Continuous long-term heart rate variability and risk assessment in pulmonary hypertension

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ABSTRACT
Objective Current multimodal risk assessment for pulmonary hypertension (PH) has been redefined with a simplified assessment for follow-up in the new European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines. Follow-up risk assessment parameters include WHO functional class, 6 min walk test and N-terminal pro-brain natriuretic peptide. Although these parameters have prognostic implications assessment reflect data relating to specific time points.

Methods Patients diagnosed with PH received an implantable loop recorder (ILR) to monitor daytime and night-time heart rate (HR), HR variability (HRV) and daily physical activity. Associations between the ILR measurements and established risk parameters were analysed using correlations, linear mixed models as well as logistical mixed models for addressing the ESC/ERS risk-score.

Results 41 patients (median age: 56 years, range: 44–61.5 years) were included. Continuous monitoring had a median duration of 755 days (range: 343–1138 days), totalling 96 patient-years. In the linear mixed models, HRV and physical activity indexed by daytime HR (PAiHR) were significantly associated with the ERS/ERC risk parameters. In a logistical mixed model, HRV revealed a significant difference between 1-year mortality (<5% vs >5%) (p=0.027) with an OR of 0.82 for being in the group with 1-year mortality >5% for every increase by one HRV unit.

Conclusions Risk assessment in PH can be refined with continuous monitoring of HRV and PAiHR. These markers were associated with the ESC/ERC parameters. Our study with continuous risk stratification in PH demonstrated that a lower HRV predict worse prognosis.

INTRODUCTION
Pulmonary hypertension (PH) is a progressive disease affecting the pulmonary vasculature leading to right-sided heart failure. Current baseline risk assessment for PH is performed using a range of clinical, haemodynamic and exercise parameters, many of which have been shown to be independent predictors of survival. A simplified follow-up risk assessment has recently been introduced in the COMPERA 2.0 and implemented in the 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines for PH. Risk assessment is generally performed on a consecutive point-by-point basis and does not include continuous heart rhythm monitoring.

It is of particular importance to recognise the early progression of PH since pathological cardiovascular changes often precede symptom progression, and early intervention can improve long-term prognosis. Heart rate (HR), HR variability (HRV) and physical activity are all easily assessable with continuous monitoring using an implantable...
loop recorder (ILR). An impaired renin–angiotensin system and an increased sympathetic tone occur during the progression of PH and influence several parameters, including HRV.\textsuperscript{7-9} HRV expresses the variation in time intervals between consecutive heart beats and has been well studied in patients with left-sided heart diseases. A low HRV correlates with a worse prognosis in patients with left-sided heart failure and coronary heart disease.\textsuperscript{10} 11 The SD of the average normal to normal distance between heart beats (SDANN) calculates longer cycles and long-term components of HRV and is correlated with both autonomic balance and renin–angiotensin system function.\textsuperscript{12} 13 Additionally, baseline HR seems to be an independent predictor of mortality in patients with PH.\textsuperscript{14}

This study aimed to assess the potential of continuous risk stratification in patients with PH based on HR, HRV and physical activity evaluated using an ILR with the hypothesis that a lower HRV and physical activity as well as a higher HR day and night predict worse prognosis.

**METHODS**

Consecutive patients with PH followed up in a single tertiary PH centre and patients registered in a nationwide PH registry were screened. The inclusion criteria included a diagnosis of PH in either WHO group 1 or 4 and hence: pulmonary arterial hypertension (PAH) or chronic thromboembolic PH (CTEPH) according to international standards verified during right heart catheterisation (RHC) and an age between 18 and 75 years. However, no patients in WHO group 1 with the subgroup PH associated with congenital heart disease was included.

PAH was defined as a mean pulmonary arterial pressure (MPAP) of >20 mm Hg, pulmonary artery wedge pressure of ≤15 mm Hg and pulmonary vascular resistance of >2 Wood units.\textsuperscript{2} CTEPH was defined as an MPAP of >20 mm Hg and the presence of mismatched segmental defects on a single-photon emission computed tomography (SPECT) CT.\textsuperscript{1} Exclusion criteria included left-sided heart failure and parenchymal lung disease.

The following established risk factors were measured at baseline and follow-up: WHO functional class (WHO-FC), N-terminal pro-brain natriuretic peptide (NT-proBNP), blood pressure and 6 min walk test (6-MWT), echocardiography, cardiac MR imaging (CMR) physical examination and 12-lead ECG. Clinical follow-up visits were performed every 6–12 months or at clinical deterioration. Patients who underwent bilateral lung transplantation or pulmonary endarterectomy were censored from the date of surgery.

**Implantable loop recorder**

Continuous heart rhythm monitoring was performed using Reveal LINQ (Medtronic, Minneapolis, Minnesota, USA) ILR. The ILR continuously monitored daytime and night-time HR, HRV and physical activity and stored a mean value for each variable once daily. Daytime HR was defined as HR from 8:00 to 20:00 hours and night-time HR from 12:00 to 4:00 hours.

The HRV calculations automatically excluded periods when patients had arrhythmia. Additionally, valid data over 20% of the day were needed to calculate an HRV datapoint/value. HRV was calculated using the SDANN, where the interval between normal ventricular beats was measured within 5 min intervals. An SD for each 5 min interval was then calculated, and a mean value for a 24-hour recording cycle was subsequently measured in milliseconds. Patients with type 2 diabetes mellitus were excluded from the HRV analyses.\textsuperscript{15}

Physical performance was evaluated based on two variables simultaneously measured by the ILR, including physical activity indexed by daytime HR (PAiHR).

**Patient and public involvement**

The patients were not involved in the recruitment or study design. However, the patients were actively encouraged to share their experience with the loop-recorder and its functions.

**Echocardiography**

Echocardiography was performed by an experienced technician or physician using Philips EPIQ 7 (Philips Ultrasound, Bothell, Washington, USA) or a General Electric 95 cardiovascular ultrasound system (General Electric Company, Boston, Massachusetts, USA). Left and right heart chamber volumes, lengths and diameters were measured at the end-diastolic frame in the apical four-chamber view.

Furthermore, ejection fraction was calculated, and tricuspid annular plane systolic excursion and tricuspid regurgitation were recorded in accordance with current guidelines.\textsuperscript{16}

**Right heart catheterisation**

The diagnosis of PH was verified in all patients before inclusion in the study. It was conducted via the jugular vein using an inflatable pulmonary catheter. The diastolic and systolic pulmonary arterial pressures, MPAP, capillary wedge pressure, right atrial pressure, mixed venous oxygen and arterial oxygen saturation were measured.\textsuperscript{3} Additionally, the pulmonary vascular resistance, cardiac index, stroke volume and cardiac output were calculated using thermodilution. The pressure measurements were performed at end-expiration.

**CMR imaging**

CMR imaging was performed using a 1.5-Tesla MR scanner (1.5 T MAGNETOM Espree, Siemens, Erlangen, Germany). The patients were examined in the supine position, and the ventricular volumes were assessed first in the scout, long-axis, transaxial plane, followed by the short-axis plane. The time–volume curves for left and right ventricular filling, ejection fraction, peak filling rate and stroke volume were calculated. The heart chamber volumes were measured during the end-expiratory cycle, and the ejection fraction, peak emptying rate and filling
rate were calculated. Aortic and pulmonary flows were evaluated using standard flow measures with phase-contrast velocity mapping.

**Statistical analysis**

The daily measurements from continuous monitoring were summarised to a single mean value per patient. To evaluate the association with the established risk markers, we summarised the ILR variables in 30-day windows (mean of all values from 15 days of ILR-measured data before until 15 days after each measurement of the risk marker). The analysis was then performed including data from each matching time frame. The PH risk assessment parameters were compared with the ILR-measured variables via analysis of repeated measurement using a linear mixed model adjusted for age. The model encompassed a random intercept accounting for repeated measurements from the same patient. The model estimates the change in each of the known PH risk assessment parameters (outcome) for every doubling of the ILR parameters (exposure).

Pearson correlation analyses were performed to evaluate baselines measures between the ILR-measured variables and the baseline PH risk markers, including haemodynamics obtained during RHC. In addition, patients were assessed continuously according to the ESC/ERS follow-up risk model and were divided in a low-risk group with an anticipated 1-year mortality <5% and a risk group with an anticipated 1-year mortality >5%, hence corresponding to the ESC/ERS intermediate-low, intermediate-high and the high-risk group together. Analysis between the two groups were carried out using a mixed logistic model accounting for repeated measurements from the same patients and adjusted for age. The model estimated the ORs for being in the high-risk group (1-year mortality >5%) per unit change of the relevant ILR variable. The ILR variables were summarised as a mean of 30 days prior to each risk score assessment.

Based on the mixed logistic model, an exploratory prediction model for the population level was performed and receiver operating characteristic curves conducted to assess the prognostic performance of ILR variables according to the new ESC/ERS/COMPERA 2–0 risk assessment score. The statistical analysis was conducted using the R statistical software V.4.1.3. The repeated

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**Table 1** Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>PAH (n=27)</th>
<th>CTEPH (n=14)</th>
<th>Total (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median, IQR)</td>
<td>56 (44–61.5)</td>
<td>68 (59.8–73.0)</td>
<td>58 (46–67)</td>
</tr>
<tr>
<td>Months with diagnosis, (mean, SD)</td>
<td>59.8 (63.3)</td>
<td>43 (56.1)</td>
<td>54 (60.8)</td>
</tr>
<tr>
<td>MPAP baseline, mm Hg, (mean, SD)</td>
<td>49.5 (8.4)</td>
<td>41.5 (13.8)</td>
<td>48 (11.2)</td>
</tr>
<tr>
<td>PVR baseline, wood units</td>
<td>7.6 (5.1)</td>
<td>5.2 (3.8)</td>
<td>6.5 (4.6)</td>
</tr>
<tr>
<td>PAH subgroups, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPAH</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPAH</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAH-CTD</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-PAH</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO-FC, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>II</td>
<td>10</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>III</td>
<td>10</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>PAH treatment, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Mono therapy</td>
<td>6</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Double therapy</td>
<td>7</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>13</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>NT-proBNP, pmol/L (median, IQR)</td>
<td>30.4 (13–67)</td>
<td>32.6 (24–209)</td>
<td>31.5 (13–76)</td>
</tr>
<tr>
<td>6MWT, metres (median, IQR)</td>
<td>484 (383–569)</td>
<td>449 (347–499)</td>
<td>458 (363–549)</td>
</tr>
</tbody>
</table>

Patient demographics at baseline. Monotherapy: PDE5-I (sildenafil and tadalafil and Ca2+ antagonist); Dual therapy: PDE5-I and endothelin-receptor antagonist (bosentan, macitentan, and ambrisentan); Triple therapy: PDE5-I, endothelin-receptor antagonist, and selective prostacyclin receptor agonist (epoprostenol, Treprostinil, iloprost, Selexipag). Values are presented as means () and medians (]. CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; FC, functional class; HPAH, heritable PAH; IPAH, idiopathic PAH; MPAP, mean pulmonary arterial pressure; 6MWT, 6 min walking test; NT-proBNP, N-terminal brain natriuretic Peptide; PAH, pulmonary arterial hypertension; PVR, Pulmonary vascular resistance;.
mixed models were conducted using LME4 and LMMstar designed for this purpose.

RESULTS
A total of 41 patients, including 27 with PAH and 14 with CTEPH were prospectively enrolled in the study. Overall, 7/41 were incident cases. The mean age was 56 years (range: 44–61.5 years), and 20 patients were women (48.8%). Almost half of the patients with PAH (48%) were on triple PAH therapy, and the majority (83%) (48.8%). Almost half of the patients with PAH (48%) had left-sided heart disease assessed by RHC and echocardiography. Two patients with type 2 diabetes mellitus had type 2 diabetes mellitus were excluded from the HRV analyses.

Haemodynamics
The seven newly diagnosed cases had a RHC performed at the study baseline and additional 14 patients had a RHC performed near the baseline due to clinical progression. The 21 patients with RHC had a mean MPAP of 48 (±11.2 mm Hg) and a mean PVR of 6.5 (±4.6) wood units. The remaining patients all had an RHC verified PH before baseline.

A negative correlation was observed between log HRV and MPAP (R=−0.41, p<0.0001), pulmonary vascular resistance (R=−0.58, p<0.0001) and the right arterial pressure (R=−0.62, p<0.0001) (table 2). In addition, significant negative correlations were found between the log PAiHR and MPAP (R=−0.47, p<0.0001), pulmonary vascular resistance (R=−0.5, p<0.0001) and right atrial pressure (R=−0.56, p<0.0001).

HR variability
In each WHO-FC group, the patients’ mean HRVs during follow-up were distributed as follows: WHO-FC I=121 ms (±34.7), II=116 (±31) ms, III=90 (±24.7) ms, IV=75 (±25.2) ms. The mixed model analysis between the consecutively monitored HRV demonstrated significant associations with WHO-FC, NT-proBNP, 6MWT and the following echocardiography parameters: tricuspid regurgitation, right ventricular ejection fraction, right ventricle end-diastolic volume, right ventricle end-systolic volume, and right ventricle diameter. Especially highly significant differences were found in the mixed model between HRV and the follow-up WHO-FC (p<0.0001), NT-proBNP level (p<0.0001) and 6MWT result (p<0.0001) (table 3 and figure 1). Both the NT-proBNP level and WHO-FC were negatively associated with HRV whereas 6MWT was positively associated with HRV. Additionally, HRV was significantly positively associated with the HR change during 6MWT. In contrast, most CMR measurements were not significantly correlated with the ILR measurements.

When grouped according to the WHO-FC, HRV yielded the same changes with an increasing WHO-FC as the NTP-proBNP level and 6MWT result. Additionally, HRV more clearly distinguished WHO-FC II from WHO-FC III (p<0.0001) than did the NT-proBNP level which was insignificant. Whereas patients in WHO-FC III had a significantly lower NT-proBNP level than those in WHO-FC II (p=0.007).

Physical activity and HR
In the mixed model, the PAiHR was negatively associated with the follow-up WHO-FC (p<0.0001) and NT-proBNP level (p<0.0001), and positively associated with 6MWT result (p<0.0001) and an association with right ventricular ejection fraction (p=0.011) (table 3 and figure 1). In contrast, no significant association was found between the PAiHR and tricuspid regurgitation insufficiency or most CMR imaging measurements.

The nighttime HR was positively associated with WHO-FC (p=0.0015) and NT-proBNP level (p<0.0001) and negatively associated with the 6MWT result (p<0.0001).

Continuously monitored variables and risk score assessment
The group with a low-risk score and 1-year mortality of <5% had a mean HRV of 127 ms (±50.1), whereas the risk group with a mortality rate >5% significantly differed

<p>| Table 2 Pearson correlations between right heart catheterisation risk parameters and ILR variables |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Log (HRV)</th>
<th>Log (heart rate at night-time)</th>
<th>Log (PAiHR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPAP (mm Hg)</td>
<td>R: −0.41 (−0.48 to −0.34) p&lt;0.0001</td>
<td>R: 0.41 (0.35 to 0.48) p&lt;0.0001</td>
<td>R: −0.47 (0.53 to −0.41) p&lt;0.0001</td>
</tr>
<tr>
<td>PVR (Wood units)</td>
<td>R: −0.58 (−0.63 to −0.52) p&lt;0.0001</td>
<td>R: 0.57 (0.51 to 0.62) p&lt;0.0001</td>
<td>R: −0.50 (0.56 to −0.44) p&lt;0.0001</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>R: −0.62 (−0.66 to −0.56) p&lt;0.0001</td>
<td>R: 0.47 (0.41 to 0.54) p&lt;0.0001</td>
<td>R: −0.56 (−0.61 to −0.50) p&lt;0.0001</td>
</tr>
</tbody>
</table>

Baseline right heart catheterisation measures and Pearson’s correlations between these and the ILR variables.
HRV, heart rate variability; ILR, implantable loop recorder; MPAP, mean arterial pulmonary pressure PAiHR, Physical activity indexed by daytime heart rate; PVR, pulmonary vascular resistance; RAP, right atrial pressure.
with an HRV of 87 ms (±26.4) (p<0.0001). Grouped according to PAiHR, the 1-year mortality group of <5% had a mean index of 2.2 (±1) whereas the 1-year mortality group of ≥5% had a mean index of 1.3 (±0.8), with a significant difference between the groups (p=0.001). Grouping the patients according to HR-night-time the patients in the 1-year mortality group of <5% had a mean HR-night-time of 69 bpm (±12) whereas the patients in the 1-year mortality group of ≥5% had a mean HR night-time of 76 bpm (±12) with a significant difference (p=0.001).

In the logistic mixed models, HRV illustrated a significant difference between 1-year mortality 5% group versus the 1-year mortality ≥5% group (p=0.027) with an OR of 0.82 for being in the 1-year mortality ≥5% group for every increase in HRV (figure 2). HR at night and PAiHR illustrated no significant differences in the mixed logistical models with a p value of 0.14 and 0.13, retrospectively.

A prediction model based on the logistical mixed model demonstrated that HRV had a significant predictive value in predicting the 1-year mortality group >5% with an area under the curve (AUC) value of 0.91 (95% CI 0.86 to 0.96, p≤0.001).

DISCUSSION

To our knowledge, this is the first study to evaluate the potential of continuous heart rhythm monitoring of HRV, HR and physical activity using an ILR in patients with PH. Our study in PH patients with continuous risk stratification by data obtained from an ILR demonstrated a lower HRV predict worse prognosis.

HRV and progression of PH

HRV has been demonstrated to correlate with the autonomic nervous system dysfunction, in which a lower HRV indicates high sympathetic tonus and low cardiac adaptability. The autonomic nervous and renin–angiotensin systems have also been described to be impaired in patients with PH. In particular, as PH progresses, right ventricular dysfunction correlates with reduced parasympathetic activity based on muscle sympathetic nerve activity, HR recovery after exercise and acetylcholinesterase activity. However, only a few short-term studies with monitoring duration less than 48 hours have demonstrated a lower HRV in patients with PAH. In contrast, HRV has been thoroughly studied in patients with left-sided heart failure. This study expands the period of monitoring beyond 48-hours and illustrates a continuous association during 96 patient years between HRV and the PH risk parameters.

In addition, this study demonstrated that the patients with the lowest HRV had a significantly reduced HR during the 6MWT (p<0.001), compatible with a high sympathetic tone at rest. Other studies testing the level of sympathetic tone in patients with PH have demonstrated a slower decrease in the HR after the 6MWT and a generally increased sympathetic activity.

The clinical applicability of HRV in patients with PH and right-sided heart failure seems relevant as the right side of the heart has demonstrated to have a higher autonomic innervation than the left and the stretch of the sinoatrial node caused by the dilatation of the right atrium may increase the sympathetic tone and hence decrease HRV.

General risk assessment via continuous heart rhythm monitoring

Risk assessment for PH has been performed comprehensively evaluating 19 variables in the REVEAL risk score and 9 primary variables in the baseline ESC/ERS guideline score. Recently, such assessments have been redefined with an extended baseline evaluation.

Table 3 Repeated mixed model analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Log2 heart rate variability Estimate</th>
<th>95% CI</th>
<th>P value</th>
<th>Log2 heart rate at night-time Estimate</th>
<th>95% CI</th>
<th>P value</th>
<th>Log2 physical activity/daytime heart rate Estimate</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up risk parameters WHO-FC</td>
<td>–0.81</td>
<td>–0.53 to –2.26</td>
<td>&lt;0.0001</td>
<td>0.95</td>
<td>0.39 to 1.68</td>
<td>0.0015</td>
<td>–0.22</td>
<td>–0.32 to –0.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log2 (NT-proBNP), pmol/L</td>
<td>–1.32</td>
<td>–1.76 to –0.89</td>
<td>&lt;0.0001</td>
<td>2.23</td>
<td>1.16 to 3.31</td>
<td>&lt;0.0001</td>
<td>–0.45</td>
<td>–0.61 to –0.30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log2 (6MWT), metres</td>
<td>0.30</td>
<td>0.20 to 0.41</td>
<td>&lt;0.0001</td>
<td>–0.42</td>
<td>–0.69 to –0.15</td>
<td>0.0021</td>
<td>0.13</td>
<td>0.09 to 0.17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Supplementary follow-up risk parameters HR change during 6MWT (HR after minus HR before)</td>
<td>16.32</td>
<td>7.7 to 24.9</td>
<td>0.0002</td>
<td>–31.28</td>
<td>–50.4 to –11.8</td>
<td>0.0001</td>
<td>4.4</td>
<td>1.24 to 7.53</td>
<td>0.0065</td>
</tr>
</tbody>
</table>

Comparisons of the ILR consecutive measurements with current risk assessment markers using repeated measurements by a linear mixed model. Estimates of the linear regression models. All the associations were adjusted for age.
and a simplified follow-up assessment including three primary variables: WHO-FC, NT-proBNP level and 6MWT result, which have the greatest prognostic impact both at the time of diagnosis and follow-up. The introduction of continuously assessed risk parameters becomes particularly pertinent since pathophysiological changes often occur before symptom progression and early treatment intervention improves the prognosis of patients with PH.

Notably, the continuously measured HRV, PAiHR and HR at night-time in this study had significant associations with the ESC/ERS/COMPERA 2.0-based variables using the mixed model analysis. A larger HRV and a higher PAiHR were inversely associated with the WHO-FC and NT-proBNP level and directly associated with the 6MWT result whereas HR at night-time positively associated with WHO-FC and NT-proBNP levels and inversely associated with 6MWT. Additionally, our study demonstrated that a higher HRV was associated with significant higher odds of a lower ESC/ERS risk score (>5% vs <5% mortality rate) and hence a better long-term prognosis. Furthermore, a risk prediction model with HRV also showed a great ability in risk prediction of annual mortality (<5% vs >5%), as indicated by an AUC of 0.91 (Figure 3).

In contrast, there was no significant association in the logistical mixed model of PAiHR or HR at night-time. However, the mean PAiHR value of 1.3 (±0.8) in the >5%
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yearly mortality group vs the mean value of 2.2 (±1) in the <5% yearly mortality group were significantly different (unpaired t test p<0.001).

HRV could contribute as an additive risk assessment marker, especially when considering the possibility of day-to-day measures and particularly in the era of new wearable devices. Further studies are needed to establish the added value and validity of the ILR-measured risk variables in combination with the current ESC/ERS guideline-based parameters including the associations with echocardiography and CMR measures.

CONCLUSION

HRV, PAiHR and HR at night-time strongly associates with current guideline-based follow-up risk markers for PH in the new ESC/ERS/COMPERA 2–0 risk assessment model, including WHO-FC, NT-proBNP level and 6MWT. Particularly HRV demonstrated its potential as a new risk-assessment parameter in PH, as a higher HRV was associated with significant higher OR of having a lower ESC/ERS/COMPERA 2–0 risk score and hence a better long-term prognosis.

Especially when considering the possibility of 24/7 measurement of HRV, HRV carries the potential as an additional marker in PH risk assessment, and with continuous monitoring earlier detection of disease deterioration in PH.

Continuous measurement of HRV, PAiHR and HR calls for further studies with the application of simpler non-invasive methodologies such as so-called wearables, with no limited functional period to monitor these parameters.

Limitations

The study cohort was restricted to one tertiary care centre specialising in PH treatment. The number of patients was also limited owing to the rare disease status of group 1 specialising in PH treatment. The number of patients was for further studies with the application of simpler non-invasive measurement of HRV. Other markers, especially when considering the possibility of the ILR-based 24/7 measurement of HRV. HRV carries the potential as an additional marker in PH risk assessment, and with continuous monitoring earlier detection of disease deterioration in PH. However, despite the relatively small cohort, continuous heart rhythm monitoring provided HR and activity data over a total follow-up period of 96 patient-years.

The HRV calculations based on the ILR data excluded time periods when patients had arrhythmia and valid data for more than 20% of the day was needed for calculation. This might have limited the data on HRV; nevertheless, none of our patients had permanent arrhythmias.

Digoxin and beta-blockers are known to increase HRV. However, only two patients in our cohort received low-dose beta-blocker treatment.

Contributors

MØA conducted the data collection and interpretation of the data as well as inclusion of patients. Furthermore, he made the interpretation of the results. MØA wrote the first draft of the manuscript and finalised the manuscript for submission and is guarantor for the work. SZD helped with the interpretation of the results and commented and contributed to the manuscript after the first draft. JC planned the methodology and design and development of the study. He established the funding. He was the primary senior supervisor and contributed with the interpretation of the results.

Funding

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Competing interests

SZD has received consultancy fees from Bristol Myers Squibb/Pfizer, Vital Beats and Acession Pharma, speaker fees from Bristol Myers Squibb, and travel grants from Abbott. JHS is a member of an advisory board for Medtronic and has received speaker fees and research grants from Medtronic. JC is a member of an advisory board for Janssen-Cilag and has received institutional research grants and speaker fees.

Patient consent for publication

Not applicable.

Ethics approval

This study involves human participants and was approved by ID-bumber: H-18005164 Name: Videnskabsetisk komité, Kongens Vænge 23400 Hillerød—Denmark. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are available on reasonable request.

Supplemental material

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