

Research Article

Importance of Heart Rate Variability in Patients with Atrial Fibrillation

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Keywords

• Atrial fibrillation; Heart rate variability; Holter monitoring, Prognostic value

Abstract

The autonomic nervous system plays an important role in the development of atrial fibrillation (AF). One of the most promising markers of autonomic activity is heart rate variability (HRV).

Aim: The aim of the study was to evaluate HRV in patients with nonrheumatic atrial fibrillation.

Patients and Methods: The study population consisted of 222 patients: group I - 75 pts with previous paroxysmal or persistent non rheumatic AF without antiarrhythmics drugs; group II - 71 pts with non-AF arrhythmias; group III - 76 healthy controls. A 24-hour measurement of HRV was carried out with Holter monitoring. The mean of the following time domain parameters were analyzed: R-R, SDNN (standard deviation of all consecutive sizes (NN) during the total ECG record), SDANN (standard deviation of all consecutive intervals, which are obtained by dividing the entire record in five-minute segments and calculating their means), SDN Ninx (the mean standard deviation of NN intervals in successive 5-minute periods), pNN50 (the proportion between adjacent NN intervals differing by more than 50 ms the percentage of the estimated total number of NN intervals), and rMSSD (square root of successive NN interval differences). Continuous variables are presented as mean \pm standard deviation. Student's t-test, Pearson Chi-square, and Mann-Whitney tests were applied where appropriate. P-value of < 0.05 was considered significant. The HRV prognostic value for AF was evaluated by using ROC curves.

Results: According to our data, HRV was significantly lower in the group I compared with the groups II and III ($p < 0.05$): low HRV ($rMSSD < 30$ ms) had 46 patients (pts) (61.3%) in the group I, 21 pts (29.6%) in the group II and 2 pts (2.6%) in the group III. Moderate HRV ($30 \leq rMSSD < 45$ ms) had 27 pts (36.0%) in the group I, 25 pts (35.2%) in the group II and 42 pts (55.2%) in the group III. High HRV ($rMSSD \geq 45$ ms) had 2 pts (2.6%) in the group I, 25 pts (35.2%) in the group II, and 32 pts (42.2%) in the group III. The ROC analysis of HRV role in AF prediction showed high AUC of 0.886 with sensitivity 90% and specificity 87% (cut-off 31.26 ms, $p < 0.001$). HRV was significantly higher in patients with beta-blockers than without ($p < 0.005$). Average heart rate was lower in the group I when beta-blockers were used ($p < 0.05$): the group I - 59.8 ± 5.7 bpm, the group II - 74.4 ± 10.5 bpm, and the group III - 72.7 ± 6.2 bpm.

Conclusion: Patients with atrial fibrillation had a reduced HRV indicating a decreased vagal input in the heart rate regulation. HRV may be used as an important marker for the development of recurrent AF and may be used to optimize treatment. Beta-blockers had an effect on HR reduction and HRV increase in our study patients.

ABBREVIATIONS

AF: Atrial Fibrillation; ANS: Autonomous Nervous System; HRV: Heart Rate Variability; HR: Heart Rate; BB: Beta-Blockers; NN: Consecutive Sizes; AUC: Area Under The ROC Curve; SDNN: Standard Deviation Of All Consecutive Sizes During The Total ECG Record; SDANN: Standard Deviation Of All Consecutive Intervals, Which Are Obtained By Dividing The Entire Record In Five-Minute Segments And Calculating Their Means; Sdnninx: The Mean Standard Deviation Of NN Intervals In Successive 5-Minute Periods; Pnn50: The Proportion Between Adjacent NN Intervals Differing By More Than 50 Ms The Percentage Of The Estimated Total Number Of NN Intervals; Rmssd: Square Root Of Successive NN Interval Differences

INTRODUCTION

Atrial fibrillation (AF) is one of the most common arrhythmias

in clinical practice that requires continuous medical treatment. Currently, AF affects about one percent of the European Union population. It is predicted that AF will have increased two - three times by the next two or three decades [1]. AF development is associated with many conditions and risk factors: cardiovascular and underlying pathology, atrial electrophysiological properties and structural changes. Since AF can be induced by the autonomous nervous system (ANS) imbalance, which is involved in the development of arrhythmias, it requires an appropriate treatment.

Studies over the last two decades have shown that ANS imbalance may cause arrhythmic effects. These effects are often caused by the parasympathetic nervous system in healthy tissue and by the sympathetic nervous system in damaged tissue [2]. Heart rate variability (HRV) reflects the best ANS influence on heart rate [3-5]. HRV is the heart rate (HR) that changes

over time against the average HR, and is expressed as time and spectrum analytical methods. It reflects the parasympathetic and sympathetic nervous system balance. It is believed that an increase of the parasympathetic nervous system tone increases HRV, and an increase of the sympathetic nervous system tone reduces HRV [2-7]. In sinus rhythm high HRV shows a good cardiovascular adaptive characteristics operating of various endogenous and exogenous factors. Meanwhile, low-HRV indicates impaired cardiac function and inadequate ANS activities [8,9]. In clinical practice, time parameters are the most commonly used in the measurement of HRV. Time parameters are calculated according to the rhythm of heart rate at any point of time and are evaluated of QRS complexes in consecutive RR interval lengths and the differences between them [3]. The gold standard for HRV assessment is a 24-hour analysis of HRV that has been recorded with a Holter monitor.

OUR AIM

was to evaluate HRV in patients with nonrheumatic repetitive AF, and to confirm or refute the claim that the ANS imbalance may be a prognostic value of AF recurrence development; the outcomes obtained may lead to a selection of more effective antiarrhythmic drugs for treatment.

MATERIALS AND METHODS

The study investigated 222 patients who were treated in Hospital of Lithuanian University of Health Sciences Kaunas Clinics, Cardiology Clinic in 2010-2013. All subjects were divided into three groups. Group I (75 patients, 33.8% of subjects) consisted of subjects with non rheumatic AF history and the sinus rhythm was registered during study. They did not use Class I and III antiarrhythmic drugs. Patients of this group were divided into two subgroups, according to beta-blockers (BB) use: the first subgroup of subjects (27 patients) was treated with BB, the second subgroup - (48 patients) did not use BB. Group II (71 patients, 32% of all subjects) included subjects who apart from AF, had a variety of arrhythmias (Supraventricular paroxysmal tachycardia, extra systoles) recorded. These subjects did not take any antiarrhythmic drugs. Group III was a control group (76 subjects, 34.2% of subjects) comprising healthy subjects who showed no rhythm disturbances and who did not use any drugs. These people did not have any cardiovascular diseases and were selected randomly. A 24- hour assessment with Schiller Holter monitor, which gives time settings for HRV analysis, was used for all subjects. Subjects with AF episodes during Holter monitoring were not analyzed. In healthy subjects group (group III) the data without any rhythm disturbances were used. The survey data were analyzed by the MT-200 Holter ECG program. The following parameters were evaluated and analyzed: the minimum, average and maximum HR and HRV time parameters (time domain): NN - consistently passing RR intervals during all ECG recording; SDNN - standard deviation of all consecutive sizes (NN) during the total ECG record; SDANN - standard deviation of all consecutive intervals, which are obtained by dividing the entire record in five-minute segments and calculating their means; rMSSD - square root of successive NN interval differences, SDANN index - the mean standard deviation of NN intervals in successive 5-minute periods, pNN50 - the proportion between adjacent NN intervals

differing by more than 50 ms the percentage of the estimated total number of NN intervals [4,5].

STATISTICAL ANALYSIS

IBM SPSS 22.0 program was used for statistical analysis. Quantitative traits of data were expressed as mean and standard deviation. Student's t-test was used to compare the average age differences. The variables of heart rate variability (rMMSD, SDNN, SDANN, pNN50, NN50) were not distributed according to Gause. Therefore, for these nonparametric variables the chi-square (χ^2) and the Mann-Whitney U test were used. The Mann-Whitney test was used to compare HRV parameters between groups, because two independent quantitative samples were analyzed. Distribution of HRV signs (medium, low, high HRV) in groups were evaluated according to the chi-square. This test was chosen because differences were compared in the frequency of occurrence of categorized quantitative traits data (rMMSD) between groups (nominal variables). The Spearman correlation coefficient was applied for two-sample non-parametric correlation. Differences were considered as statistically significant when $p < 0.05$.

The HRV prognostic value for AF was evaluated by using ROC curves. A subject was assessed as positive or negative according to whether the parameter value was greater than a given cut-off value, less, or equal. Associated with any cut-off value was the probability of a true positive (sensitivity) and a true negative (specificity). Commonly used index of accuracy is the area under the ROC curve (AUC), values close to 1.0 indicating high diagnostic accuracy. To evaluate inter-observer variability two specialists blinded to previously obtained data performed the same measurements. Intra-observer and inter-observer variability values were calculated as the absolute difference between the corresponding two measurements as a percent of the mean.

RESULTS

Clinical characteristics of patients

Out of 222 subjects, 105 men (47.3% of subjects) and 117 women (52.7% of subjects) were explored using Holter ECG data. The age ranged from 18 to 87 years, and distribution by age was as follows: the group I - 32 men, 43 women, mean age 61.5 ± 13.0 years; the group II - 48 men, 31 women, mean age 56.9 ± 18.2 years; the group III - 33 men and 43 women, mean age 56.5 ± 16.5 . There were no significant differences by sex and age between groups ($p > 0.05$).

Holter ECG data

Group I HRV parameters (SDNN, SDANN, rMMSD, SDNNind, pNN50) were significantly lower ($p < 0.05$) compared with respective parameters in the groups II and III (Table 1). The analysis of subgroups showed that HRV in patients with BB was significantly higher than in patients without BB ($p < 0.005$) (Table 2). Assessing the overall HRV under rMMSD Figures (1-3), we found that low HRV dominated in the group I (46/75 patients, 61.3%), the average HRV - in 36% (27/75 patients), but only 2.6% of cases (2/75 patients) were presented with increased HRV. In the group III moderate HRV dominated (55.2%, 42/76 patients), 42.2% of cases (32/76 patients) were with increased HRV, and

Table 1: The distribution of HRV time parameters values between the groups.

Groups	Time parameters				
	SDNN (ms)	SDANN (ms)	rMSSD (ms)	SDNNinx (ms)	pNN50 (%)
I	111,43 ± 47,121	97,00 ± 43,78	29,44 ± 7,458	41,88 ± 18,302	5,267 ± 3,473
II	133,03 ± 42,625	112,17 ± 39,557	45,92±27,897	65,79 ± 23,887	11,265 ± 8,93
III	134,18 ± 38,014	110,53 ± 36,179	47,82±13,501	68,63±16,490	15,208 ± 8,26

Table 2: Patients with a history of AF (Group I) HRV time settings according to taking of the beta blockers.

Subgroup	SDNN (ms)	SDANN (ms)	SDNNinx (ms)	rMSSD (ms)	pNN50 (%)
Without BB	99,86 ± 51,39	86,35 ± 48,67	38 ± 16,903	27,39 ± 5,167	5,139 ± 2,91
With BB	132,7 ± 26,88	116,3 ± 21,93	49,63 ± 18,68	33,19 ± 9,303	5,57 ± 4,221

Abbreviations: BB: Beta Blockers

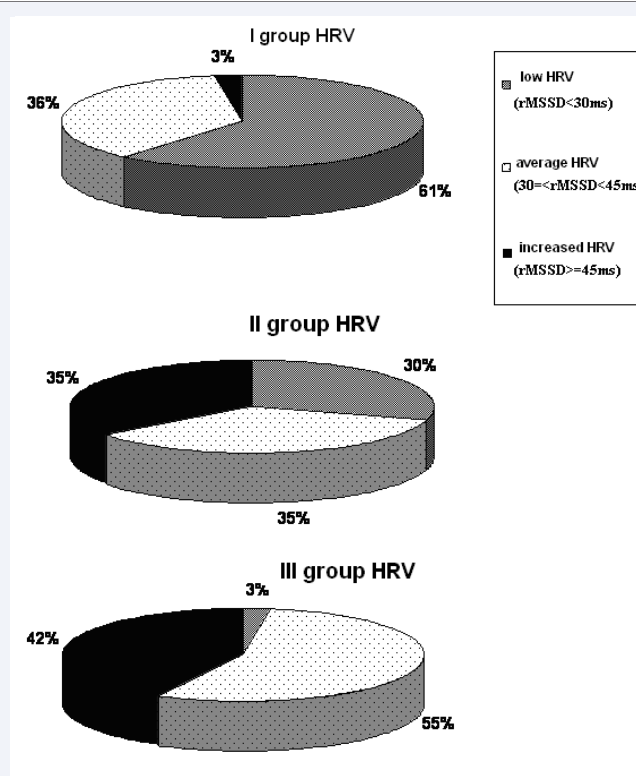


Figure 1 Low, medium and increased HRV distribution in groups.

only two patients (2.6%) had low HRV. Among the subjects in the group II, the general distribution of HRV was consistent: low HRV in 29.6% of patients (21/71 patients), moderate HRV -in 35.2% (25/71 patients), increased HRV- in 35.2% (25/71 patients).

The average minimum HR was in the group I (59.8 ± 5.7 beats / min, $p < 0.05$) comparing to the group II (74.4 ± 10.5 beats / min) and the group III (72.7 ± 6.2 beats / min). For all subjects the minimum and maximum HR was correlated with HRV according to all time parameters ($p < 0.05$), while the average HR correlated with certain values of HRV (SDNNinx, rMSSD). However, the correlation between minimum HR and HRV was stronger than the maximum HR and HRV. The higher minimum HR was observed, the lower HRV parameter values were received (Table 3, Figures 4-6).

ROC analysis of AF prediction revealed that HRV (evaluating rMSSD parameter) had high AUC of 0.886 with sensitivity 90%, specificity 87% (cut-off 31.26 ms, $p < 0.001$) Figure (5). Interobserver and intraobserver agreement for evaluation of rMSSD parameter was 98% and 97%, respectively, for SDNN - 97% and 98%, for SDANN - 99% and 98%, for SDNNinx - 99% and 99%, for pNN50 - 97% and 98%.

DISCUSSION

Despite an easy way to use Holter monitor, in clinical practice HRV assessment and analysis in predicting AF still have not often used. Therefore, not suprisingly why more and more studies (in Italy, Germany, Lithuania) are analyzing HRV changes in patients with atrial fibrillation [10-12]. Studies have shown

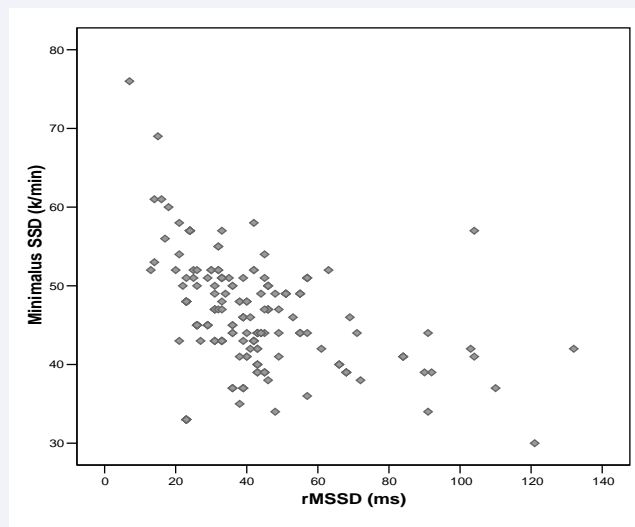


Figure 2 Coherency between minimum HR and rMSSD.

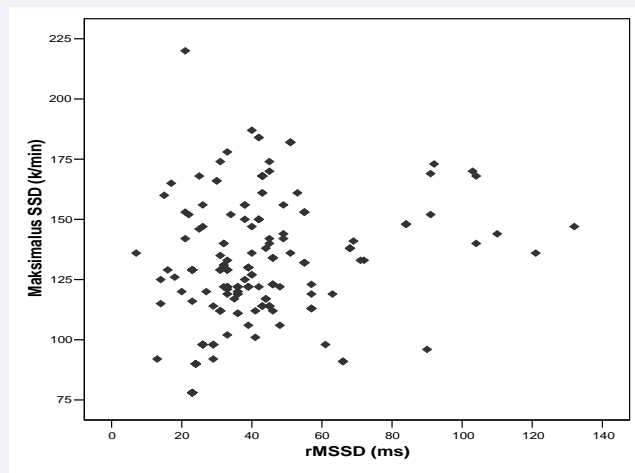


Figure 3 Coherency between maximum HR and rMSSD.

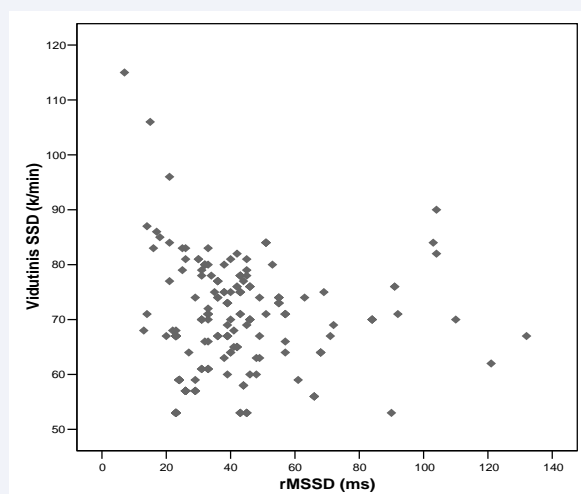


Figure 4 Coherency between average HR and rMSSD.

Table 3: Patients the minimum, average and maximum HR correlation with the HRV time parameters.

Heart rate	SDNN (ms)		SDANN (ms)		SDNNinx (ms)		rMSSD (ms)		pNN50 (%)	
	KK	p	KK	p	KK	p	KK	p	KK	p
Minimum	-0,55	0,00	-0,58	0,00	-0,31	0,00	-0,33	0,00	-0,32	0,00
Average	-0,008	0,9	-0,08	0,2	0,24	0,00	0,15	0,03	0,13	0,06
Maximum	0,5	0,00	0,39	0,00	0,59	0,00	0,37	0,00	0,47	0,00

Abbreviations: KK: Spearman correlation coefficient

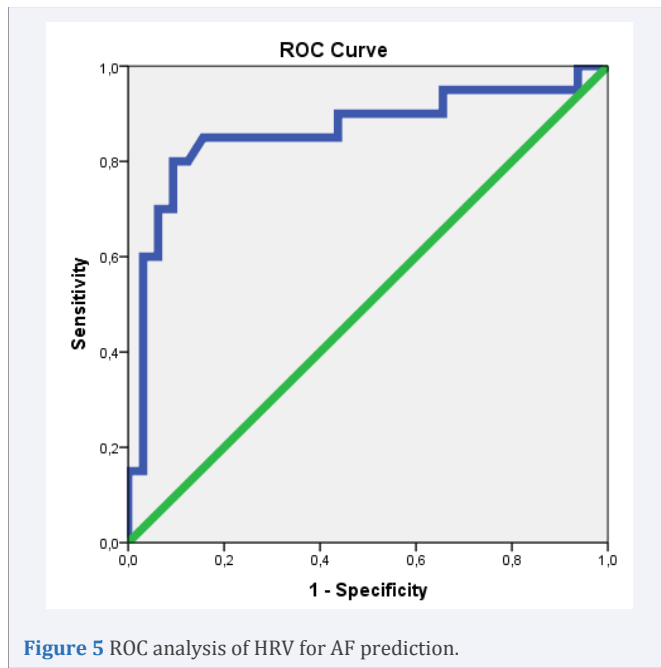


Figure 5 ROC analysis of HRV for AF prediction.

that very low and low-frequency HRV induced arrhythmias associated with sudden death compared with deaths due to other causes [13]. Reduction of HRV is associated with the influence of the parasympathetic nervous system (*vagus*) on HRV. The role of the sympathetic nervous system is still not fully understood. Therefore, this study was carried out to assess the HRV as a possible prognostic factor in nonrheumatic atrial fibrillation.

When AF is permanent, the HRV should be carefully assessed. HRV unconditional analysis is possible only if AF episodes are recorded in the background of sinus rhythm. It shows the limitations of this test for patients with ongoing persistent AF [14]. Our study examined HRV of patients who had recurrent AF episodes recorded in the past, and during all Holter monitoring sinus rhythm was recorded. This represented a more accurate assessment.

Our survey shows that patients with a history of AF record episodes HRV is significantly reduced under rMSSD (<30ms). The analysis of this parameter is intended for long RR intervals. It is sensitive to fluctuations of high frequencies. Therefore, rMSSD is used to evaluate the influence of ANS on HRV, especially parasympathetic effects during physical exertion, or ingestion of drugs [3,7]. Other time parameters (SDNN, SDANN, SDNNinx, pNN50) also show a downward trend of HRV. SDNN parameter is often used to measure vagal effect, which indicates parasympathetic effects. SDNN can be used only for short

sequences of RR intervals, since many other factors appear to have an influence on heart rate while increasing the length of the sequence [3,15]. In our study all the time parameters in HRV were assessed. It was found that the influence of the parasympathetic nervous system on HRV has been reduced in subjects who had episodes of AF in the past. This corresponds with the survey data presented by the Italian researchers in 2008, who found a decrease in HRV and HR in patients with persistent AF and registered with symptomatic heart failure [10].

As we know, it is the first study analyzing the HRV sensitivity and specificity for the AF prediction. Our study shows that HRV is sensitive and a specific marker for AF prediction and low HRV dominates in patients with recurring AF, while moderate or high HRV – in healthy group. In 1994, Coumel Ph. and others [2] drew attention to the fact that the damaged atrial fibers may be sensitive to increased adrenergic stimulation opposite to healthy. Vagal influence is dominated in normal atrium. When this influence reduces, sympathetic tone increases. The ANS imbalance can be a prognostic marker of AF recurrences. Ignorance of this imbalance can result in medical errors, therefore it explains why the treatment can be ineffective. Thus, in order to choose an effective anti-arrhythmic therapy is appropriate to identify HRV and evaluate the ANS influence on AF development.

The analysis of the effects of beta blockers on HR and HRV showed that patients who constantly received BB with repetitive AF had lower HR and higher HRV compared with those who did not use them. This trend is confirmed by the research from Moscow scientists. It showed that taking of atenolol, acebutamolol, tamolol and the reduction in HR over 10 beats per minute increased HRV [16]. Our study confirms the benefits of BB in HR decrease and HRV increase, also diminution of the development of AF with increased sympathetic nervous system interference.

Tuomo Nieminen and others [17] defined the correlation between the HR and HRV parameters in 2007. It was found that inverse non-linear mathematical interface links successive consecutive QRS complexes RR interval and HR. With an increase of HR, RR interval is shortening, in HRV all settings are decreasing too. Our study shows that patients with higher HR had the lower HRV. We found that the correlation between HRV time parameters and minimum HR was greater than the average and maximum HR. The U.S. and the Joint Scientific Study presented similar results [18, 19]. It is known that the increase in HR and decrease in HRV are independent risk factors of sudden cardiovascular death in previous myocardial infarction, heart failure or diabetic neuropathies [3,4]. Therefore, our analysis of the literature and survey data suggest that low HRV showing

increased arrhythmogenic effect may be seen as a prognostic marker of AF development.

CONCLUSION

Patients with atrial fibrillation had reduced heart rate variability indicating decreased vagal input in heart rate regulation. Beta-blockers played a role in reducing heart rate in our patients with atrial fibrillation and increasing heart rate variability. Similarly, it reduces the parasympathetic nervous system effect on atrial fibrillation development.

Heart rate variability by showing increased arrhythmogenic effect may be used as an important marker for the development of recurrent AF and may be used to optimize treatment. Ignorance of the autonomic nervous system imbalance can result in medical errors. It explains why AF treatment with antiarrhythmic drugs may be ineffective.

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