 3]. Depending on clinical status, office assessments are typically performed 2–4 times annually. PAH patients are quite sedentary [4] and may not recognize increased dyspnea with activity until they are substantially worse, delaying a recognition of clinical worsening for a previously stable patient. We and others have postulated that remote passive monitoring in the home setting can help fill this gap by identifying changes in clinical status between visits [4, 5].

In left ventricular systolic heart failure [6] and diabetes [7], low heart rate variability (HRV) measured in the home setting with wearable devices is associated with worse outcomes. HRV is the

inter-beat difference in impulses originating from the sinoatrial node and most accurately measured with chest-based patches capable of reporting a single lead electrocardiogram; it provides an indirect assessment of autonomic function [8]. The two most common ways to analyze HRV are time-domain and frequency-domain analyses. Shortened HRV reflects increased sympathetic tone. Patients with PAH have abnormalities in autonomic function [9] including increased sympathetic tone [10, 11] and renin-angiotensin-aldosterone system (RAAS) activation [12]; HRV could provide insight into this altered autonomic activity. HRV is a secondary outcome in at least one current PAH clinical trial [13]. However, little is known about therapy-associated changes in HRV for PAH patients; whether HRV can aid in identifying treatment-responsive patients or those at risk for clinical worsening; and how it correlates with established PAH variables.

In this study, we measured rest and sleep HRV calculated by root mean square of successive RR interval differences (RMSSD, time domain) and as ratio of low frequency (LF) to high frequency (HF) (LF/HF, frequency domain) [8] obtained through continuous electrocardiogram heart rate monitoring for 7 days at home in patients with PAH. Heart rate data during activity bouts (determined using actigraphy) were removed to minimize the influence of activity time (increase sympathetic tone) on HRV and heart rate. Rest and sleep heart rate data have less motion artifact, allowing for more accurate analysis. We explored whether there was any change in HRV after adding PAH treatment, the reproducibility of the measurement in patients without therapy change, its correlation with PAH variables of interest, and its association with clinical worsening (PAH hospitalization, initiation parenteral prostacyclin therapy, or death). We hypothesized that RMSSD HRV would increase and LF/HF would decrease after adding vasodilator therapy; we further postulated that HRV would be lowest in patients who ultimately had clinical worsening (as a measure of higher sympathetic activity).

2 | Methods

This was a prospective observational single-center study with Institutional Review Board approval completed between 2020 and 2022. Patients were recruited from our Pulmonary Hypertension Association Comprehensive Care Clinic as they followed up for routine care in clinic. Patients were eligible if they had Group 1 PAH [14]. Subjects were categorized into two groups: (a) Stable group, defined as stable PAH therapy at least 90 days before study enrollment with no intent to change therapy during study (regardless of treatment outcome; stable did not necessarily mean low risk); (b) Treatment intensification group defined as patients with a new diagnosis of PAH or those requiring intensification of therapy based on clinical status. In this group, baseline monitoring occurred before a therapeutic change was made. With the relatively high rate of obesity [15], diabetes [16], and atrial arrythmias in PAH [17], we did not exclude patients with co-morbidities or medications (e.g., beta-blockers) as we wanted to see how this measurement would perform in a general PAH cohort.

At baseline, clinical and demographic information was collected. Both groups completed emPHasis 10 questionnaire [18], unmasked 6-min walk test (6MWT) [19], Cardiac Effort with MC10 Biostamp nPoint (number of heart beats used during 6MWT/6MWD) [20, 21], functional class assessment, NT-proBNP, and REVEAL Lite 2 score [22]. After completing baseline testing, patients wore MC10 Biostamp nPoint for 7 days [23]. The MC10 Biostamp nPoint is a pair of small lightweight patches worn on the chest and thigh with a disposable adhesive. The Biostamp has been shown to accurately report HRV (RMSSD and LF/HF) and activity [24]. The chest device is both an accelerometer and single lead electrocardiogram (lead II electrocardiogram collected at 250 Hz). Subjects removed the Biostamp every 24 h to download the data and charge the sensor (typically ~1 h of time). They would reapply the sensor in the same location with a disposable adhesive. The electrocardiogram data generated RMSSD and LF/HF in 1-min intervals, and the proprietary algorithm classified the activity as rest, sleep, or activity using the accelerometer in the sensor. HRV during activity was excluded from analysis as activity increases sympathetic activity. HRV was separately averaged each day during rest and sleep (Figure 1); daily values were averaged during each monitoring period. Complete testing was repeated in the stable group within 4 weeks of baseline to assess the reproducibility of HRV in PAH. The treatment intensification group repeated testing 12 weeks later to assess for change after adding therapy. We hypothesized HRV would remain unchanged in the stable group and increase after adding PAH approved therapy (reflecting higher parasympathetic activity).

2.1 | Statistical Analysis

Continuous variables are reported as median with interquartile range. Categorical variables are reported as counts with percentages. To be included for analysis, subjects needed to wear MC10 for >12 h for at least 3 days during both monitoring periods and have both sleep and rest data. Non-parametric testing was used to compare for changes between the two-monitoring periods and differences between the two groups. Spearman correlation coefficient was used to compare common clinical PAH variables with HRV (only at baseline). Clinical worsening was defined as initiation of parenteral prostacyclin therapy, PAH hospitalization, or death from any cause; all patients were followed for 2 years. Logistic regression was performed to evaluate HRV (measured at the second monitoring) for patients with and without clinical worsening. GraphPad Prism 9 was used for statistical analysis.

3 | Results

3.1 | Baseline Demographics and Follow-Up

Thirty-four patients enrolled in the study. Four patients withdrew after completing the first monitoring period (two did not like the sensor, one died, and one moved out of state). Of the remaining 30, 24 wore the MC10 Biostamp during both monitoring periods with at least 3 days of >12 h including both sleep and rest data; for the other six, recording times (either at baseline or follow up) did not meet our pre-specified criteria.

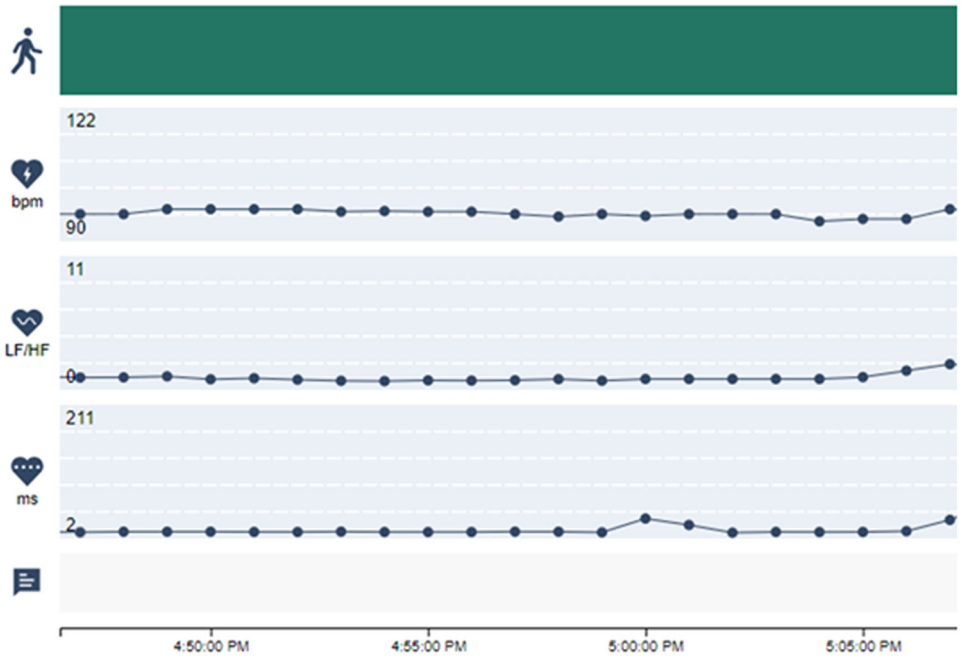

FIGURE 1 | Summary heart rate and heart rate variability (HRV) obtained by MC10 Biostamp. nPoint from a patient with PAH. The top (green) shows the person is sitting based on the chest and thigh-based accelerometers. The second row from the top shows resting heart rate. The third row shows calculated HRV ratio of low frequency (LF) to high frequency (HF), LF/HF. The bottom row shows root mean square of successive RR interval differences (RMSSD) HRV.

The stable group consisted of 10 patients and the treatment intensive group had 14 patients. Baseline characteristics are in Table 1. No new medications were added to the stable group between the two visits. Three stable participants were on beta blocker therapy (one for atrial fibrillation; two for systemic hypertension); one treatment intensification was on verapamil for cluster headache. No participant changed or added a drug intended to change heart rate. As expected, initiation or addition of PAH therapy resulted in clinically relevant improvements (Table 1) for REVEAL Lite 2 score [−1 (−4, −1,) vs. 0 (0, 0), $p = 0.0003$], 6MWD [51 m (9, 69) vs. 4 (−17, 32), $p = 0.03$], emPHasis 10 [−14 (−17, −8) vs. −2 (−8, 0), $p = 0.002$], and functional class [−1 (−1, 0) vs. 0 (0, 0), $p = 0.002$], when compared to the stable group where no changes occurred. There was a median drop of −359 pg/mL ($p = 0.08$) in NT-proBNP at follow up in the treatment group from baseline. Cardiac Effort, a novel way to integrate physiology into the 6 MW test, improved [−0.2 beats/m (−0.5, 0.1) vs. 0.04 beats/m (−0.1, 0.1), $p = 0.03$].

3.2 | Changes in Heart Rate

At baseline, the median rest and sleep heart rate in the stable group was 88 (80, 99) and 74 (67, 91) beats/min, respectively. The median rest and sleep heart rate in the treatment group was 82 (76, 92) and 71 (66, 77) beats/min. There were no statistical differences in heart rate values at baseline or follow-up within either stable PAH patients or those requiring treatment escalation. Additionally, the change in heart rate from baseline to follow-up did not differ significantly between the two groups (Figure 2). The results did not change if rest and sleep heart rates were averaged (together, not separately) over each monitoring period.

3.3 | Changes in HRV

At baseline, the median rest and sleep HRV calculated by RMSSD was 44 (18, 91) and 56 (10, 134) msec in the stable group. The median rest and sleep HRV in the treatment group was 28 (16, 50) and 31 (18, 59) msec. For frequency-domain, at baseline, the median rest and sleep HRV calculated by LF/HF was 2.51 (1.49, 2.83) and 1.64 (1.14, 2.60) in the stable group. The median rest and sleep LF/HF HRV in the treatment group was 2.83 (1.87, 4.44) and 2.71 (1.87, 6.73). There were no statistical differences in HRV at baseline or follow-up within either stable PAH patients or those requiring treatment escalation. Additionally, the change in HRV from baseline to follow-up did not differ significantly between the two groups (Figure 2). There was no difference if rest and sleep HRV were averaged over each monitoring period.

3.4 | Clinical Worsening

There were seven patients who had clinical worsening after their second monitoring session (three deaths, one hospitalization related to PAH, and three parenteral prostacyclin initiation) within 2 years of follow up; two were in the group initially identified as stable and five were in the treatment intensification group. Using data from the second monitoring period, both rest and sleep heart rate were lower in patients without clinical worsening (Figure 3). Two out of the three patients who had average resting and sleep heart rate > 96 beats/min died. In line with the higher resting heart rates, rest and sleep RMSSD were slightly but not significantly lower in those with clinical worsening (Figure 3). Because resting heart rate was different in those who ultimately suffered clinical

TABLE 1 | Demographics and clinical parameters at baseline and follow up.

	Stable ($n = 10$)		Treatment intensification ($n = 14$)	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**
Age, years	50 (40, 67)	—	60 (43, 69)	—
Female (%)	7/10	—	8/14	—
Body mass index, kg/m^2	32 (27, 40)	—	28 (25, 33)	—
Atrial fibrillation (%)	1 (10%)	—	0 (0%)	—
Diabetes mellitus Type II (%)	0 (0%)	—	0 (0%)	—
Obstructive sleep apnea (%)	8 (80%)	—	6 (43%)	—
Beta blocker/calcium channel blocker	3 (30%)	3 (30%)	1 (7%)	1 (7%)
Pulmonary arterial hypertension (%)				
Idiopathic/heritable	7 (70%)	—	10 (71%)	—
Connective tissue disease	2 (20%)		4 (29%)	
Congenital heart disease	1 (10%)		0	
Functional class, II/III (%)	10/0	10/0	4/10	13/1
6-min Walk distance, m	383 (359, 482)	389 (352, 507)	399 (297, 438)	436 (349, 466)
Cardiac effort, beats/m	1.65 (1.45, 2.0)	1.72 (1.49, 1.99)	1.88 (1.46, 2.52)	1.68 (1.4, 2.03)
N-terminal pro-B-type natriuretic peptide, pg/mL	212 (137, 361)	—	1810 (112, 3852)	392 (72, 1694)
REVEAL Lite 2	4 (3, 6)	4 (3,6)	7 (4, 10)	5 (2, 7)
PAH Meds (%)				
None	0	0	8 (57%)	0
Monotherapy	1 (10%)	1 (10%)	1 (7%)	2 (14%)
Combination	5 (50%)	5 (50%)	4 (29%)	7 (50%)
Prostacyclin + background				
Oral	1 (10%)	1 (10%)	1 (7%)	4 (29%)
Parenteral	3 (30%)	3 (30%)	0 (0%)	1 (7%)
Right heart catheterization				
Right atrial pressure, mmHg	11 (6, 13)		9 (7, 12)	
Mean pulmonary artery pressure, mmHg	39 (26, 44)	—	47 (43, 53)	—
Pulmonary vascular resistance, WU	4 (3, 6)		12 (6, 14)	
Cardiac index, L/min/m^2	2.2 (2, 2.9)		1.8 (1.5, 2.3)	
emPHasis 10	22 (18, 33)	20 (14, 27)	33 (25, 37)	18 (12, 24)
MC10 Biostamp nPoint				
Average daily wear time, min	1290 (1124, 1340)	1303 (1232, 1337)	1208 (1058, 1315)	1263 (1119, 1301)
Average daily steps	1689 (1366, 2501)	1594 (1243, 2798)	1443 (860, 2220)	2166 (1220, 2887)
Average activity time, min	91 (68, 130)	89 (61, 157)	61 (48, 145)	88 (65, 162)
Heart rate, beats/min				
Rest	88 (80, 99)	85 (80, 101)	82 (76, 92)	87 (77, 93)
Sleep	74 (67, 91)	73 (63, 90)	71 (66, 77)	68 (66, 86)
Heart rate variability, RMSSD msec				
Rest	44 (18, 91)	33 (15, 102)	28 (16, 50)	26 (16, 48)
Sleep	56 (10, 134)	51 (11, 144)	31 (18, 59)	26 (17, 43)

(Continues)

TABLE 1 | (Continued)

	Stable ($n = 10$)		Treatment intensification ($n = 14$)	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**
Heart rate variability, LF/HF				
Rest	2.51 (1.49, 2.83)	2.59 (1.18, 3.79)	2.83 (1.87, 4.44)	3.43 (2.03, 5.09)
Sleep	1.64 (1.14, 2.60)	1.66 (0.70, 2.88)	2.71 (1.87, 6.73)	3.83 (1.51, 6.10)

Note: Right heart catheterization was performed in 5 stable and 12 treatment intensification patients within 21 days of baseline testing. Root mean square of successive RR interval differences (RMSSD). Ratio of low frequency (LF) to high frequency (HF) (LF/HF). Values are median with interquartile range or count and percentage.

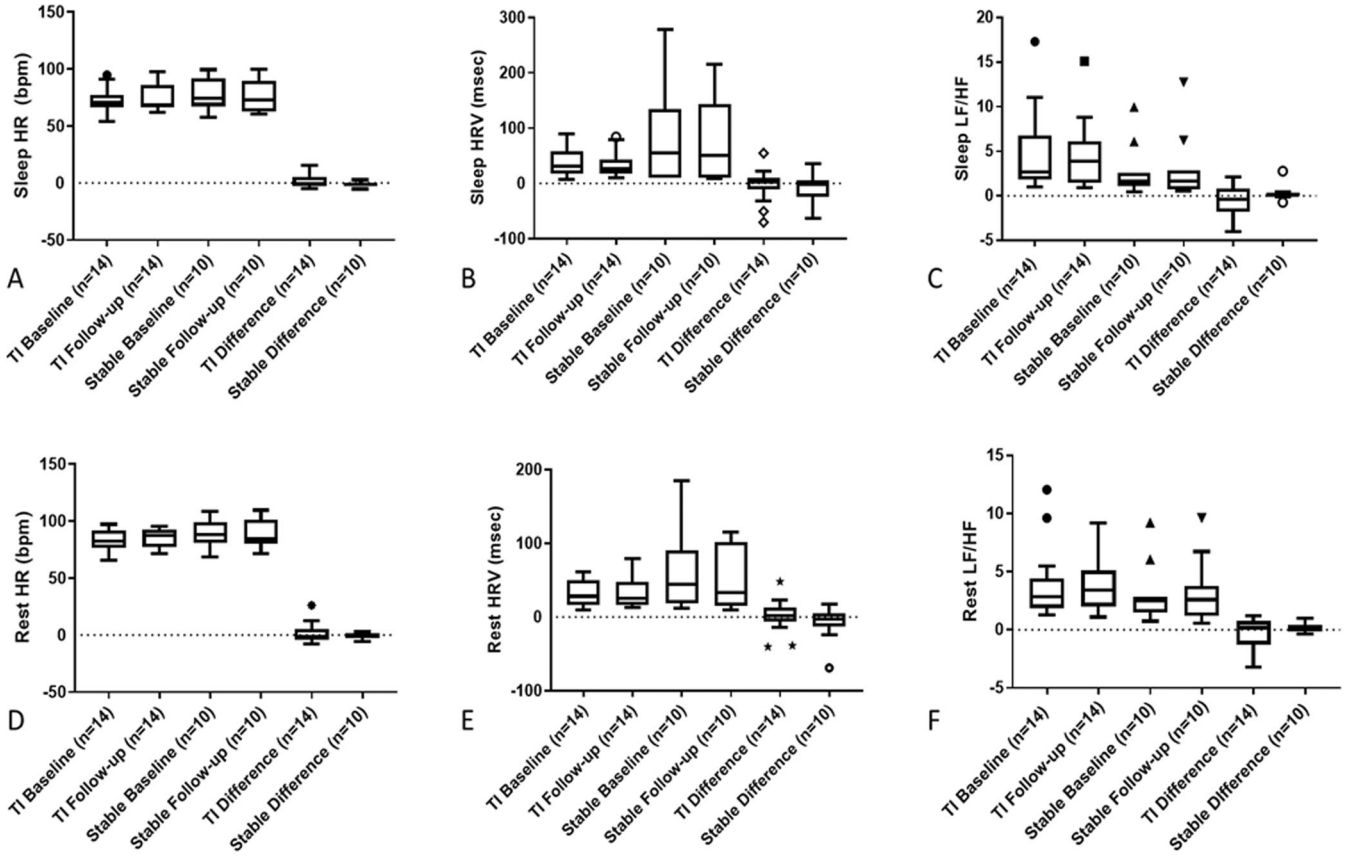

FIGURE 2 | Heart rate (HR) and heart rate variability (HRV) in patients with pulmonary arterial hypertension. (A–F) There were no differences in baseline, follow-up, or changes between baseline and follow-up values of heart rate or HRV, either during sleep or rest, within stable patients or treatment intensification (TI) patients, or when comparing stable to TI patients. Panel B and E show root mean square of successive RR interval differences (RMSSD) HRV and C and F show the ratio of low frequency (LF) to high frequency (HF) (LF/HF) HRV. Wilcoxon matched-pairs signed rank test was used for paired comparison and Mann–Whitney nonparametric test was used for unpaired comparison.

worsening, we looked at resting heart rate segregated by REVEAL Lite 2. In the 16 patients with low risk REVEAL Lite 2 (< 6), resting heart rate was 84 beats/min (80, 95); in the eight with intermediate/high risk (≥ 6), resting heart rate was 89 beats/min (76, 93). There were no differences in REVEAL Lite 2 score, NT-proBNP, 6MWD, and Cardiac Effort between patients with clinical worsening (data not shown).

3.5 | HRV and Heart Rate Correlation With PAH

Spearman correlations from baseline HRV and HR are listed in Table 2. The majority of variables did not correlate with either HRV or HR. Resting HR and HRV correlated with age. NT-proBNP and resting LF/HF had a moderate correlation. The directionality of the correlation was opposite of what would be hypothesized and could be spurious given the number of comparisons.

4 | Discussion

In this small cohort of patients with PAH, measuring HRV over 7 days at home using time domain (RMSSD) and frequency domain (LF/HF) did not add significantly to routine clinical assessments; specifically, it did not show changes suggesting

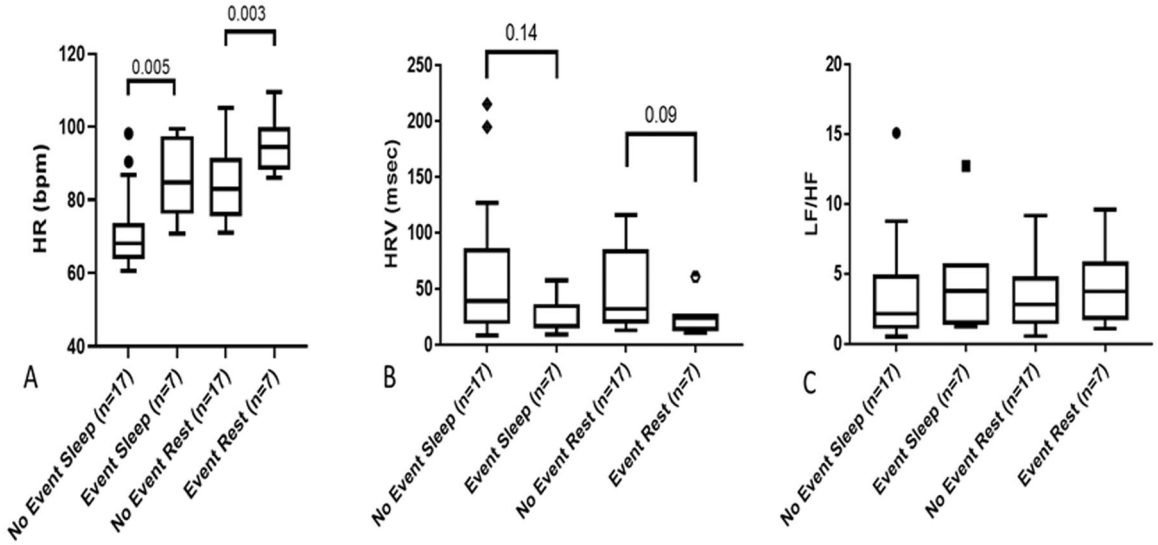

FIGURE 3 | Heart rate (HR) and heart rate variability (HRV) in patients with and without clinical worsening (heart failure hospitalization, parenteral prostacyclin initiation, or death) over 2 years after the last monitoring period. (A) Both heart rate at sleep and rest were lower in patients without clinical worsening. (B) There was a trend for patients without clinical worsening having higher root mean square of successive RR interval differences (RMSSD) HRV during sleep and rest. (C) There was no difference in the ratio of low frequency (LF) to high frequency (HF), LF/HF, HRV between patients with and without clinical worsening. Mann–Whitney nonparametric test was used for comparison.

increased parasympathetic activity after adding PAH therapies. We think that the negative finding is especially compelling as our treatment intensification cohort included 8 incident patients in whom the signal for change might be largest; moreover, this group enjoyed a very large clinical benefit with treatment (Table 1). REVEAL Lite 2 incorporates resting heart rate [22] because of its prognostic significance, and we replicated this in our observation that an elevated rest and sleep heart rate in the home setting was associated with increased risk of clinical worsening. One important limitation to our treatment intensification cohort is that it was older (median 60 years) and enriched for obstructive sleep apnea (but not obesity, diabetes, or atrial fibrillation). This older age may have prevented us from observing a change in HRV. On the other hand, we observed robust signals for improvement in other variables, and at this time, it seems unlikely that incorporating home HRV monitoring will add much to our current management strategies in PAH.

The control of heart rate is an important and complex process in PAH. Chronotropic response during exercise (peak—resting heart rate) is associated with 6MWD in PAH [25]. The heart rate slope [26] and recovery [27] during 6MWT are associated with clinical worsening. Resting heart rate is an important prognostic variable in REVEAL Lite 2 risk assessment [22] and has been shown to be associated with outcomes in other cohorts [28, 29]. We have previously shown that integration of continuous heart rate monitoring improves interpretation of 6-min walk distance through Cardiac Effort [20, 21]. Therefore, we hypothesized that continuous electrocardiogram heart rate monitoring in the home setting should yield novel markers of treatment response or prognosis.

HRV, or beat to beat variation in heart rate, was first recognized by the ancient Greek physician Herophilos [30] and remains an active area of research today. With the addition of electrocardiogram heart rate monitors in wearable devices, HRV is an easy to measure physiologic marker in the home setting. HRV can be influenced by non-modifiable factors (age, ethnicity, sex) and modifiable factors (fitness level, anxiety, diabetes, and obesity) [31]. Low HRV is associated with increased mortality [32] and likely a marker of increase sympathetic tone [8]. Electrocardiogram is the gold standard for HRV analysis and has less error than photoplethysmography (pulse wave measurement). When calculating HRV, only beats originating from the sinoatrial node are included in analysis to isolate input from the autonomic nervous system. Atrial fibrillation and premature atrial contractions may falsely increase HRV measurement; therefore, it is important to be able to evaluate p waves when analyzing the data. We wanted to interrogate rest and sleep HRV to minimize the impact activity would have on sympathetic tone and evaluate if there were differences between sleep and rest, especially in the setting of sleep apnea.

There is little reported on HRV in PAH and the majority of observations are from a single time point. In our approach, we used RMSSD and LF/HF to interrogate both the time and frequency domains that would provide insight into the parasympathetic and sympathetic autonomic system, respectively. It has been previously reported that RMSSD (time domain) correlated with pulmonary artery pressure and may help to predict outcomes in idiopathic PAH [33]. In a separate, more advanced group of patients awaiting transplantation, the authors found HRV during 24-h monitoring was lower than a control group, and a group of left ventricular systolic heart failure patients had lower HRV than PAH. In this cohort, they did not find a correlation between HRV and mPAP [34]. In a group of 26 idiopathic PAH patients, primarily functional class III and low 6MWD, investigators monitored heart rate during a single 24-h period. The authors found RMSSD was negatively correlated with mPAP, and there was a difference between average heart

TABLE 2 | Correlation between baseline heart rate variability and heart rate with pulmonary arterial hypertension variables.

	RMSSD				LF/HF				Heart rate			
	Sleep		Rest		Sleep		Rest		Sleep		Rest	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Age, years	0.3 (−0.2, 0.6)	0.2	0.4 (0.0, 0.7)	0.04	−0.1 (−0.5, 0.3)	0.7	−0.5 (−0.7,−0.1)	0.01	−0.2 (−0.6, 0.2)	0.3	−0.4 (−0.7 −0.0)	0.04
BMI, kg/m^2	−0.4 (−0.7, 0.1)	0.1	−0.3 (−0.7, 0.1)	0.1	0.3 (−0.1, 0.6)	0.2	0.3 (−0.2, 0.6)	0.2	−0.1 (−0.5, 0.4)	0.8	0.1 (−0.3, 0.5)	0.6
REVEAL Lite 2 Score	0.0004 (−0.4, 0.4)	0.9	0.1 (−0.6, 0.2)	0.6	−0.1 (−0.4, 0.2)	0.4	−0.4 (−0.6 −0.1)	0.01	0.2 (−0.2, 0.6)	0.3	−0.2 (−0.5, 0.3)	0.5
NT-proBNP, pg/mL	0.2 (−0.3, 0.6)	0.4	0.2 (−0.2, 0.6)	0.3	−0.2 (−0.5, 0.1)	0.1	−0.5 (−0.7 −0.2)	0.001	0.1 (−0.3, 0.5)	0.6	−0.1 (−0.5, 0.3)	0.5
6MWD, m	0.2 (−0.2, 0.6)	0.3	0.1 (−0.3, 0.5)	0.5	0.04 (−0.3, 0.3)	0.8	0.2 (−0.1, 0.4)	0.3	−0.2 (−0.6, 0.2)	0.3	−0.1 (−0.5, 0.4)	0.8
Cardiac effort, beats/m	−0.2 (−0.6, 0.2)	0.3	−0.1 (−0.5, 0.3)	0.6	−0.1 (−0.4, 0.2)	0.3	−0.2 (−0.5, 0.05)	0.1	0.1 (−0.3, 0.5)	0.5	0.1 (−0.3, 0.5)	0.7
emPHasis 10	−0.2 (−0.6, 0.2)	0.3	−0.2 (−0.6, 0.2)	0.3	0.1 (−0.2, 0.4)	0.4	0.1 (−0.2, 0.4)	0.4	−0.1 (−0.5, 0.4)	0.7	−0.2 (−0.6, 0.2)	0.3
Cardiac index, L/min/m^2	−0.2 (−0.6, 0.3)	0.4	−0.1 (−0.6, 0.4)	0.7	−0.04 (−0.5, 0.5)	0.9	0.4 (−0.1, 0.8)	0.1	0.2 (−0.3, 0.7)	0.4	0.3 (−0.3, 0.7)	0.3
PVR, WU	0.1 (−0.4, 0.6)	0.6	0.1 (−0.4, 0.5)	0.8	0.04 (−0.5, 0.5)	0.9	−0.3 (−0.7, 0.2)	0.2	−0.4 (−0.7, 0.2)	0.1	−0.3 (−0.7, 0.2)	0.2
Steps/day	0.1 (−0.4, 0.5)	0.8	−0.1 (−0.5, 0.4)	0.8	0.2 (−0.1, 0.5)	0.2	0.3 (−0.1, 0.6)	0.2	0.0 (−0.4, 0.4)	0.9	0.1 (−04, 0.5)	0.7
Activity time, min	0.1 (−0.3, 0.5)	0.5	−0.01 (−0.4, 0.4)	0.9	0.1 (−0.2, 0.4)	0.5	0.4 (−0.1, 0.7)	0.1	−0.1 (−0.6, 0.3)	0.4	0.0 (−0.4, 0.4)	0.9

Note: Spearman correlation was performed.
Abbreviations: BMI, body mass index; HF, high frequency; LF, low frequency; LF/HF, ratio of low frequency to high frequency; 6MWD, 6-min walk distance; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PVR, pulmonary vascular resistance; RMSSD, root mean square of successive RR interval differences.

rate and RMSSD between patients with PAH and controls [33]. In a retrospective study investigators used data from an overnight sleep study in 38 Group 1 PAH patients; they identified at least 5 min of stage N2 sleep with no apnea or hypopnea to calculate HRV. The authors found heart rate was higher in the pulmonary hypertension group compared to disease controls undergoing a sleep study for other reasons; however, there was no between—group difference in RMSSD. Interestingly, RMSSD was different in non-PAH patients with and without sleep apnea [35]. In 48 functional class III PAH patients, HRV was measured under highly-controlled conditions during a single monitoring period. Monitoring occurred during the same time of day in all subjects; they sat in a quiet air-conditioned room, fasted at least 2 h, and were not allowed to smoke, drink alcohol, or use caffeine for 24 h before monitoring. During that 20-min recording, patients with PAH had a reduction in HRV compared to controls [36]. Most recently, an implantable loop recorder was studied in 27 PAH and 14 chronic thromboembolic pulmonary hypertension patients without diabetes. The median follow up was 2 years, and the majority of their patients were male. The authors did not report how many patients were offered a loop recorder and refused. They also sensibly excluded periods of arrhythmia in analysis but did not report length of arrhythmias or the number of patients for whom that occurred. They used Standard Deviation of the 5-min average NN (SDANN) and did not report RMSSD; they summarized 30 days of data with each clinical assessment. Interestingly, they found HRV (SDANN) correlated with hemodynamics but not cardiac MRI variables. They found a higher HRV was associated with lower risk while lower HRV predicted worse outcomes [37].

In contrast to this previous work, our study is unique in that we were assessing for early changes that would track with treatment response. We were surprised that we did not see a change in HRV to suggest increased parasympathetic activity despite improvement in other PAH parameters, especially since half were treatment naïve. All of the reported studies had different patient populations, co-morbidities, and duration of monitoring that could explain different findings. The modifiable portion of HRV may be a global measure of fitness and health that is resistant to change in our cohort of patients who were quite inactive (Table 1), older, and enriched with sleep apnea (five out six in the treatment group were on treatment). Low physical activity contributes to lower HRV [38]. Since PAH patients are generally inactive (including this cohort) [4], increasing physical activity may also need to be addressed to improve HRV after adding therapy.

Patient acceptance was not uniform. In our highly motivated research cohort, we had two patients drop out of the study because they didn't like the reusable adhesive. Another 6 did not wear it enough to meet our pre-specified criteria (which may have been unnecessarily demanding). Based on the available data and patient acceptance, we don't think HRV monitoring at rest for 7 days continuously at home adds much to the current comprehensive, clinic-based assessment. HRV at rest did not identify patients at risk of progressing compared to our standard assessment. Although future studies are incorporating HRV as part of an implantable monitoring system [13], given the heterogenous nature of PAH and co-morbidities that influence HRV, our data of 7 days of continuous HRV monitoring suggest that there may be too much 'noise' in the HRV system to provide useful, PAH-specific health information.

There are limitations to our study. It was a single center study completed during the COVD-19 pandemic. We don't know what influence the added stress of COVID-19 and inactivity from lockdowns had on HRV and whether it blunted any treatment response. On the other hand, multiple prior reports have shown patients with PAH are very inactive before COVID-19 [4] and to date no study has shown that activity has increased after adding therapy [39, 40]. We had small numbers in both the treatment intensification and control PAH group, and they were not age-matched; the treatment intensification group was older (60) than the median age from most recent clinical studies. Four patients were on therapies that could have influenced heart rate or HRV, and one person had congenital heart disease. A total of 25% of patients withdrew or were excluded from analysis because they did not meet our pre-specified criteria for wear time. It's entirely possible that we missed a modest treatment effect on HRV, such as that observed in a recent carvedilol study [41]. Nonetheless, we think that the available data in PAH, as well as recent findings from other disease states [41, 42], does not support the idea that we have missed a large magnitude effect with this study of HRV in PAH. The strength of current multi-parametric assessments in PAH implies that additional metrics will need to have a large magnitude and independent effect to be salient additions to our current evaluation in response to new therapy. We are also aggressive with early prostacyclin therapy, which was the reason for three people having clinical worsening. REVEAL risk score has been most rigorously studied for outcomes at 1 year, and this is also a likely reason that we didn't observe a difference between the groups (in terms of REVEAL score) considering events occurring out to 2 years.

In conclusion, in our small prospective study we found that continuously measured HRV (RMSSD and LF/HF) obtained during rest and sleep in the home setting did not change after adding PAH approved therapy and was not associated with clinical worsening. HRV is influenced by many factors (activity level, atrial arrythmias, obesity, diabetes); these factors increase the noise of the test and may limit utility in PAH. Current assessments (BNP, 6MWT, FC) and novel measures like Cardiac Effort or right ventricular imaging, appear to be better markers of treatment response in PAH than continuously measured HRV in the home setting.

Author Contributions

Daniel Lachant: study design, data analysis, interpretation, and writing of the manuscript. **Michael Lachant:** data acquisition, data analysis. **Bishal Gyawali:** data acquisition, data analysis, writing of the manuscript. **Dominick Roto:** data acquisition, data analysis. **R. James White:** study design, data analysis, interpretation, and writing of the manuscript. **All Authors:** approve the manuscript.

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Ethics Statement

The University of Rochester RSRB approved the protocol before the research was completed.

Conflicts of Interest

Daniel Lachant received consulting and speaking fees from United Therapeutics within the past 24 months. United Therapeutics also provides University of Rochester with research funding for industry and investigator sponsored studies. The other authors declare no conflicts of interest.

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