Advanced and traditional electrocardiographic risk factors in pulmonary arterial hypertension: the significance of ventricular late potentials

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Abstract

Background: Whether non-invasive electrocardiographic parameters may be of similar relevance in pulmonary arterial hypertension (PAH) as in left ventricular heart failure (LVHF) remains unclear.

Aim: To examine a profile of electrocardiographic parameters in PAH and to determine their prognostic significance. Comparison of profile in patients with pulmonary hypertension secondary to left ventricular dysfunction was planned in order to put PAH group results into context.

Methods: We included 41 patients with type 1.1/1.4.4 (according to the European Society of Cardiology) PAH and 31 patients with LVHF and type 2.1 pulmonary hypertension. All patients underwent 24-h ambulatory electrocardiography monitoring.

Results: Among heart rate variability parameters, only RMSSD was different (mean, 75 ms [PAH] vs. 112 ms [LVHF], p = 0.016). In PAH, fewer patients had ventricular tachycardia (15% vs. 48%, p = 0.004), abnormal deceleration capacity (54% vs. 84%, p = 0.011), positive heart rate turbulence (11% vs. 48%, p = 0.003), severe autonomic failure (10% vs. 39%, p = 0.005), and ventricular late potentials (LP) (19% vs. 62%, p = 0.001). In PAH, four deaths occurred in 42 months. In univariate analysis, the risk factors for death were: LP (hazard ratio 13.55, 95% confidence interval 1.41–130.72; p = 0.024), age, N-terminal prohormone of B-type natriuretic peptide, while the protective factors were minimal and mean heart rate, as well as the six-minute walk test (6MWT) distance. In multivariate analysis, the influence of LP and the 6MWT distance remained significant.

Conclusions: Ventricular LP were present in 19% of PAH patients and were the most powerful risk factor of mortality.

Key words: pulmonary arterial hypertension, ventricular late potentials, ambulatory electrocardiography monitoring, heart failure

INTRODUCTION

Both left ventricular heart failure (LVHF) and right ventricular failure due to pulmonary hypertension (PH) are related to unfavourable long-term prognosis. Since pulmonary arterial hypertension (PAH) is a rare disease, its pathophysiology remains not fully explained. There are ongoing efforts to better understand this condition, to facilitate prognosis assessment, and to develop new treatment options.

Various electrocardiographic (ECG) parameters were proposed for risk stratification in cardiovascular diseases. Autonomic imbalance with the hyperactivity of the sympathetic system is a well-described feature of left ventricular (LV) systolic heart failure (HF). Non-invasive ECG parameters related to autonomic modulation were proved useful for the evaluation of prognosis in HF patients. Evidence regarding the importance of analogous parameters in PAH is scarce. Increased sympathetic activity in right ventricular failure was also described in several studies, on the basis of norepinephrine plasma levels and measured sympathetic nerve activity [1]. In patients with LVHF, the incidence of ventricular arrhythmias increases with the progression of the disease. Prevention of sudden death due to ventricular tachycardia or fibrillation is one of the main goals of treatment. On the other hand, in PAH the risk of deaths due to ventricular arrhythmias was assessed as 8% to 26%, while the incidence of supraventricular arrhythmias is higher and may cause clinical deterioration [2].
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Therefore, although some pathophysiological mechanisms in PAH look similar to those that play a significant role in the much better-described LVHF, the clinical observations of ECG events are divergent. Thus, it seems that patients with PAH may be described as having a unique pattern of ECG risk factors.

The main aim of this study was to assess the comprehensive profile of non-invasive ECG parameters and to investigate their possible prognostic usefulness in patients with PAH. We wanted not only to describe the potentially detected irregularities and to present their frequency of occurrence, but also to test selected parameters as potential prognostic factors in a survival analysis. We also compared the characteristics of the established parameters in PAH patients with analogical parameters in PH secondary to LV systolic dysfunction. It must be emphasised that these are dramatically different groups of patients. They are connected by a widely understood HF; a shorter survival time than in the general population, and by the presence of PH. Comparing these two groups of patients makes it possible to show the results of patients with a relatively rare disease (PAH) in the context of the results obtained in the patients met more frequently in clinical practice, i.e. patients with LVHF.

**METHODS**

**The study population**

The PAH group comprised 41 patients with pulmonary arterial hypertension, including 22 subjects with type 1.1. PH, i.e. idiopathic PH, and 19 subjects with type 1.4.4, i.e. related to congenital heart defect — according to the European Society of Cardiology (ESC) classification [3]. The diagnosis was established by means of right heart catheterisation.

In the congenital heart defect subset, the aetiology included atrial septal defect (five patients), atrial septal defect with patent ductus arteriosus (one patient), atroventricular septal defect (two patients), ventricular septal defect (seven patients), patent ductus arteriosus (two patients), double inlet ventricle (one patient), mitral atresia with hypoplastic left ventricle and multiple shunt lesions (one patient).

All the patients received treatment according to the national therapeutic programme, supervised in a single reference medical centre. Specific drug therapy for PAH was administered for at least one month before the 24-h ECG monitoring. At the time of 24-h ECG monitoring the therapy consisted of:

- bosentan in monotherapy — 12 patients;
- sildenafil in monotherapy — 11 patients;
- calcium channel blocker in monotherapy — two patients;
- sildenafil and treprostinil — five patients;
- sildenafil and bosentan — five patients;
- sildenafil and iloprost — four patients;
- sildenafil and selexipag — one patient;
- sildenafil and bosentan and selexipag — one patient.

Additional drugs were also used due to specific indications, it should be noted that 66% of the patients received beta-blockers due to arrhythmia (supraventricular tachycardia, paroxysmal atrial flutter or fibrillation, ventricular arrhythmia) or systemic arterial hypertension.

The LVHF group comprised 31 patients with stable LV systolic dysfunction, with LV ejection fraction (LVEF) < 45% and type 2.1 PH.

Six patients had LVEF 40–45%, so they were in the HF with mid-range ejection fraction category; 25 patients had LVEF 14–36%, so they were in HF with reduced ejection fraction category according to the latest ESC guidelines [4]. The aetiology of LV dysfunction was either coronary artery disease (27 subjects) or dilated cardiomyopathy (four patients). Patients with moderate or severe valvular heart disease were excluded. The diagnosis of PH was established by means of echocardiographic examination, based on estimated systolic pulmonary arterial pressure (SPAP) with a cut-off point > 40 mmHg. Although right heart catheterisation remains the best method of pulmonary pressure assessment, in the LVHF group it was not routinely performed, and thus we had to adopt an alternative approach. According to the literature, this cut-off point of SPAP is reliable [5]. In four patients right heart catheterisation was performed due to specific indications, and mean pulmonary arterial pressure was confirmed to be > 25 mmHg in all cases. The patients were optimally treated for HF (including beta-blocker in 90% of the group, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in 97%) as recommended by the ESC.

We enrolled patients with sinus rhythm and without an implanted pacemaker.

This study was conducted according to the Declaration of Helsinki regulations. The protocol was approved by the Local Bioethics Committee (RNN/194/15/KE). All the participants of this study signed an informed consent form.

The clinical status of the PAH patients was assessed according to the World Health Organisation (WHO) classification, and the clinical status of the LVHF patients was assessed according to the New York Heart Association (NYHA) classification.

**Examinations**

Exercise tolerance was assessed using the six-minute walk test (6MWT) and a cardiopulmonary exercise test. The cardiopulmonary exercise test was performed according to the modified Bruce protocol, using a ZAn-680 ErgoSpire device and software, and a Fullvision TMX425 treadmill. Peak oxygen uptake (VO2peak) was analysed.

The transthoracic echocardiographic examination was performed by means of a Vivid E9 device with an M5S-D 2D 1.5–4.5 MHz probe. Standard measurements were taken in typical views. The echocardiographic measurements were performed in accordance with the guidelines of the American
The heart rate variability (HRV) parameters included

- **SDNN** — standard deviation of NN intervals (normal-to-normal, or sinus beat-to-beat intervals), which represents overall variability during the whole time of the recording. SDNN was analysed both as a continuous variable and also as a normal versus diminished variable (since in the previous studies of people with LVHF, the threshold which separated patients with different prognosis was taken to be 50, 80, or 100 ms; here we adopted the cut-off point of SDNN < 75 ms).
- **RMSSD** — the square root of the mean of the squares of the successive differences between adjacent NNs, which represents short-term variability.
- **pNN50** — the percentage of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording, which represents short-term variability.
- **Triangular index** — the integral of the density distribution (the number of all NN intervals) divided by the maximum of the density distribution, which represents overall HRV measured over 24 h and is more influenced by the lower than by the higher frequencies [7].

Deceleration capacity is a measure of all deceleration-related oscillations over the entire 24-h recording, and thus a measure of cardiac vagal modulations. The value of ≤ 4.5 ms is considered protective factors that influenced survival.

Heart rate turbulence (HRT) is a measure of baroreflex-mediated oscillation of HR after ExV. HRT was automatically measured by means of the CardioDay software, and the parameters included turbulence onset (TO) and turbulence slope (TS). The normal values of these are: TO < 0% and TS > 2.5 ms/RR interval. The patients were divided into three categories: (1) with both TO and TS values normal, (2) with one value abnormal, and (3) with both values abnormal (positive HRT) [9]. Severe autonomic failure was defined as the coexistence of abnormal deceleration capacity and of positive HRT [10].

Ambulatory T wave alternans was analysed in three channels from 24-h recordings, using the modified moving average method. The algorithm separates odd and even beats to create a template for both every 10 s. These templates are superimposed, and the difference is defined as the T-wave alternans (TWA) value. In this method, TWA voltage > 65 µV is considered abnormal, and the patient was assigned the “positive TWA” category when there was an abnormal value in at least two channels [11–13].

The parameters connected with ventricular late potentials (LP) included: the width of the filtered QRS complex, abnormal fQRS when > 114 ms; low-amplitude signal (LAS) voltage < 20 µV in the terminal part of QRS complex, abnormal LAS when lasting > 38 ms; and root-mean square (RMS) voltage in the last 40 ms of fQRS, abnormal RMS when < 20 µV. The patient was assigned the “positive LP” category when at least two of these parameters were within abnormal values, as was previously applied in studies concerning LVHF [14, 15].

In the follow-up of the PAH group, the main assessed event was all-cause death. Mean time of observation was 42.2 months (minimal eight months, maximal 77 months, median 39 months). We determined the risk factors and the protective factors that influenced survival.

Society of Echocardiography and the European Association of Echocardiography [6]. Specifically, wall thickness, LV, right ventricular, and left atrial diameters were measured from two-dimensional echocardiography in parasternal long-axis view. To calculate the SPAP, estimated right atrial pressure was added to the peak gradient of tricuspid regurgitation, recorded typically with continuous wave Doppler from apical four-chamber view. Right atrial pressure was estimated on the basis of the diameter of the inferior vena cava and its maximal change during inspiration. Right atrial pressure was assumed to be 3 mmHg when the inferior vena cava diameter was < 21 mm and the collapsibility index > 50%, to be 8 mmHg when the one parameter exceeded upper limit, and to be 15 mmHg when the inferior vena cava diameter was enlarged and also did not collapse significantly during inspiration. Simpson’s modified biplane method using four-chamber and two-chamber apical views was applied to assess LVEF.

We performed 24-h ECG monitoring using seven electrodes and a CardioMem CM 3000 recorder (GETEMED Medizin- und Informationstechnik AG, Teltow, Germany), obtaining a three-channel signal. The sampling rate was 1024 Hz in 12-bit resolution. The patients’ skin was shaved if necessary and then prepared with abrasive paste. Before the start of the recording, the technical quality of the signal was checked on the device’s display to ensure minimal noise. Only high-quality recordings were included in this study. The analysis was done with CardioDay software (GETEMED). We determined a set of parameters that were considered to be “traditional” electrocardiographic risk factors. These included: mean, minimum and maximum heart rate (HR), the presence and the number of premature supraventricular beats (ExSV), supraventricular tachycardia, ventricular beats (ExV), non-sustained ventricular tachycardia, bradycardia < 45 bpm, and pauses > 2 s. We also analysed a broad range of “advanced” parameters.

We conducted blood tests for the estimated glomerular filtration rate, using Cockroft-Gault formula and N-terminal prohormone of B-type natriuretic peptide concentrations.

The duration of the QRS complex was assessed manually in a standard 12-lead ECG, which was recorded by means of an analogue device (AsCARD MrSilver and AsCARD MrBlue, Aspel, Poland).

We performed 24-h ECG monitoring using seven electrodes and a CardioMem CM 3000 recorder (GETEMED Medizin- und Informationstechnik AG, Teltow, Germany), obtaining a three-channel signal. The sampling rate was 1024 Hz in 12-bit resolution. The patients’ skin was shaved if necessary and then prepared with abrasive paste. Before the start of the recording, the technical quality of the signal was checked on the device’s display to ensure minimal noise. Only high-quality recordings were included in this study. The analysis was done with CardioDay software (GETEMED). We determined a set of parameters that were considered to be “traditional” electrocardiographic risk factors. These included: mean, minimum and maximum heart rate (HR), the presence and the number of premature supraventricular beats (ExSV), supraventricular tachycardia, ventricular beats (ExV), non-sustained ventricular tachycardia, bradycardia < 45 bpm, and pauses > 2 s. We also analysed a broad range of “advanced” parameters.
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**Statistical analysis**

The comparisons of frequencies or distributions of frequencies (discrete variables) were performed by means of the $\chi^2$ test of independence or Fisher’s exact test according to the expected frequencies in contingency table cells. Because the mean age was significantly different between the two study groups, the covariance analysis model with age as the covariate was used for inter-group comparison of the expected values. The analysis of the prognostic factors that affected survival was done by means of the Cox proportional hazards model — for one variable and for many variables. In these models two outcomes are analysed: death or time of survival (uncensored time or censored time). The level of significance was assumed to be $p < 0.05$. The analysis was performed by means of SPSS Statistics, version 22.0 (IBM, NY, USA).

**RESULTS**

There were 21 (51%) women in the PAH group versus five (16%) in the LVHF group, which is a significantly different proportion, with $p = 0.003$.

The profile of functional class categorisation was similar. In PAH, six (14.6%) patients were in WHO class I, 20 (48.8%) in WHO class II, and 15 (36.6%) in WHO class III. In LVHF, 19 (61.3%) patients were in NYHA class II and 12 (38.7%) were in NYHA class III.

The mean age was significantly different between the two groups: in PAH it was 52 ± 17 vs. 62 ± 11 years in LVHF, $p = 0.004$. Therefore, in further comparisons, the values of the parameters are presented after the adjustment for age.

A inter-group comparison is presented in Table 1.

The traditional ECG parameters are presented in Table 2. The PAH group had a higher mean HR as well as maximum HR. The LVHF group was more prone to ventricular tachycardia. There were no other significant differences.

The advanced ECG parameters are presented in Table 3. The mean value of RMSSD was lower in the PAH group, the mean values of other HRV parameters were similar. Deceleration capacity was higher in PAH. HRT assessment was possible for 36 patients in the PAH group and for 29 patients in the LVHF group. In the PAH group there were more patients with normal values of both TO and TS, at the same time in this group fewer patients were in the “positive HRT” category. Severe autonomic failure and ventricular LP were found more frequently in the LVHF group. The incidence of “positive TWA” was similar in both groups.

The follow-up

In the PAH group, after the mean follow-up period of 42.2 months, there were four deaths: two sudden cardiac deaths and two deaths due to HF deterioration.

In a univariate analysis, we identified several risk factors and protective factors affecting survival; these are presented in Table 4. The most powerful factor that affected survival was the presence of ventricular LP (hazard ratio [HR] 13.55, 95% confidence interval [CI] 1.41–130.72, $p = 0.024$).

In a multivariate analysis, the negative influence of ventricular LP ($p = 0.018$) and the protective influence of the 6MWT distance (HR 0.98, 95% CI 0.96–0.99, $p = 0.008$) remained significant.

### Table 1. Comparison of groups — general characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PAH</th>
<th>LVHF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF [%]</td>
<td>56 ± 1</td>
<td>28 ± 1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SPAP [mmHg]</td>
<td>87.5 ± 3.7</td>
<td>57.7 ± 4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NT-proBNP [pg/mL]</td>
<td>1304 ± 391</td>
<td>3770 ± 453</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>eGFR [mL/min/1.73 m²]</td>
<td>83.5 ± 3.8</td>
<td>87.7 ± 4.4</td>
<td>0.475</td>
</tr>
<tr>
<td>QRS duration [ms]</td>
<td>117 ± 3</td>
<td>102 ± 4</td>
<td>0.003</td>
</tr>
<tr>
<td>6MWT distance [m]</td>
<td>403 ± 18</td>
<td>351 ± 21</td>
<td>0.071</td>
</tr>
<tr>
<td>VO₂peak [mL/(kg×min)]</td>
<td>14.8 ± 0.8</td>
<td>15.4 ± 1.1</td>
<td>0.652</td>
</tr>
</tbody>
</table>

Data as shown as adjusted mean ± standard deviation. 6MWT — six-minute walk test; eGFR — estimated glomerular filtration rate; LVEF — left ventricular ejection fraction; LVHF — left ventricular heart failure; NT-proBNP — N-terminal prohormone of B-type natriuretic peptide; PAH — pulmonary arterial hypertension; SPAP — systolic pulmonary arterial pressure; VO₂peak — peak oxygen uptake

### Table 2. Comparison of groups — traditional electrocardiographic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PAH</th>
<th>LVHF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR mean [bpm]</td>
<td>72 ± 2</td>
<td>66 ± 1</td>
<td>0.026</td>
</tr>
<tr>
<td>HR minimal [bpm]</td>
<td>55 ± 2</td>
<td>54 ± 2</td>
<td>0.628</td>
</tr>
<tr>
<td>HR maximal [bpm]</td>
<td>111 ± 3</td>
<td>93 ± 3</td>
<td>&lt; 0.0005</td>
</tr>
</tbody>
</table>

Number of:

- ExSV
- ExV
- msVT
- Bradycardia events
- Pauses

<table>
<thead>
<tr>
<th>Incidence of:</th>
<th>PAH</th>
<th>LVHF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ExSV</td>
<td>404 ± 240</td>
<td>843 ± 275</td>
<td>0.247</td>
</tr>
<tr>
<td>ExV</td>
<td>419 ± 185</td>
<td>839 ± 212</td>
<td>0.153</td>
</tr>
<tr>
<td>msVT</td>
<td>0.7 ± 0.5</td>
<td>1.1 ± 0.5</td>
<td>0.633</td>
</tr>
<tr>
<td>Bradycardia events</td>
<td>33 ± 21</td>
<td>69 ± 24</td>
<td>0.271</td>
</tr>
<tr>
<td>Pauses</td>
<td>1.6 ± 0.8</td>
<td>0.4 ± 1</td>
<td>0.376</td>
</tr>
</tbody>
</table>

Data as shown as adjusted mean ± standard deviation or number of patients (percentage).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PAH</th>
<th>LVHF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVT</td>
<td>16 (40%)</td>
<td>16 (52%)</td>
<td>0.275</td>
</tr>
<tr>
<td>msVT</td>
<td>6 (15%)</td>
<td>15 (48%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Bradycardia events</td>
<td>11 (28%)</td>
<td>15 (48%)</td>
<td>0.086</td>
</tr>
<tr>
<td>Pauses</td>
<td>3 (8%)</td>
<td>3 (10%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Data as shown as adjusted mean ± standard deviation or number of patients (percentage). ExSV — supraventricular extrasystoles; ExV — ventricular extrasystoles; HR — heart rate; LVHF — left ventricular heart failure; msVT — non-sustained ventricular tachycardia; PAH — pulmonary arterial hypertension; SVT — supraventricular tachycardia

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Table 4. Risk factors of survival in the pulmonary arterial hypertension group — results of the univariate Cox proportional hazards model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular late potentials</td>
<td>13.552</td>
<td>1.405–130.722</td>
<td>0.024</td>
</tr>
<tr>
<td>Age</td>
<td>1.091</td>
<td>1.014–1.174</td>
<td>0.020</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>1.001</td>
<td>1.000–1.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Protective factors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR minimal from 24-h monitoring</td>
<td>0.954</td>
<td>0.916–0.994</td>
<td>0.023</td>
</tr>
<tr>
<td>HR mean from 24-h monitoring</td>
<td>0.962</td>
<td>0.934–0.991</td>
<td>0.011</td>
</tr>
<tr>
<td>6MWT distance</td>
<td>0.985</td>
<td>0.975–0.994</td>
<td>0.001</td>
</tr>
</tbody>
</table>

6MWT — six-minute walk test; CI — confidence interval; HR — heart rate; NT-proBNP — N-terminal prohormone of B-type natriuretic peptide
In the LVHF group there was one death at the time of database closure.

**DISCUSSION**

In our study we performed a comprehensive assessment of advanced ECG parameters in a rare disease — PAH. We put these findings into the clinical context by comparing them with an analogous profile of patients with LVHF. Moreover, we evaluated the influence of advanced ECG parameters on survival in the PAH group, obtaining new and original findings. The homogeneity of the PAH group is another important asset of our study, because often in the literature patients with PH of diverse aetiology are merged into one study group. To obtain advanced ECG parameters, we used sophisticated software for ambulatory ECG monitoring. This allows the assessment of microvolt TWA even in patients with very limited exercise tolerance. We used well-established criteria for each parameter [16].

Generally speaking, the ECG risk factor profiles of our two groups were clearly different, with the LVHF patients being more prone to abnormal findings in terms of the respective parameters.

The lower minimum and mean HRs in the LVHF group were probably related to the fact that they were all given beta-blockers (90% of the patients), unlike the PAH group (only 66%).

The impaired cardiac autonomic control as reflected by the frequency-domain HRV parameters, related to the peak oxygen uptake as a marker of the severity of the disease, had been reported in PAH previously [17]. It was also stated that higher pulmonary arterial pressure was correlated with lower time-domain and frequency HRV indices [18]. Abnormal frequency- and time-domain HRV indices remain compromised even after one year of disease-specific treatment [19]. Even if some improvement is noted, the values of HRV indices still are lower than in the healthy controls [20]. The participants of our study, both in the PAH and in the LVHF group, were already receiving appropriate treatment when the ECG monitoring was performed. In time-domain HRV parameters, an inter-group difference was noted only in one index — RMSSD, which was lower in PAH. Thus, on the basis of our study the HRV parameter profile seems comparable in PAH and LVHF. On the other hand, the mean values of the novel parameter of deceleration capacity were clearly lower in the LVHF group, and a significantly higher percentage of the LVHF subjects had deceleration capacity below the established threshold (84% in the LVHF group vs. 54% in the PAH group).

In a recent study, Bienias et al. [21] described HRT impairment in patients with PH (in a composite study group of 22 subjects with PAH of varied aetiology, 11 with chronic thromboembolic PH; in comparison with healthy controls. Abnormal TO and/or TS were found in 63.3% of the PH group, and 24.2% had both TO and TS abnormal. In our study, 53% of the patients of the PAH group had at least one parameter abnormal — which seems close to the previously reported occurrence, and which is probably influenced by the lower mean TO value in this group. Nevertheless, eventually only 11% of PAH patients had both TO and TS abnormal (had positive HRT), which is significantly less than 48% in the LVHF group. Thus, on the basis of our results, it can be stated that in the PAH patients HRT impairment is less evident than in the PH secondary to LV dysfunction. In another report, based on a similarly composed study group, Bienias et al. [22] showed a correlation between a higher WHO functional class and an impairment of both HRT and HRV time-domain parameters. More importantly, the authors also found a correlation between the aetiology of the PH and HRT/HRV with worse outcomes in chronic thromboembolic PH. This finding confirms that in small-group studies in rare diseases, it is beneficial to maintain high homogeneity of the study group.

Since both positive HRT and abnormal deceleration capacity were more frequently found in the LVHF group, not surprisingly the derivative parameter of severe autonomic failure was also noted more often in the LVHF group than in the PAH group.

T-wave alternans readings analysed separately in a single channel were higher in the PAH group; however, this did not result in a significant difference in the occurrence of positive TWA (55% vs. 39%, p = NS). Still, the occurrence of positive TWA in PAH was high and resembled the amount of positive microvolt TWA reported by Lewicka et al. [23]. The authors employed a conventional approach to the assessment of TWA on the basis of an exercise test and analytic spectral method. They found positive microvolt TWA in 67% of patients.

The duration of the QRS complex measured manually from a standard 12-lead ECG was longer in the PAH group, but still the mean value was 117 ± 3 ms. Thus, we used standard criteria for ventricular LP because the mean QRS duration in both groups was < 120 ms, and in patients with a minor conduction defect there is no need to apply modified thresholds [24]. The inter-group difference in the QRS duration was absent in high-resolution, signal-averaged ECG. To our knowledge, there is no similar previous report of the significance of ventricular LP in PAH. Morelli et al. [25] published a study about a possible link between LP and myocardial involvement in systemic sclerosis, but with no clear connection between PH and LP. The prognostic importance of ventricular LP was well described for patients with systolic HF, both after myocardial infarction [26] and in idiopathic dilated cardiomyopathy [27] — so in a population similar to our LVHF group. As to right ventricle failure, the recording of signal-averaged ECG is recommended in arrhythmogenic right ventricular cardiomyopathy, to improve diagnosis by revealing regions of abnormal myocardium with slow conduction, the substrate of life-threatening ventricular arrhythmias [28]. Among the “advanced” noninvasive parameters that we
investigated, at the current state of knowledge, assessment of ventricular LP is the only one that may influence clinical practice. In our study, the PAH group had a lower occurrence of positive LP in comparison with the LVHF patients: 19% vs. 62%. Though less often noted, positive LP was the most powerful negative prognostic factor in PAH, increasing the risk of death by 13.6 times. Perhaps also in PAH, the presence of ventricular LP indicates an unfavourable structural remodelling of the right ventricle. Future studies should enable further investigation of this novel finding and of its clinical and therapeutic implications.

CONCLUSIONS

Although the profile of ECG risk factors is more favourable in PAH than in LV dysfunction with secondary PH, comprehensive assessment of the advanced parameters should not be neglected. Ventricular LP is found in 19% of the PAH patients and is related to poor prognosis.

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Conflict of interest: none declared

References


Significance of ventricular late potentials in pulmonary arterial hypertension