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Continuous heart monitoring to evaluate treatment effects in pulmonary hypertension

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ABSTRACT

Background The treatment of pulmonary hypertension (PH) has improved rapidly in recent decades. There is increasing evidence to support the role of early intervention and treatment in affecting clinical outcomes in PH.

Objectives To assess treatment effects before and after the escalation of specific PH treatments using continuous heart monitoring with a Reveal LINQ loop recorder.

Methods Patients were compared before and after treatment escalation. Treatment escalation was defined as an additional pulmonary arterial hypertension (PAH) drug, pulmonary endarterectomy, percutaneous balloon angioplasty or bilateral lung transplantation. Specifically, changes in heart rate variability (HRV), heart rate (HR) and physical activity were assessed.

Results In this prospective study, 41 patients (27 with PAH and 14 with chronic thromboembolic pulmonary hypertension (CTEPH)) were enrolled. Among them, 15 (36.6%) patients underwent PH treatment escalation. Prior to escalation, patients were monitored for a median of 100 (range: 68–100) days and after therapy escalation for a median duration of 165 (range: 89–308) days. In the escalation group, there was a significant increase in HRV, physical activity indexed by daytime HR and a significant decrease in nighttime HR assessed at baseline and after treatment escalation in both the PAH and CTEPH groups. This was paralleled by significant improvements in WHO functional class, 6-min walking distance and N-terminal pro-b-type natriuretic peptide.

Conclusions This is the first study to demonstrate an association between specific PH therapies and changes in HRV, HR nighttime and physical activity. This indicates the potential of continuous monitoring in the evaluation of treatment effects in PH.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Increasing evidence supports early intervention for improved clinical outcomes in patients with pulmonary hypertension (PH).
⇒ Combination therapy is now common in management of patients with PH which can hinder the demonstration of additional treatment effects based on traditional methods.

WHAT THIS STUDY ADDS

⇒ This is the first study to link specific PH therapy with heart rate variability, nighttime heart rate and physical activity via continuous monitoring in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.
⇒ Importantly, the changes found via continuous heart monitoring were paralleled by changes in the current follow-up risk assessment parameters.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results suggest that continuous heart monitoring could be a valuable tool for assessing treatment effects in patients with PH, potentially aiding in guiding future treatment strategies.

INTRODUCTION

The treatment of pulmonary hypertension (PH) has evolved rapidly in recent decades, especially for patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic hypertension (CTEPH) classified as WHO PH group 1 and 4, respectively.[1 2] Today, 12 approved PAH drugs focusing on three vasodilatory pathways are used in the treatment of PAH.[1] Most of the treatment effects produced by the approved PAH drugs are based on the improvement of the 6-min walking distance (6MWD).[3–5]

There is increasing evidence to support the importance of early intervention and treatment in improving clinical outcomes in PAH.[1 6 7] Consequently, the management of PAH has evolved to include upfront double and triple combinations of PAH drugs.[1 8] However, PAH remains incurable, and the mortality rate is high.[1 9] Risk assessment has also become an integral part of treatment strategies in addition to the earlier detection of disease deterioration.[1] In the most recent European Society of Cardiology and European Respiratory Society (ESC/ERS) guidelines (2022), a 4-strata follow-up risk assessment model was introduced, which included three risk determinants:

Table 1 Baseline characteristics

Variable	Treatment escalation (n=15)	Non-escalation (n=26)	Total (n=41)	P value
Age, years (mean, SD)	60.1 (10.6)	53.7 (13.8)	55.8 (13.2)	<0.0001*
Female, n (percentage of patients)	5 (33%)	15 (58%)	20 (49 %)	<0.0001*
Months with diagnosis (median, IQR)	16 (2, 52)	51 (14, 114)	44 (13, 87)	<0.0001*
NT-proBNP (median, IQR)	51 (22.2, 359)	27.2 (8, 65,2)	34 (14.4, 160)	<0.0001*
6MWD (mean, SD)	403 (130.6)	511.3 (105)	475.2 (125.1)	<0.0001*
WHO-FC, n				
I	0	5	5	<0.0001*
II	4	13	17	
III	9	7	16	
IV	2	1	3	
WHO-FC (mean, SD)	2.8 (0.9)	2.2 (0.7)	2.4 (0.8)	
Echocardiography				
TRI, mm Hg (mean, SD)	63.2 (22.1)	43.8 (14.9)	50.3 (19.9)	<0.0001*
TAPSE, cm	1.8 (0.4)	2.2 (0.3)	2.1 (0.4)	<0.0001*
RVESV, mL	86.6 (57.2)	50.8 (31.2)	62.1 (44.4)	<0.0001*
RVEDV, mL	129.3 (62.8)	88 (40.5)	101 (52.3)	<0.0001*
Right atrial area (cm^2)	27.3 (11.1)	20.5 (7.7)	22.6 (9.5)	<0.0001*
CMR				
RVEF, %	36.9 (12.2)	49.8 (10.6)	45.5 (12.7)	<0.0001*
RVEDV, mL	139.1 (54.3)	95.4 (35.5)	109.9 (47.4)	<0.0001*
RVESV, mL	168.4 (91.9)	100.1 (64.2)	122.7 (81.2)	<0.0001*

Patient demographics at baseline including echocardiography and CMR scans according to treatment group. Values are presented as means and medians.[12]
CMR, cardiac magnetic resonance; 6MWD, 6-min walking distance; NT-proBNP, N-terminal brain natriuretic in pmol/L; RVEDV, right ventricle end-diastolic volume; RVEF, right ventricle ejection fraction; RVESV, right ventricle end-systolic volume; TAPSE, tricuspid annular plane systolic excursion; TRI, tricuspid regurgitation; WHO FC, WHO functional classification.

WHO functional class (FC), 6MWD and N-terminal pro-b-type natriuretic peptide (NT-proBNP).[1] The autonomic nervous system, which controls heart rate (HR), has been reported to be involved in the pathogenesis of PAH, with increased sympathetic activity and autonomic imbalance as the disease progresses.[10–13] Heart rate variability (HRV) may represent a novel risk factor for PH as it is considered a surrogate marker of autonomic nervous system function.[10] We hypothesised that continuous 24/7 monitoring might further increase the validity of risk assessment and improve the evaluation of treatment effects. The present study aimed to use continuous monitoring to assess changes in HRV, HR and physical activity in patients with PH on specific stable or escalating PH treatments to determine whether these parameters can be valuable in the future validation of treatment effects and the necessity of treatment escalation.

METHODS

The study was approved by a regional ethical committee (no. H-18005164) and registered at ClinicalTrials.gov (protocol no. H-18005164). Informed consent was obtained from all patients. We prospectively screened patients in the Danish Pulmonary Hypertension (DANPH) register using specific inclusion criteria, including patients aged >18 years with a diagnosis of PAH or CTEPH verified by right heart catheterisation. PAH was defined as the presence of a mean pulmonary arterial pressure (mPAP) >20 mm Hg, pulmonary artery wedge pressure ≤15 mm Hg and pulmonary vascular resistance >2 Wood units. CTEPH was defined as mPAP >20 mm Hg, pulmonary artery wedge pressure ≤15 mm Hg and the presence of mismatched segmental defects on Single Photon Emission Computed Tomography scan with CT (SPECT-CT). Patients were adjudicated via their electronic healthcare record and echocardiography by a senior cardiologist, and patients with left-sided heart failure or parenchymal lung disease were excluded from the study.

At both baseline and follow-up, the study assessed several established risk factors, including WHO FC, NT-proBNP level, systemic blood pressure, 6MWD, echocardiographic parameters, cardiac magnetic resonance (CMR) parameters, physical examination and 12-lead ECG. Clinical follow-up was performed every 6–12 months and at clinical deterioration.

Table 2 Right heart catheterisation at baseline

Variable	Treatment escalation (n=10)	Non-escalation (n=11)	Total (n=21)	P value
PVR, WU (mean, SD)	9.9 (5.4)	4.5 (2.3)	7.1 (4.9)	<0.0001*
Atrial pressure, mm Hg (mean, SD)	10.3 (5.9)	8.4 (3.4)	9.4 (5)	<0.0001*
mPAP, mm Hg (mean, SD)	49.8 (11.1)	42.3 (10)	46.2 (11.2)	<0.0001*

Patients' baseline right heart catheterisation measurements according to treatment group.
mPAP, mean arterial pulmonary pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; WU, Wood units.

Implantable loop recorder

The Reveal LINQ (Medtronic, Minneapolis, Minnesota, USA) implantable loop recorder (ILR) was used for continuous heart rhythm monitoring. This ILR continuously monitors the patient's HR (daytime and nighttime) and HRV, storing a mean value for each variable once daily. Daytime HR was defined as HR in sinus rhythm from 08:00 hours to 20:00 hours, and nighttime HR was recorded from 24:00 hours to 04:00 hours. HRV in milliseconds (ms) was calculated for sinus rhythm using the SD of 5 min average normal to normal (NN) intervals (SDANN) method; the SD was calculated using rolling 5-min periods, and a mean value for each day was obtained. HRV calculations automatically excluded periods of arrhythmia and required valid data covering more than 20% of the day. In addition, the ILR continuously monitored physical activity using a built-in accelerometer to record the minutes above the threshold for physical activity (corresponding to 70 steps per minute). To evaluate physical performance, measurements of two variables from the ILR were used, including physical activity indexed by daytime heart rate (PAiHR).online supplemental figure 1

Echocardiography

An experienced technician or physician performed echocardiography using either the Philips EPIQ 7 (Philips Ultrasound, Bothell, Washington, USA) or the General Electric 95 (General Electric Company, Boston, Washington, USA) cardiovascular ultrasound system. Measurements of left and right heart chamber volumes, lengths, and diameters were obtained using the end-diastolic frame in the apical four-chamber view. The ejection fraction was also calculated, and tricuspid annular plane systolic excursion and tricuspid regurgitation were assessed as per current guidelines.[14]

Right heart catheterisation

Before enrolment in the study, a PH diagnosis had been verified in all patients by right heart catheterisation (RHC). A pulmonary artery catheter containing a balloon was inserted through the jugular vein, and the following parameters were measured: diastolic and systolic pulmonary arterial pressures, mPAP, capillary wedge pressure, right atrial pressure, mixed venous oxygen, arterial oxygen saturation and cardiac output (CO) using thermodilution.[1] Pulmonary vascular resistance, cardiac index, stroke volume and CO were then calculated. Pressure measurements were obtained at end-expiration.

Cardiac magnetic resonance imaging

A 1.5-Tesla magnetic resonance scanner (1.5 T MAGNETOM Espree, Siemens, Erlangen, Germany) was used for CMR imaging. Patients were examined in the

Table 3 Linear mixed model analysis of differences in risk parameters before and after treatment escalation

Variable	PAH			CTEPH		
Follow-up risk parameters	Estimate	CI	P value	Estimate	CI	P value
Heart rate variability, ms	24.96	22.9 to 26.94	<0.0001*	12.47	9.78 to 15.16	<0.0001*
Physical activity, minutes	20.5	15.1 to 25.88	<0.0001*	26.1	19.16 to 33.10	<0.0001*
Physical activity indexed by daytime heart date	0.22	0.16 to 0.28	<0.0001*	0.32	0.25 to 0.40	<0.0001*
HR at night, bpm	−5.5	−6.11 to −4.87	<0.0001*	−4.11	−4.83 to −3.40	<0.0001*
NT-proBNP, doubling	−0.32	−0.69 to 0.039	0.083	−2.62	−3.51 to −1.64	0.0001*
6MWD, metres	37.95	5.22 to 71.10	0.024*	151.50	47.27 to 222.15	0.0002*
WHO FC	−0.45	−0.89 to 0.03	0.047*	−0.84	−1.5 to 0.22	0.0048
COMPERA score	−0.58	−1.16 to −0.047	0.041*	−1.00	−1.71 to −0.41	<0.0001*

Comparisons of differences in risk parameters before and after treatment escalation in the 15 patients who underwent a treatment change during the study grouped as patients with PAH (n=10) and patients with CTEPH (n=5). The comparisons are made in the ILR and European Society of Cardiology and European Respiratory Society (ESC/ERS) (ESC/ESR) risk assessment parameters using a linear mixed model. Estimates of the linear regression models. All associations were adjusted for age.
CTEPH, chronic thromboembolic pulmonary hypertension; HR, heart rate; ILR, implantable loop recorder; 6MWD, 6-min walking distance; PAH, pulmonary arterial hypertension; WHO FC, WHO functional classification.

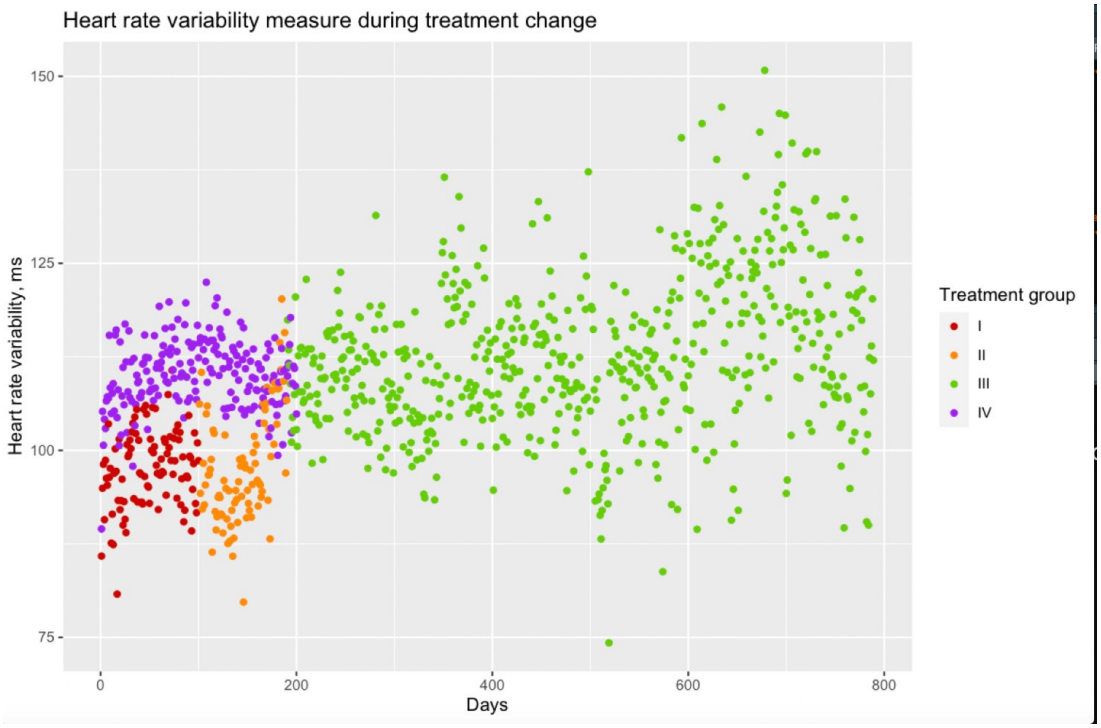

Figure 1 HRV measured during treatment change. Mean HRV values (ms) for each patient-groups plotted as dots, showing HRV increase from group I to IV ($p<0.001$ in the linear mixed model). No significant difference between group III (after escalation) and IV (non-escalation). Groups: I (red, pre-escalation), II (orange, escalation), III (green, post-escalation), IV (purple, no changes). Monitoring: 100 days pre-escalation, up to 100 days escalation, followed by 600 days postescalation. y-axis: HRV (ms); x-axis: days. HRV, heart rate variability.

supine position, and ventricular volumes were evaluated in the scout, long-axis and transaxial planes followed by the short-axis plane. Time–volume curves for left and right ventricular filling, ejection fraction, peak filling rate and stroke volume were derived. Heart chamber volumes were measured during the end-expiratory cycle, and the ejection fraction, peak emptying rate, and filling rate were computed.[15] Standard flow measures with phase-contrast velocity mapping were used to evaluate aortic and pulmonary flows.

Treatment escalation and grouping of patients according to treatment escalation

Treatment escalation was defined as an additional PAH drug, pulmonary endarterectomy (PEA), percutaneous balloon angioplasty (PBA) or bilateral lung transplantation (BLTX). Patients with PH were grouped according to their treatment status during follow-up: (I) before treatment escalation, (II) during treatment escalation, (III) after treatment escalation and (IV) non-escalation (patients with no changes in PH treatment). Patients transitioned from patient-group I to II on the day of initiation of at least one additional specific PAH drug or on the day that PEA, PBA or BLTX was performed. Patients transitioned from patient-group II to III at 30 days after the last day of uptitration of the added drugs, at 30 days after the last of the series of PBA treatments or at 60 days after PEA or BLTX.

Statistical analysis

For each patient, all ILR-measured variables were analysed using all data points per patient within each patient-group: (I) days before treatment escalation, (II) days during treatment escalation, (III) days after treatment escalation and (IV) in patients without treatment escalation. The PH risk assessment parameters of NT-proBNP, 6MWD, WHO FC and Comparative, prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) score were likewise analysed using all available data points per patient within each patient-group. These variables were then compared between the groups using analysis of repeated measurement via a linear mixed model adjusted for age. The model encompassed a random intercept accounting for repeated measurements from the same patient and estimated the differences between the patient- groups. Statistical analysis was conducted using R statistical software V.4.1.3, and the repeated mixed models were analysed using the R package LME4.[16]

RESULTS

A total of 41 patients, including 27 patients with PAH and 14 patients with CTEPH, were prospectively enrolled in the study (table 1). The enrolment period was from September 2018 to January 2022. On enrolment, all patients were implanted with an ILR. Throughout the study period the patients were continuously monitored for

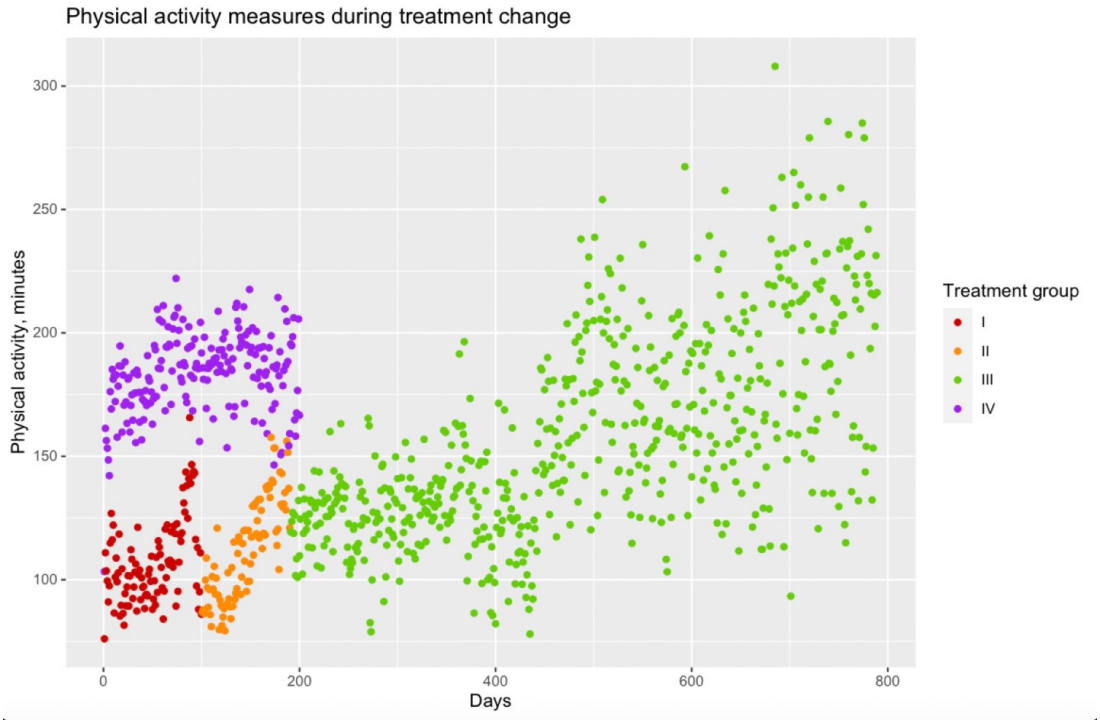

Figure 2 Physical activity measured during treatment change. Mean physical activity values (minutes) for each group plotted as dots, showing increased activity from group I to IV (p<0.001, based on a linear mixed model). No significant difference between group III (after escalation) and IV (non-escalation). Groups: I (red, pre-escalation), II (orange, escalation), III (green, postescalation), IV (purple, no changes). Monitoring: 100 days pre-escalation, up to 100 days escalation, followed by 600 days postescalation. y-axis: physical activity (minutes); x-axis: days.

102 patient-years. Of the patients with PAH, 16 had idiopathic PAH, 3 had heritable PAH, 7 had PAH associated with connective tissue disease and 1 had HIV-associated PAH. At the time of inclusion, none of the patients had documented arrhythmias or anaemia. Furthermore, none of the patients exhibited left-sided heart disease as determined by RHC and echocardiography.

During the study period, 15 (36.6%) patients underwent escalation of their specific PH treatment, including 10 patients with PAH and 5 patients with CTEPH. The treatment escalation group included seven patients who received increased oral PAH therapy (three patients with selective prostacyclin receptor agonists, two patients with phosphodiesterase 5 inhibitors and two patients with endothelin receptor antagonists). In addition, one patient underwent PEA surgery, three patients underwent a series of PBAs and four patients underwent BLTX surgery. The patients underwent continuous heart monitoring measurements with a median monitoring duration of 100 (range: 68–100) days prior to escalation (patient-group I), 70 (range: 31.5–90) days during escalation (patient-group II) and 165 (range: 89–308) days following escalation (patient-group III).

The number of measurements corresponding to each PH risk assessment parameter were as follows: a median of 1 (range: 1–3) measurement before escalation (patient-group I) and 1 (range: 1–2) measurement after escalation (patient-group III) for WHO-FC, a median of 1 (range: 1–5) measurement before escalation (patient-group I) and 3 (range: 1–3) measurements after escalation (patient-group III) for NT-proBNP, a median of 1 (range: 1–3) measurement before escalation (patient-group I) and 1 (range: 1–3) measurement after escalation (patient-group III) for 6MWT, and a median of 1 (range: 1–2) measurement before escalation (patient-group I) and 1 (range: 1–3) measurement after escalation (patient-group III) for COMPERA.

Baseline differences

At baseline, the treatment escalation group (patient-group I) was characterised by a greater disease burden compared with the non-escalation group (patient-group IV), as evidenced by a higher NT-proBNP level (200 pmol/L vs 56 pmol/L, p≤0.001), lower 6MWD (403 m vs 511 m, p≤0.001) and higher WHO FC (2.8 vs 2.2, p≤0.001) (table 1). Similarly, RHC, echocardiography and CMR indicated that PH was more advanced in the treatment escalation group than in the non-escalation group (tables 1 and 2). Notably, patients in the treatment escalation group had the disease for a significantly shorter duration (median of 16 months) than the non-escalation group (51 months) (p<0.001) (table 1).

Changes after treatment escalation

ILR parameters, including HRV, PAiHR and nighttime HR, in the escalation group when comparing measurements obtained at baseline and after treatment escalation in the PAH and the CTEPH group are presented in table 3.

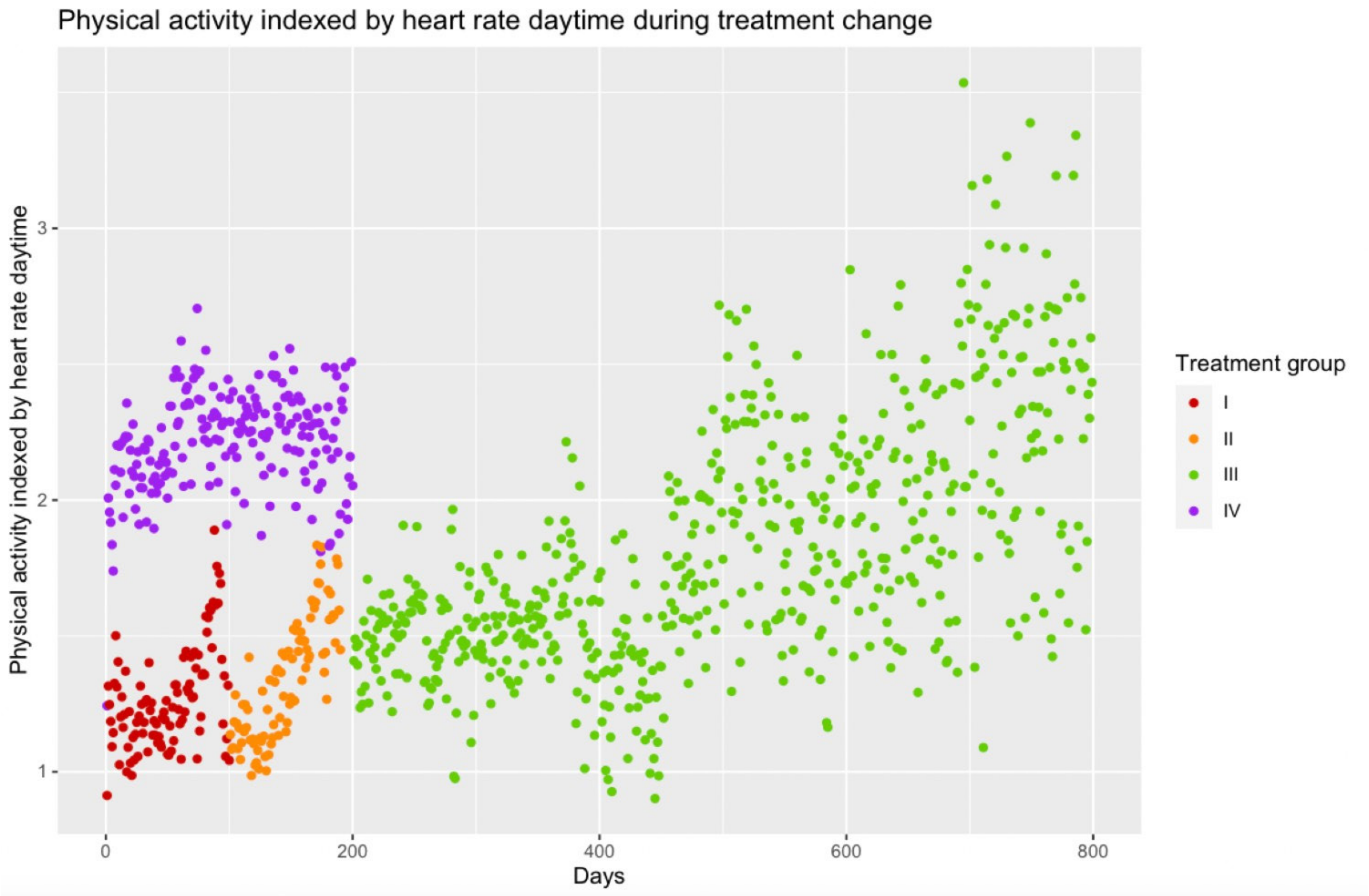

Figure 3 PAiHR daytime measured during treatment change. Mean PAiHR daytime values (minutes) for each patient-group plotted as dots, showing increased PAiHR from group I to IV ($p < 0.001$, based on a linear mixed model). No significant difference between group III (after escalation) and IV (non-escalation). Groups: I (red, pre-escalation), II (orange, escalation), III (green, post-escalation), IV (purple, no changes). Monitoring: 100 days pre-escalation, up to 100 days escalation, followed by 600 days post-escalation. y-axis: PAiHR; x-axis: days. PAiHR, physical activity indexed by daytime heart rate.

The patients with PAH in the escalation group exhibited a significant increase in HRV by 25 (range: 22.9–26.94) ms (figure 1) (p<0.001), physical activity increase by 20.5 (range: 15.1–25.88) min, PAiHR increase by 0.22 (0.16–0.28) (p<0.0001), HR nighttime a significant decrease of −5.5 bpm (range: −6.11 to −4.87) (p<0.0001). The escalation group of patients with CTEPH had a significant increase in HRV by 12.47 ms (9.78–15.16), physical activity increase by 26.1 (19.16–33.10) min (p<0.0001), PAiHR increase by 0.32 (0.25–0.4) (p<0.0001) and a significant decrease in HR nighttime by −4.11 (range: −4.83 to −3.4) (p<0.0001).

Similarly, significant changes were observed in the treatment escalation group regarding all ESC/ERS-COMPERA 2.0 risk assessment parameters, including a decrease in NT-proBNP from 343 (range: 47–554) pmol/L to 103 (range: 20–190) pmol/L (p<0.001), a significant decrease in WHO-FC from 2.75 (range: 2–3) to 2.3 (range 2–3) (p=0.008), and a significant increase in 6MWD from 375 m (range: 335–433) to 475 m (range: 437–595) (p<0.001) (table 3).

Treatment escalation group as compared with the non-escalation group

After therapy escalation, the linear mixed models revealed no significant differences between the escalation (patient-group III) and non-escalation (patient-group IV) groups in contrast to the baseline comparisons (patient-group I vs patient-group IV), with no differences in all ESC/ERS follow-up parameters (ie, NTP-proBNP, WHO-FC and 6MWD). Furthermore, there were no significant differences in any of the ILR parameters (nighttime HR, HRV, physical activity and PAiHR) (figures 1–3) between the escalation group (patient-group III) and non-escalation group (patient-group IV).

Treatment subgroup analysis

A preliminary subgroup analysis was conducted in the escalation group to assess the changes in the different treatment escalation modalities from before treatment escalation (patient-group I) to after treatment escalation (patient-group III). The treatment escalation group was subcategorised into PBA (n=3), pharmacological escalation (n=7) and BLTX (n=4) groups. In the pharmacological escalation group, HRV was significantly increased,

Table 4 Subgroup analysis: linear mixed model analysis of differences in risk assessment parameters before and after treatment changes

Variable	Within-individual comparison before and after treatment escalation		
Follow-up risk parameters	**Estimate**	**CI**	**P value**
Pharmacological PH drugs, n=7			
Heart rate variability, ms	8.38	6.11 to 10.64	<0.0001*
Heart rate at nighttime, bpm	−1.04	−1.76 to 0.32	0.0049*
Physical activity, minutes	−9.8	−15.99 to 2.61	0.0061*
Physical activity indexed by daytime heart rate	−0.07	−0.15 to 0.004	0.062
NT-proBNP, doubling	−0.022	−0.49 to 0.45	0.93
6MWD, metres	10.67	−13.85 to 34.85	0.40
WHO FC	0.057	−0.35 to 0.51	0.80
BLTX, n=4			
Heart rate variability, ms	38.74	35.62 to 41.84	<0.0001*
Heart rate at nighttime, bpm	−9.21	−10.07 to −8.35	<0.0001*
Physical activity, minutes	52.56	46.12 to 59.03	<0.0001*
Physical activity indexed by daytime heart rate	0.52	0.45 to 0.59	<0.0001*
NT-proBNP, doubling	−1.78	−2.24 to −1.19	<0.0001*
6MWD, metres	139.92	92.54 to 187.29	<0.0001*
WHO FC	−1.78	−2.24 to −1.19	<0.0001*
PBA, n=3			
Heart rate variability, ms	20.43	16.90 to 23.88	<0.0001*
Heart rate at nighttime, bpm	−8.21	−9.27 to 7.04	<0.0001*
Physical activity, minutes	36.59	30.23 to 43.28	<0.0001*
Physical activity indexed by daytime heart rate	0.46	0.40 to 0.53	<0.0001*
NT-proBNP, doubling	−2.15	−3.27 to 1.04	<0.0001*
6MWD, metres	161.87	41.17 to 258.87	0.0009*
WHO FC	1.32	−1.98 to −0.67	0.0005*

Comparisons of changes in three treatment subgroups before and after treatment escalation. Comparisons of the ILR and ESC/ESR risk assessment parameters were made using a linear mixed model; estimates of the linear regression model's classification are shown. All associations were adjusted for age.
BLTX, bilateral lung transplantation; BPM, beats per minute; HR, heart rate; 6MWD, 6-minute walking distance; NT-proBNP, N-terminal brain natriuretic in pmol/l; PBA, percutaneous balloon angioplasty; WHO FC, WHO functional classification.

and physical activity was significantly decreased (table 4); no other parameters, including the ESC/ERS parameters, were significantly different (table 4). In contrast, in both the BLTX and PBA groups, significant increases in HRV, physical activity, PAiHR, and 6MWD and significant decreases in nighttime HR, NT-proBNP, and WHO-FC were observed.

DISCUSSION

This study is the first to demonstrate an association between specific PH therapy and HRV, nighttime HR and physical activity in patients with PAH and CTEPH using continuous heart monitoring. Interestingly, a positive association was identified between direct PH treatments and HRV, where an intensified PH treatment led to a significant increase in HRV. Importantly, changes in HRV were paralleled by changes in the newest ESC/ERS risk assessment parameters, including WHO-FC, NT-proBNP and 6MWD.[1]

Evaluation of treatment effects

Currently, most treatment effects for approved PAH drugs are based on documentation of increased 6MWD, as this parameter has been used as the primary endpoint in most studies assessing novel PAH therapies and as the basis for regulatory approval.[3 5] This parameter was also included in the recommendations for a combined uniform validation tool of time to clinical worsening at the fourth World Symposium on Pulmonary Hypertension in 2008.[17] However, the applicability of 6MWD is challenged by multiple influencing factors, including weight, height, gender, supplemental O_2 use, encouragement, mood and comorbidities.[3 4] In addition, younger patients with severe PAH have been reported to walk

distances over 500 m.[18] Some studies have reported that positive changes in 6MWD do not correlate with long-term outcomes or the validation of PAH drugs, as additional therapy for patients on background-specific PAH therapy can result in modest changes in 6MWD.[3 19 20]

Earlier studies reported an association between HRV and PH risk assessment parameters within a 48-hour period.[21] Moreover, among patients with acute pulmonary embolism, impaired HRV is associated with increased mortality.[22] Our group previously demonstrated an association between HRV and established PH risk assessment parameters using continuous heart monitoring.[13] Therefore, the evaluation of PH therapy could be strengthened by cosurrogate risk parameters, such as HRV, HR and all-day physical activity, that allow for continuous risk assessment. Analysis of such parameters may contribute to even earlier detection of clinical deterioration and ineffective treatment.[23 24]

Changes in ILR parameters after treatment escalation

The current study revealed significant increases in HRV after different treatment modalities, with the greatest effects detected in the surgical interventional groups. The modest changes in the PAH drug group were in line with earlier observations; 3/7 (43%) patients in the PAH drug escalation group had treatment escalation with selective per oral prostacyclin receptor agonists, which have been reported to produce limited changes in 6MWD (an increase of 4 metres vs a decrease of 9 m in the placebo group over 26 weeks) and no changes in WHO FC in a phase III trial.[25] Moreover, some patients with PAH remain refractory to pharmacological therapy.[26 27] Of note, no significant changes were observed in the ESC/ERS risk assessment parameters in the PAH drug intervention group, which can be attributed to the low power of the study. However, a significant increase in HRV was consistently observed in all three treatment modality subgroups, which indicates a high sensitivity (table 4).

Changes in general PH risk assessment

Risk assessment in PH has evolved from the frequent validation of multiple risk parameters to the use of three primary risk parameters in the follow-up risk assessment regimen, with subsequent supplementary examinations according to clinical status in the most recent ESC/ERS guidelines (2022).[1] To enhance the prompt detection and validation of treatment effects, risk assessment and treatment evaluation in PH can be shifted from intermittent assessments of 6MWD, WHO-FC and NT-proBNP every 3–6 months[1 3] to daily measurements of more easily assessable parameters. Our results suggest that HRV and physical activity could serve as complementary day-to-day indicators in the assessment of treatment efficacy alongside 6MWD, as these parameters increase significantly after specific PH treatment. These continuous risk assessment variables, when monitored at home, increase reliability compared with the current snapshot tests performed whenever the patient presents to the clinic for risk assessment.

CONCLUSION AND PERSPECTIVES

This is the first study to demonstrate an association between specific PH treatments and changes in continuous HRV measurements in patients with CTEPH and PAH. In addition, we observed a significant increase in PAiHR and a decrease in nighttime HR during specific PH treatments. The results of this study indicate the potential utility of continuous monitoring, namely HRV, nighttime HR and PAiHR, in the evaluation of treatment effects in patients with PH. Specifically, 24/7 monitoring may facilitate more precise validation and earlier detection of treatment effects. This is especially relevant considering the increasing availability of wearables that allow for the continuous non-invasive measurement of HRV, physical activity and HR.

LIMITATIONS

The number of patients in the study was limited because of its single-centre design and the strict inclusion criteria. To increase the generalisability of the results, the study should be extended to include a validation cohort. Furthermore, a higher number of patients could enhance the validation of HRV, PAiHR and nighttime HR. However, despite a low number of patients, the continuous monitoring identifies significant changes in the measured parameters. The different types of PH treatments in the subgroup analysis warrant further validation. Including changes in the ILR risk assessment parameters after de novo treatments may also shed light on the applicability of continuous heart monitoring in risk assessment in PH. Additionally, more studies are needed to elucidate when the changes in the ILR parameters becomes clinically significant.

Contributors MOA took the lead in drafting the article, conducting loop recorder implantations, interpreting data and analysing findings. Additionally, he made the final draft. MOA is responsible for the overall content as guarantor. JC initiated the study's secured funding, crafted the methodology and had the role of main supervisor throughout its development. SZD provided support in both data interpretation and loop recorder implantation. He actively participated in the production of the article, consistently providing comments and feedback throughout its development. JHS offered input on methodology and contributed to data interpretation. He actively participated in the production of the article, consistently providing comments and feedback throughout its development.

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Competing interests Mads Ørbæk Andersen has nothing to declare. Søren Zöga Diederichsen has received consultancy fees from Bristol Myers Squibb/Pfizer, Vital Beats and Acesion Pharma, speaker fees from Bristol Myers Squibb, and travel grants from Abbott. Jesper Hastrup Svendsen is a member of an advisory board for Medtronic and has received speaker fees and research grants from Medtronic. Jørn Carlsen is a member of an advisory board for Merck and has received institutional research grants and institutional speaker fees.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by H-18005164—Videnskabsetisk komité, Kongens Vænge 2 3400 Hillerød—Denmark Participants gave informed consent to participate in the study before taking part.

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