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Deriving electrophysiological phenotypes of paroxysmal atrial fibrillation based on the characteristics of heart rate variability

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Abstract

Aim. To analyze heart rate variability of patients with paroxysmal atrial fibrillation and identify electrophysiological phenotypes of the disease by using methods of exploratory analysis of twenty-four-hour electrocardiographic (Holter) recordings.

Methods. 64 electrocardiogram recordings of patients with paroxysmal atrial fibrillation were selected from the open Long-Term Atrial Fibrillation Database (repository — PhysioNet). 52 indices of heart rhythm variability were calculated for each recording, including new heart rate fragmentation and asymmetry indices proposed in the last 5 years. Data analysis was carried out with machine learning methods: dimensionality reduction with principal component analysis, hierarchical clustering and outlier detection. Feature correlation was checked by the Pearson criterion, the selected patient's subgroups were confirmed by using Mann–Whitney and Student's tests.

Results. For the vast majority of patients with paroxysmal atrial fibrillation, heart rate variability can be described by five parameters. Each of these parameters captures a distinct approach in heart rate variability classification: dispersion characteristics of interbeat intervals, frequency characteristics of interbeat intervals, measurements of heart rate fragmentation, indices based on heart rate asymmetry, mean and median of interbeat intervals. Two large phenotypes of the disease were derived based on these parameters: the first phenotype is a vagotonic profile with a significant increase of linear parasympathetic indices and paroxysmal atrial fibrillation lasting longer than 4.5 hours; the second phenotype — with increased sympathetic indices, low parasympathetic indices and paroxysms lasting up to 4.5 hours.

Conclusion. Our findings indicate the potential of nonlinear analysis in the study of heart rate variability and demonstrate the feasibility of further integration of nonlinear indices for arrhythmia phenotyping.

Keywords: paroxysmal atrial fibrillation, arrhythmia phenotyping, exploratory data analysis, heart rate variability, HRV, Holter monitor.

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Background. Atrial fibrillation (AF) is one of the most common rhythm disorders in the population. Paroxysmal AF is of considerable interest for cardiologists since correct drug therapy and interventional treatment methods restore the rhythm for a long time, which improves the patient's quality of life and reduces the burden on the healthcare system in the country.

At the moment, no consensus was found on the mechanisms of initiation, maintenance, and termination of AF paroxysm. AF was believed as an arrhythmological pathology that can be divided into several phenotypes that result from a complex combination of genetic factors, comorbidities, human lifestyle, and environmental conditions. The phenotypes of AF were previously identified based on clinical manifestations [1, 2], genetic characteristics [3], and valve apparatus characteristics [4]. In addition, studies highlighted various types of paroxysms based on the indexes of rhythm variability [5] or the characteristics of the sympathetic nerve activities that are located in the skin [6].

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One of the approaches in isolating the disease phenotypes is the use of heart rate variability (HRV) indices. Many works are focused on the analysis of the characteristics that are often used for analysis, such as root mean square of successive differences (RMSSD), pNN50, pNN20[1], and range frequency bands [7]. However, over the past few years, additional indices of asymmetry and fragmentation of the heart rhythm have been proposed [8–10]. Their physiological rationale and clinical significance nowadays have not been fully studied; however, these indices have a significant sensitivity to pathology, which has been demonstrated in large groups of people [8], and therefore, require clinical and physiological interpretation.

Our work determined the phenotypes of AF based on the calculated HRV indices on the electrocardiograms (ECG) of daily monitoring. The study was conducted on the Long Term AF Database (LTAFDB) open database of electrocardiographic signals [11] using exploratory data analysis methods [12]. Previous works, which use this database, attempt to analyze the HRV to identify episodes of AF [13]; however, our work performed a more detailed study of the HRV characteristics, presented an analysis of the relationships between heart rate indicators, identified two phenotypes of paroxysmal AF, and substantiated statistically their existence in the population.

This study aimed to analyze the HRV parameters in patients with paroxysmal AF and isolate the electrophysiological phenotypes of the disease using the methods of exploratory analysis of daily ECG monitoring data.

Materials and methods. The LTAFDB database consists of 84 ECG records for 24–25 h in length, which makes it the most extensive bank with episodes of paroxysmal AF [11]. Records from LTAFDB include signals from two electrodes with a sampling of 128 Hz, which was sufficient for identifying the heart rate and calculating the HRV indicators.

Data processing included several stages. First, the data of patients with paroxysmal AF were isolated among all the records according to the database abstract. Further, for each ECG record, the HRV indices were calculated, after which the principal component method was applied to reduce the number of descriptive signs. The available data included records of patients with additional arrhythmological pathology that are different from AF, thus all outliers were excluded for the analysis integrity and the principal component method was reapplied. Subsequently, the method of hierarchical clustering was used to search for the disease phenotypes. The subgroups of patients with paroxysmal AF identified using it were additionally confirmed by analysis of variance.

At stage 1, 20 records with a total duration of >24 hours of AF paroxysms were excluded from the data set. Episodes of sinus rhythm that are available for analysis were isolated from the remaining records with paroxysmal AF, and ectopic impulses were excluded, after which chronograms were constructed. The resulting chronograms were processed to obtain the following 52 HRV characteristics:

– 14 time-domain indicators that statistically characterize the distribution of interpeak intervals [7] (RMSSD, MeanNN, SDNN, SDSD, CVNN, CVSD, MedianNN, MadNN, MCVNN, IQRNN, pNN50, pNN20, TINN, and HTI);

– 9 indices of HRV frequency characteristics that are excluded from the analysis of the spectral power density of the chronogram [7] (power of ULF, VLF, LF, HF, VHF frequency bands; HFn, LFn, LF/HF, and LnHF);

– 7 nonlinear characteristic indicators of the geometry of the Poincaré graph [7] (SD1, SD2, SD1/SD2, S, CSI, CVI, and Modified CSI);

– 16 indicators of heart rate asymmetry [8, 9] (GI, SI, AI, PI, C1d, C1a, SD1d, SD1a, C2d, C2a, SD2d, SD2a, SDNNd, SDNNa, Cd, and Ca);

– 4 indexes of heart rate fragmentation [10] (PIP, IALS, PSS, and PAS);

– 2 metrics of approximation of entropy [7] (ApEn and SampEn).

In total, the attribute vector consists of 52 values. It is noteworthy that the metrics GI, SI, AI, PI, PIP, IALS, PSS, and PAS [9, 10] were proposed <5 years ago.

Many of the obtained attributes showed a linear interdependence, thus the principal component method was used to reduce the number of analyzed attributes. This performed a linear decreased dimensional space and reduce the number of attributes from 52 to 7. This number of components was selected following the value of the explained covariance coefficient. The data were first normalized in the range before applying the principal component method (0.1) and then presented as deviations from the mean. This approach differs from the traditional principal component method, but more effectively reduces the dimension of the parameter space [12].

A voting method with four jury algorithms was implemented to detect outliers, which includes a robust covariance matrix estimate, a single-class support vector machine, an isolation forest, and a local

[1] RMSSD: root mean square value of successive differences; NN50 and NN20: the number of pairs of consecutive NNs that differ by >50 and 20 ms, respectively; pNN50 and pNN20: proportion of NN50 and NN20 divided by the total number of NNs.

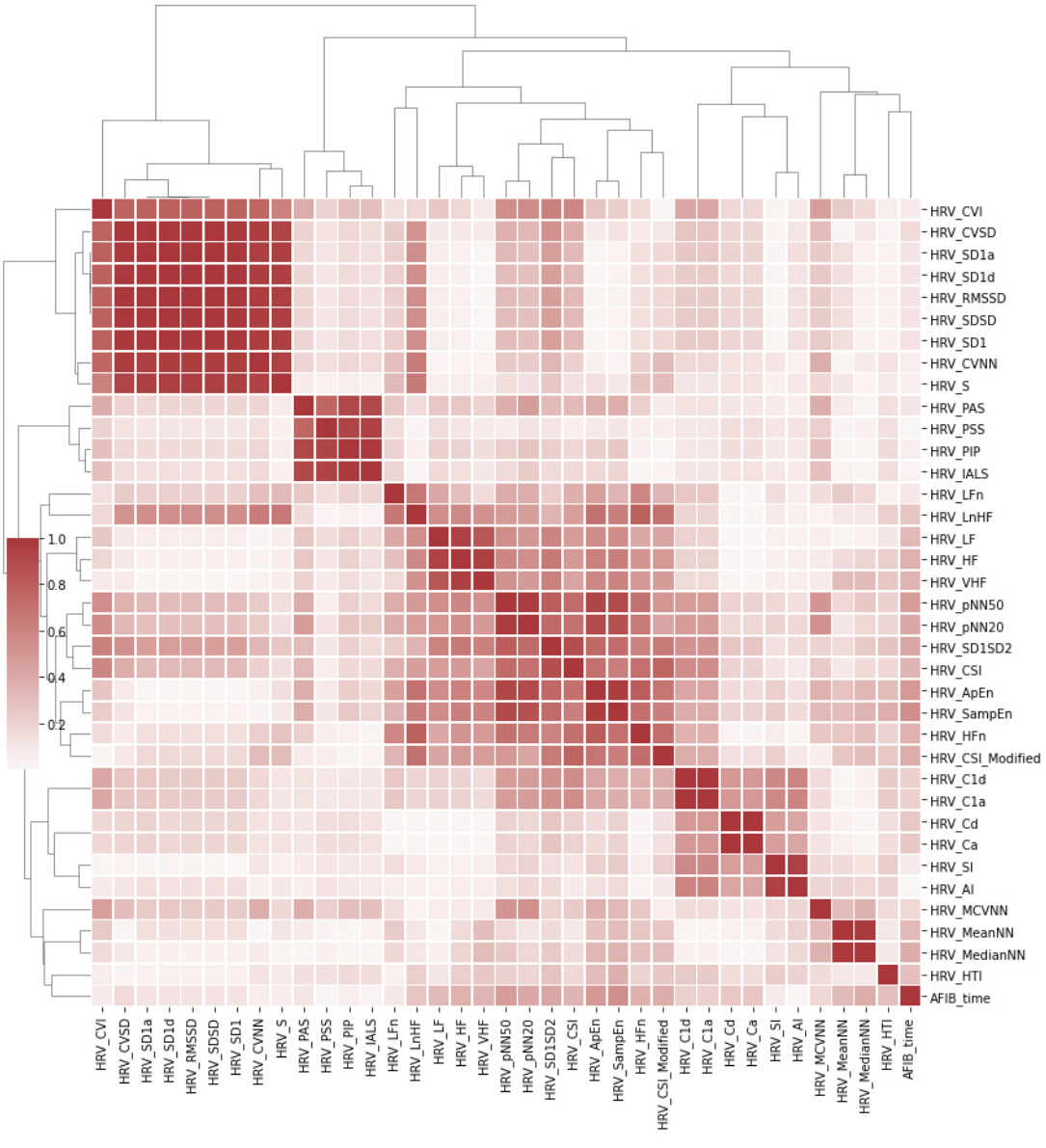

Fig. 1. Diagram of the correlation between indices of heart rate variability in patients with paroxysmal atrial fibrillation. The color scale indicates the absolute values of the correlation coefficients between the attributes. The proximity of the indices to each other is demonstrated using dendrograms on the axes.

outlier level [12]. The vectors of the attributes were marked as outliers if at least three out of four algorithms "voted for them." ECG records that correspond to the marked vectors were separately analyzed by a cardiologist. Then the linear space dimension reduction was repeated for the data without outliers, which further reduced the number of attributes to 5.

The resulting dataset was analyzed using hierarchical linkage clustering according to the Ward test [12]. This method of analysis is often used in bioinformatics to identify disease phenotypes [1]. According to the dendrogram constructed, two groups of patient data records are distinguished.

Since the dendrogram serves as an exploratory method of analysis, obtained results were additionally verified using the analysis of variance and data on the duration of pathology that is excluded from the initial processing. Statistical tests (Student's *t*-test and Mann–Whitney–Wilcoxon test) were used for the analysis of each of the 52 HRV attributes to test the two-sided hypothesis about the inequality of the mean values. The total duration of AF paroxysms over the entire duration of the recording was used as information that was not used before applying the principal component analysis.

Results. For each of the 64 records, 52 HRV indicators were calculated. Some were correlated with each other. Figure 1 presents several large groups among all HRV indicators.

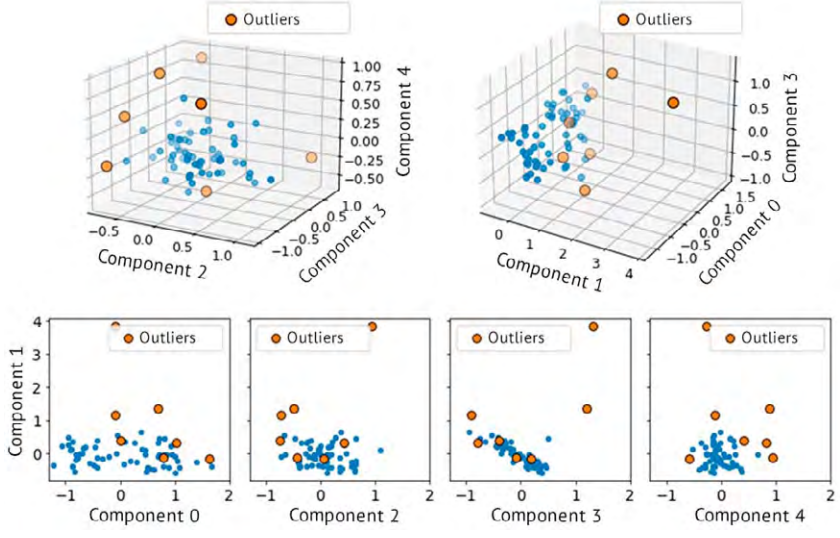

Fig. 2. Space of characteristics of heart rate variability after application of the method of principal components. The five-dimensional space of the principal components is presented in three-dimensional and two-dimensional projections, respectively. For distribution clarity, the graphs below have a single Y-axis (component 1). Outliers are marked with orange dots.

Group 1 of HRV indices strongly correlated according to Pearson ($0.61 < r < 0.96$) that represents the characteristics of the variance of the interpeak intervals (representatives of RMSSD, SD1, SDSD, CVI, and CVNN). The extensive group 2 of correlated attributes includes the frequency characteristics of the chronogram, as well as the cardiosympathetic index and entropy indices (representatives of CSI, pNN50, LF, HF, SD1/SD2, and SampEn; $0.16 < r < 0.97$). Group 3 represents indices of fragmentation of the heart rate (PAS, PSS, PIP, and IALS; $0.75 < r < 0.97$). Group 4 represents signs of asymmetry of the heart rhythm (representatives of SI, AI, Cd, and Ca; $0.6 < r < 0.99$). Group 5 represents the mean and median values of the sequence of peak intervals (MeanNN and MedianNN; $r = 0.97$).

The indices and characteristics of signals include the attributes that are weakly correlated with anything, for example, some indicators of the time domain that statistically characterize the distribution of interpeak intervals (MCVNN and HTI), as well as an AF time indicator (AFIB Time).

The calculation of HRV indicators and a two-stage application of the principal component method convert 52 HRV characteristics into five parameters (principal components). This five-dimensional space was visualized by presenting it in projections as seen in Fig. 2. Some vectors of HRV characteristics were located at a distance from the main data distribution and were considered outliers.

The four methods listed above were used to detect outliers. Only 9 (14%) of 64 vectors were marked as outliers based on the voting results of at least three outlier detection algorithms. The HRV characteristics of these patients were excluded from the main data set.

After eliminating the outliers, the data were subjected to hierarchical clustering, based on which the dendrogram was constructed (Fig. 3). Depending on the cut-off threshold, 11 to 2 clusters can be distinguished. Two clusters were chosen because the justification of a more detailed division was impossible due to the sample size. The analysis of the isolated phenotypes is presented below.

In the extensive literature on HRV, the RMSSD and pNN50 indices serve as the main indicators of the used time domain to assess the vagal tone and activity of the parasympathetic nervous system [7]. Figure 4 presents the RMSSD and pNN50 indices in the reduced-dimensional space from a gradient of values that increases along with two closely oriented directions.

The separability of the two clusters was additionally confirmed by testing the inequality of the mean values of the attributes using the Student's *t*-test and the Mann–Whitney–Wilcoxon statistical test. The *p*-values of both tests did not exceed 0.01 for 31 HRV indices, which confirmed the difference in the phenotypes of paroxysmal AF. The average values of the indices in the data clusters and the *p*-values of their differences are presented in Table 1 for some of the HRV parameters.

As a result of the analysis, all records were classified into the structure of 2 major phenotypes of paroxysmal AF (Table 1). The phenotype 1 indicates vagotonic tendencies in heart rate regulation as confirmed not only by linear parasympathetic indicators (pNN50 and RMSSD) but also by

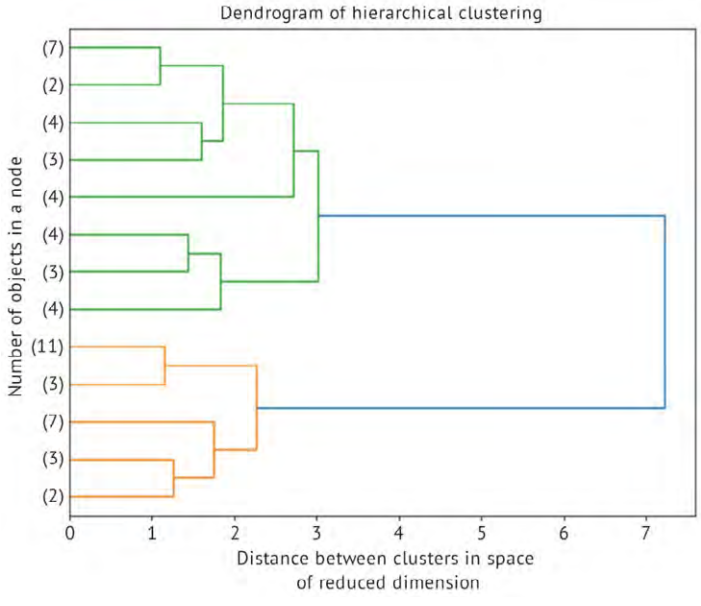

Fig. 3. Dendrogram reflects the closeness of heart rate variability parameters in patients. In the captions, the Y-axis represents the number of patients in a group, and the X-axis represents the distance between the patient groups. Two clusters of data are well traced; they are presumably associated with different phenotypes of atrial fibrillation, which are prominent at the very base of the dendrogram.

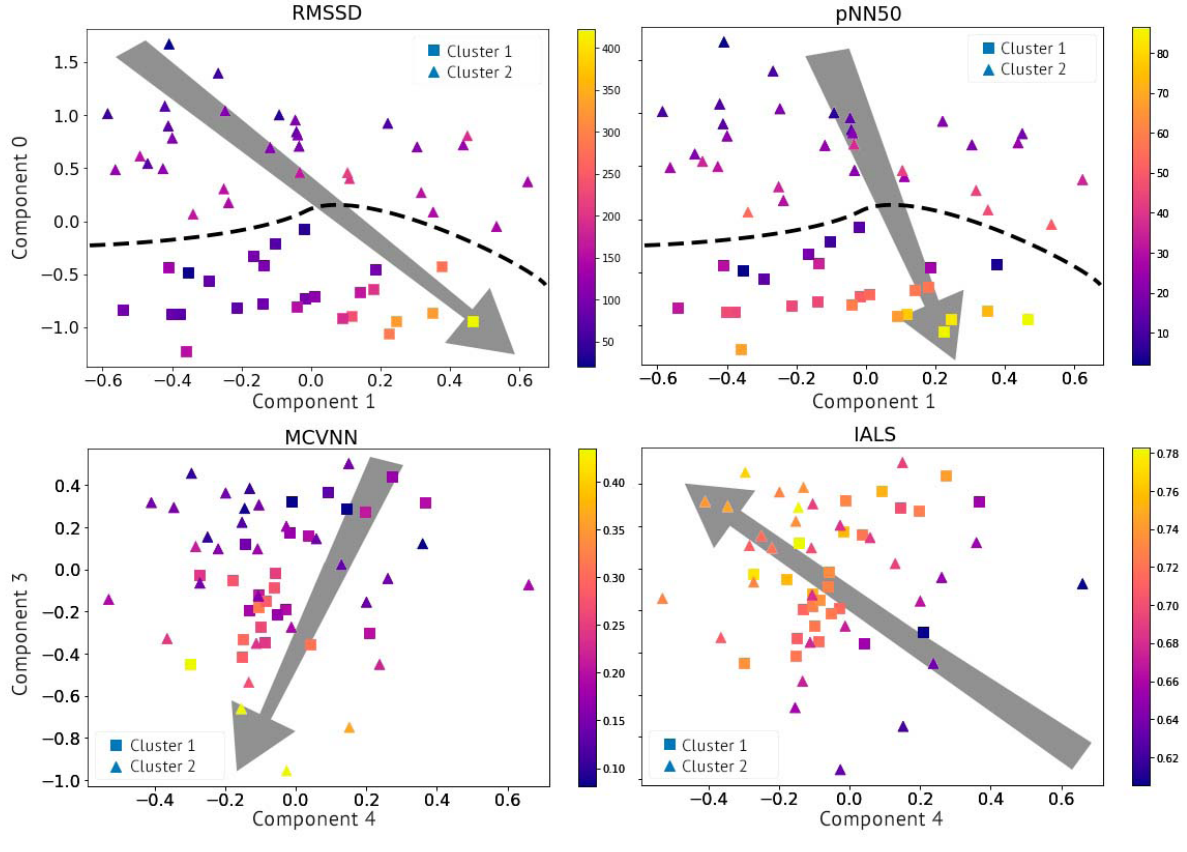

Fig. 4. Visualization of data after removing the outliers in two projections. The images in the upper panels are based on the principal components 0 and 1, whereas those below are based on components 3 and 4. Data related to different phenotypes are indicated by rectangles and triangles, respectively. The dotted line in the top panel shows a clear separation of clusters in space. The arrows indicate the directions of the gradients along which the increased attributes are noted. The top and bottom plots have pairwise common Y axes.

Table 1. Values of mean and standard deviation of heart rate variability indices for the revealed phenotypes of paroxysmal atrial fibrillation

Parameter	Phenotype 1	Phenotype 2	Mann–Whitney *U*-test (*p*-value)	Student's *t*-test (*p*-value)
AFIB time, min	399.1±378.4	1202.3±293.8	0.00000	0.00000
pNN50	25.3±13.5	71.9±9.3	0.00000	0.00000
pNN20	46.4±17	87.4±5.6	0.00000	0.00000
ApEn	0.9±0.3	2±0.2	0.00000	0.00000
SampEn	0.4±0.2	1.7±0.3	0.00000	0.00000
CVSD	0.1±0.1	0.3±0.1	0.00000	0.00000
VHF	0.00002±0.00002	0.00017±0.00019	0.00000	0.00011
SD1/SD2	0.3±0.1	0.7±0.1	0.00000	0.00000
CSI	3.4±1.4	1.5±0.4	0.00000	0.00000
HF	0.0001±0.00009	0.00068±0.0006	0.00000	0.00000
LnHF	–9.5±0.9	–7.6±0.8	0.00000	0.00000
HFn	0.3±0.1	0.5±0	0.00000	0.00000
RMSSD	114.6±48.9	219.9±77.6	0.00000	0.00000
SDSD	114.6±48.9	219.9±77.6	0.00000	0.00000
SD1	81±34.6	155.5±54.9	0.00000	0.00000
SD1a	55.9±24.2	109.1±38.6	0.00000	0.00000
SD1d	58.6±24.8	110.8±39.1	0.00000	0.00000
LF	0.00008±0.00007	0.00037±0.00028	0.00000	0.00000
CSI Modified	3103.2±1441.9	1454.3±583.2	0.00000	0.00000
PIP	0.7±0	0.7±0	0.00018	0.00033
PAS	0.3±0.1	0.3±0	0.00023	0.00014
MCVNN	0.2±0.1	0.2±0.1	0.00033	0.00921
LFn	0.2±0.1	0.3±0.1	0.00037	0.00379
C1d	0.5±0	0.5±0	0.00037	0.00040
C1a	0.5±0	0.5±0	0.00037	0.00040
PSS	0.9±0	0.9±0	0.00059	0.00352
S	64 099.3±38 559.1	123 348.3±81 939.3	0.00078	0.00072
CVI	5.4±0.3	5.7±0.3	0.00078	0.00039
CVNN	0.2±0.1	0.3±0.1	0.00191	0.00218
IALS	0.7±0	0.7±0	0.00382	0.00634
MedianNN	843.8±146.4	723.6±173.8	0.00505	0.00640
HTI	23±6.9	27±6.6	0.01688	0.03099
MeanNN	840.3±136.2	752.3±180.5	0.01976	0.04070
Cd	0.5±0	0.5±0	0.01976	0.01255
Ca	0.5±0	0.5±0	0.01976	0.01255
SI	49.9±0.1	50±0	0.02579	0.02388
AI	50.1±0.1	50±0	0.06917	0.04510

Note: 31 heart rate variability indicators have statistically significant differences ($p < 0.01$). Below the number 31, the significance exceeds the required level in one of the statistical tests.

the indices of the frequency characteristics of HRV from the analysis of the spectral power density of the chronogram (LnHF; $p < 0.0000001$), as well as by nonlinear characteristic indicators of the geometry of the Poincaré graph (SD1/SD; $p < 0.0000001$) [7]. The phenotype 2 is characterized by a great sympathetic influence in heart rate regulation, which is confirmed by higher sympathetic indices CSI and CSI Modified and lower indices of parasympathetic activation RMSSD and pNN50 [7].

Records that belong to phenotype 2 were characterized by a longer duration of registered AF paroxysms, which exceeded 4.5 h (AFIB Time indicator in Table 1).

Some patient data were excluded from our analysis. Three of the four methods for detecting outliers in the data have identified the records of 7 (11%) patients. All outlier detection methods identified 2 patients with significant differences in HRV parameters. Figure 2 presents the HRV characteristics in these patients that are located at a significant distance from the general point cloud.

A qualitative analysis of the records from 7 patients was performed. Unfortunately, the absence of signals from 12 standard leads hindered the unambiguous and reasonable diagnoses. However, the signals were visually analyzed, taking into account the mentions of abnormal rhythms in the data abstracts of these patients in the used database. The electrophysiological phenomena can be assumed, namely, sinus bradycardia and AF with prolonged pauses, Wolff–Parkinson–White syndrome, shortened delay in the atrioventricular junction, left bundle branch block, high respiratory rate or dyspnea, ectopic supraventricular tachycardia, extrasystole, electrode dislocation, large areas under T-waves that are caused possibly by outflow tract obstruction of the left ventricle, ventricular ectopia, and rigid ectopic rhythm with replacement complexes.

Discussion. HRV has been studied since the invention of electrocardiography by V. Einthoven. During this time, many HRV indices have been proposed. Some are aimed at identifying specific diseases, whereas others identified the ranges of norms in the population, and others have a statistically significant difference in the values of indices in the population, but no proposed explanation of the process physiology that determines the index.

The analyses of HRV characteristics in patients with paroxysmal AF identified five main groups of attributes, namely attributes that characterize the statistical HRV characteristics according to the chronogram, attributes that characterize the frequency of chronogram characteristics, indices of HRV fragmentation, signs of asymmetry in HRV, and signs of average HRV characteristics. The intergroup correlation of HRV characteristics is low for such groups, whereas the intragroup correlation is high (Fig. 1). In this case, any measured characteristics of the rhythm correlate weakly with the total AF time in the daily ECG recording.

The phenotyping of any disease characterizes large groups of patients. However, complex clinical cases and rarer arrhythmological types of the pathology were found, which not only complicate the data analysis but also significantly affect all HRV characteristics.

Our results excluded all such cases from consideration, and then all patients with paroxysmal AF can be characterized by only five HRV attributes (one attribute for each category). This finding is supported by the explained variance (0.11) when applying the principal component method, which reduces 52 characteristics to 5 (Fig. 2), as well as hierarchical clustering of the columns of the correlation matrix (Fig. 1). Concurrently, nonlinear HRV indices (SD1a, C1a, PIP, PAS, and IALS) provide new information about patient records and are not correlated with linear parasympathetic indices RMSSD or pNN50. Their significance in the analysis of AF requires further study.

Hierarchical clustering and dendrograms were also used to isolate the disease phenotypes [1]. Figure 3 presents a hierarchical clustering of HRV characteristics. The dendrogram presented repeats very closely a part of the dendrogram from work [1], which corresponds to the phenotype with low comorbidity. Comparison of the list of diseases of patients from the original work on the LTFADB dataset that was used [11] and patients with a low comorbidity phenotype from work [1] confirm the revealed similarity. Thus, our phenotyping based on HRV characteristics correlates with phenotyping based on clinical signs.

However, in addition to the patients studied in our work, patients with atherosclerotic-comorbid cluster, tachy-brady/device implantation cluster, and behavioral disorder cluster were found. The rhythm aspects in such patients remained beyond the scope of our analysis since they are not represented in the LTFADB database. The AF phenotypes proposed in [2–6] could not be directly compared with our results.

The identified AF phenotypes can be explained by parasympathetic and sympathetic HRV indices. Patients without organic heart disease, as a rule, are known to have a parasympathetic pattern of the onset of AF (nocturnal and postprandial arrhythmia), whereas a sympathetic pattern is more common in the presence of structural heart disease. However, several experimental studies on the developmen-

tal analysis of AF in models with heart failure have demonstrated the leading role of combined sympathovagal activation in the initiation of arrhythmia paroxysm compared with isolated sympathetic or parasympathetic influences [14].

Adrenergic stimulation has been demonstrated to lead to focal ectopic activity through increased automatism, as well as the implementation of early and delayed postdepolarizations, whereas vagal influences play a primary role in shortening the action potential of the atrial tissue. In some cases, cholinergic stimulation often becomes the major factor in the spontaneous onset of arrhythmia, whereas adrenergic stimulation can only act as an electrophysiological modulator that supports the development of cholinergic-mediated AF [15].

This study revealed an increase not only in heart rate indices but also in the total duration of registered AF paroxysms in the group of records that describe the predominance of vagotonic influences (cluster 2) on heart rate regulation. Taking into account the rather clear phenotyping of the paroxysmal form of AF according to the analysis of HRV parameters and the revealed predictive ability to predict the duration of AF, it seems promising to conduct a study that is aimed at finding the relationships between the electrophysiological and clinical characteristics of patients, which will more accurately determine the characteristics of the subgroup of patients with vagus-dependent heart rhythm disorders in the future.

Our work demonstrates that five HRV parameters out of five main groups of HRV parameters fully characterize the common forms of AF due to "inorganic" causes. Among patients with AF, the existence of two large electrophysiological phenotypes of the disease can be distinguished and statistically confirmed. The clusters revealed were believed to also be associated with sympathetic and parasympathetic forms of AF. In addition to the common linear parasympathetic indices, RMSSD and pNN50, indicators of asymmetry of heart rate SD1a and C1a, as well as indices of fragmentation of heart rate PIP, PAS, and IALS, can become promising metrics for HRV analysis.

CONCLUSIONS

1. The use of exploratory data analysis of daily monitoring of the electrocardiogram identified two electrophysiological phenotypes of paroxysmal AF, namely the profile 1 is a vagotonic profile with a significant increased linear parasympathetic indices with a duration of >4.5 h of AF paroxysm and the profile 2 with increased values of sympathetic indices, low values of parasympathetic indices, and paroxysms of up to 4.5 h long.

2. The obtained data indicate the potential of nonlinear analysis in the study of rhythm variability and demonstrate the feasibility of further incorporation of nonlinear indices for solving the problem of phenotyping heart rhythm disorders.

Author contributions. N.S.M. and K.S.U. performed mathematical research; Ya.G.B. was responsible for clinical and electrophysiological analysis of the work results; M.V.A. and O.E.S. were the work supervisors.
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