Article

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Data Analysis of Heart Rate Variability and Arrhythmia in Patients with Paroxysmal Atrial Fibrillation

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Background: Atrial fibrillation (AF) is the most common type of arrhythmia. Heart rate variability (HRV) may be associated with AF risk. The aim of this study was to test HRV indices and arrhythmias as predictors of paroxysmal AF based on 24-hour dynamic electrocardiogram recordings of patients.

Methods: A total of 199 patients with paroxysmal AF (AF group) and 204 elderly volunteers over 60 years old (Control group) who underwent a 24-hour dynamic electrocardiogram from August 2022 to March 2023 were included. Time-domain indices, frequency-domain indices, and arrhythmia data of the two groups were classified and measured. Binary logistic regression analysis was performed on variables with significant differences to identify independent risk factors. A nomogram prediction model was established, and the sum of individual scores of each variable was calculated.

Results: Gender, age, body mass index and low-density lipoprotein (LDL) did not differ significantly between AF and Control groups ($p > 0.05$), whereas significant group differences were found for smoking, hypertension, diabetes, and high-density lipoprotein (HDL) ($p < 0.05$). The standard deviation of all normal to normal (NN) R-R intervals (SDNN), standard deviation of 5-minute average NN intervals (SDANN), root mean square of successive NN interval differences (rMSSD), 50 ms from the preceding interval (pNN50), low-frequency/high-frequency (LF/HF), LF, premature atrial contractions (PACs), atrial tachycardia (AT), T-wave index, and ST-segment index differed significantly between the two groups. Logistic regression analysis identified rMSSD, PACs, and AT as independent predictors of AF. For each unit increase in rMSSD and PACs, the odds of developing AF increased by 1.0357 and 1.0005 times, respectively. For each unit increase in AT, the odds of developing AF decreased by 0.9976 times. The total score of the nomogram prediction model ranged from 0 to 110.

Conclusion: The autonomic nervous system (ANS) plays a pivotal role in the occurrence and development of AF. The individualized nomogram prediction model of AF occurrence contributes to the early identification of high-risk patients with AF.

Keywords: paroxysmal atrial fibrillation; Holter; heart rate variability; arrhythmia

Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, with incidence increasing with age, and in developed countries, the prevalence of AF is estimated to be 2–4% [1]. It is estimated that the prevalence of AF in the United States will increase from about 5.2 million in 2010 to 12.1 million in 2030 [2]. There is evidence that psychosocial (posttraumatic stress disorder) and lifestyle factors (smoking, alcohol, obesity, extreme sports) are important modulators of the development of AF [3,4]. Moreover, AF is primarily secondary to hypertension, ischemia, and/or structural heart disease [5], mainly characterized by atrial remodeling [6]. Autonomic nervous system (ANS) activity has been shown, experimentally (*in vivo*) and clinically, to trigger AF and induce atrial remodeling, highlighting the role of the atrial substrate in the initiation and maintenance of AF [7,8]. Currently, the clinical classification of AF is still based on its episode duration and manner of termination, rather than the severity of alteration of the atrial substrate.

Recent years have witnessed increasing attention on the correlation between heart rate variability (HRV) and AF, in the hope of developing a non-invasive method for the prediction of AF risk. HRV is an indirect and non-invasive marker reflecting the activity of the ANS, and HRV measures are obtained by measuring the differences between successive respiratory rate (R-R) intervals of sinus beats; these differences represent the balance between the activity of the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS) [9,10]. Evaluation of HRV mainly depends on time- and frequency-domain methods [11], and a low HRV may be associated with a higher AF risk [12]. The main mechanism causing HRV reduction involves abnormal signals from the pulmonary veins that stimulate sympathetic nerve fibers and cause parasympathetic withdrawal [13]. Thus, regulation of HRV might prevent AF in the general population [14]. Furthermore,

Table 1. Comparisons of clinical data between Control and AF groups.

Indicator	Control group (n = 204)	AF group (n = 199)	Z/χ^2/t	*p*
Gender			2.161	0.142
Male	103 (50.49%)	115 (57.79%)		
Female	101 (49.51%)	84 (42.21%)		
Age	70 (64, 76)	71 (65, 77)	–1.459	0.145
Smoking	54 (26.4%)	76 (38.2%)	6.332	0.012
Body Mass Index	23.9 ± 2.9	24.2 ± 3.1	–1.004	0.306
Hypertension	78 (38.2%)	124 (62.3%)	23.357	<0.001
Diabetes	17 (8.3%)	44 (22.2%)	14.885	<0.001
HDL	1.13 ± 0.36	1.01 ± 0.24	3.946	<0.001
LDL	2.42 ± 0.78	2.46 ± 0.84	–0.496	0.710

AF, atrial fibrillation; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2. Comparisons of time-domain indices, frequency-domain indices, and arrhythmia data between Control and AF groups.

Indicator	Control group (n = 204)	AF group (n = 199)	Z/χ^2	*p*
SDNN (ms)	103.5 (81, 120.5)	90 (67, 132)	–1.982	0.047
SDANN (ms)	90 (71.5, 108.5)	82 (57, 116)	–2.287	0.022
SDNN index (ms)	41 (33, 51.5)	43 (28, 60)	–0.560	0.576
rMSSD (ms)	23 (17, 32)	27 (19, 44)	–3.476	0.001
pNN50 (%)	2.425 (0.76, 6.685)	4.03 (1.24, 11.9)	–2.659	0.008
LF/HF	1.155 (0.745, 2.21)	0.91 (0.55, 1.49)	–3.277	0.001
LF (Hz)	185 (106.4, 312.4)	149.28 (50, 307)	–2.604	0.009
HF (Hz)	146 (85, 252.5)	142 (61, 279)	–0.879	0.379
PACs	56.5 (14, 300.5)	1569 (295, 5023)	–11.313	0.000
AT	1 (0, 5)	11 (3, 36)	–8.934	0.000
PVCs	4 (0, 155)	10 (0, 133)	–1.197	0.231
T-wave index (mV)	0.21 (0.1, 0.3)	0.2 (0.05, 0.25)	–2.126	0.033
ST-segment index (mV)	0 (0, 0)	0 (–0.05, 0)	–2.331	0.020

SDNN, standard deviation of all normal to normal (NN) R-R intervals; SDANN, standard deviation of 5-minute average NN intervals; rMSSD, root mean square of successive NN interval differences; pNN50, 50 ms from the preceding interval; LF/HF, low-frequency/high-frequency; PACs, premature atrial contractions; AT, atrial tachycardia; PVCs, premature ventricular contractions.

using simple classification methods and iterative selection of easily available HRV and clinical feature sets, the recurrence of AF after ablation can be predicted to varying degrees [15]. Although HRV can reflect the influence of the ANS on heart rate (HR) [16], the effect of HR on the prognosis of AF patients has been inconsistent among existing studies. A previous study showed that HR rate was associated with adverse outcomes in persistent AF, but not in patients with paroxysmal AF [17].

Therefore, this study was designed to test HRV indices and arrhythmias as predictors of paroxysmal AF.

Materials and Methods

Participants

The study subjects included 199 patients with paroxysmal AF (AF group) and 204 elderly volunteers over 60 years old (Control group). All subjects underwent 24-hour dynamic electrocardiogram examination in the People's Hospital of Shaoxing from August 2022 to March 2023. Inclusion criteria were as follows: (1) patients with paroxysmal AF detected by 24-hour dynamic electrocardiogram examination, with AF duration <24 hours; (2) patients and their families signed written informed consent and voluntarily participated in this study. Exclusion criteria were: (1) patients with continuous AF detected by 24-hour dynamic electrocardiogram examination; (2) patients with pacemaker implantation surgery; (3) patients with second-degree or higher atrioventricular block or second-degree or higher sinoatrial block; (4) patients that took drugs affecting the ANS. This study was approved by the ethics committee of Shaoxing People's Hospital (No. IEC-K-AF-016-1.2), and the experiment complied with the Helsinki Declaration.

Research Design

The 24-hour data of enrolled patients were recorded using the CT-086S series dynamic electrocardiogram machine (BENEWARE, Hangzhou, China), and then imported into the Baihui electrocardiogram data analysis system. Paroxysmal AF events in the AF group were marked on the

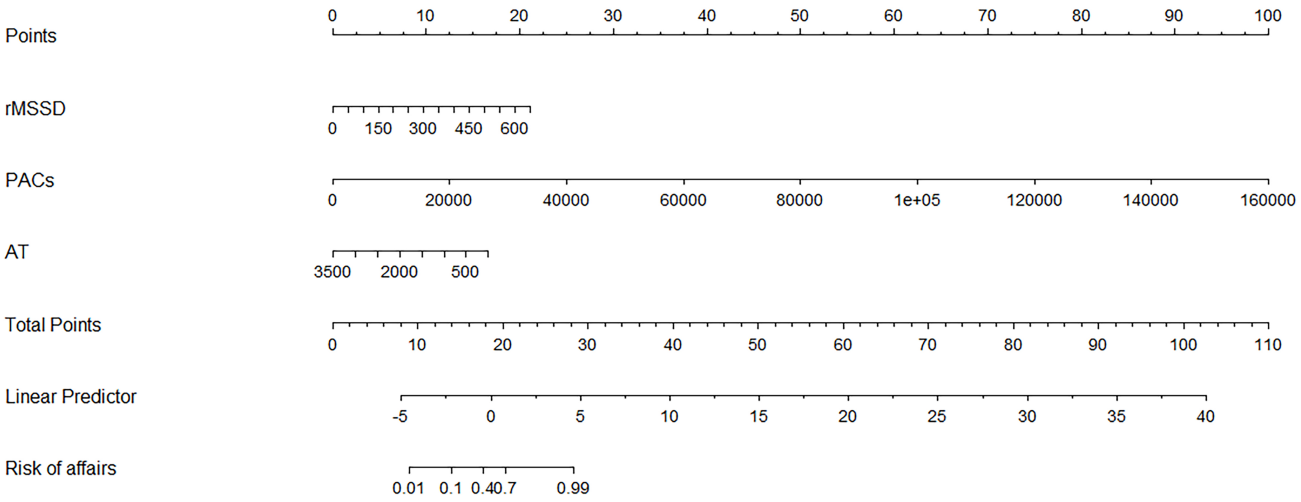

Fig. 1. Nomogram predictive model of AF risk.

recording (the heart rate data during AF events were not included in the HRV analysis). The time-domain indices, frequency-domain indices, and arrhythmia data were cataloged in the two groups. Time-domain indices included the standard deviation of all normal to normal (NN) R-R intervals (SDNN), the standard deviation of 5-minute average NN intervals (SDANN), the mean of the standard deviations of all NN intervals for all 5-minute segments in 24 hours (SDNN index), and root mean square of successive NN interval differences (rMSSD), and were calculated in the two groups over the entire recording. The percentage of NN intervals differing by more than 50 ms from the preceding interval (pNN50) was also calculated. The frequency-domain indices consisted of low-frequency (LF), high-frequency (HF), and the LF/HF ratio. Arrhythmia data included premature atrial contractions (PACs), premature ventricular contractions (PVCs), atrial tachycardia (AT), T-wave, and ST-segment indices.

Statistical Analysis

Data analyses were conducted with SPSS 25.0 (IBM Corp., Armonk, NY, USA). Non-normally distributed data were expressed as an interquartile range [M(P25, P75)], and a two-group comparison was performed using the Mann–Whitney U test and the chi-square test. Count data were described as n [%] [18]. A p-value < 0.05 was determined to be statistically significant. Variables with significant differences between groups were included in a binary logistic regression analysis to explore independent influencing factors, with $\alpha = 0.05$, and a nomogram prediction model was established using a DynNom 5.0.2 software (R package, https://cran.r-project.org/web/packages/DynNom/index.html).

Results

Comparison of Basic Data between the Two Groups

As shown in Table 1, there were no significant differences in gender, age, body mass index, or low-density lipoprotein (LDL) between the Control and AF groups ($p > 0.05$). In contrast, smoking, hypertension, diabetes, and high-density lipoprotein (HDL) differed significantly ($p < 0.05$) between the Control group and the AF group.

Comparison of Time-Domain Indices, Frequency-Domain Indices, and Arrhythmia Data between the Two Groups

As shown in Table 2, there were significant differences between the Control and AF groups in terms of SDNN, SDANN, rMSSD, pNN50, LF/HF, LF, PACs, AT, T-wave index, and ST-segment index ($p < 0.05$), and non-significant differences in SDNN index, HF and premature ventricular contractions (PVCs) ($p > 0.05$).

Binary Logistic Regression Analysis

Binary logistic regression was conducted with SDNN, SDANN, rMSSD, pNN50, LF/HF, LF, PACs, AT, T-wave index and ST-segment index as independent variables, and the occurrence of AF as dependent variable. The results indicated that rMSSD, PACs, and AT were significant predictors of AF (Table 3, $p < 0.05$). For every unit increase in rMSSD and PACs, the odds of AF occurrence were increased by a factor of 1.0357 and 1.0005, respectively. For every unit increase in AT, the odds of AF occurrence were decreased by a factor of 0.9976.

Establishment of a Nomogram Prediction Model

Based on the results of the logistic regression analysis, a nomogram prediction model was established (Fig. 1), the total score for which ranged from 0 to 110, and the sum of the individual item scores for each variable was calculated.

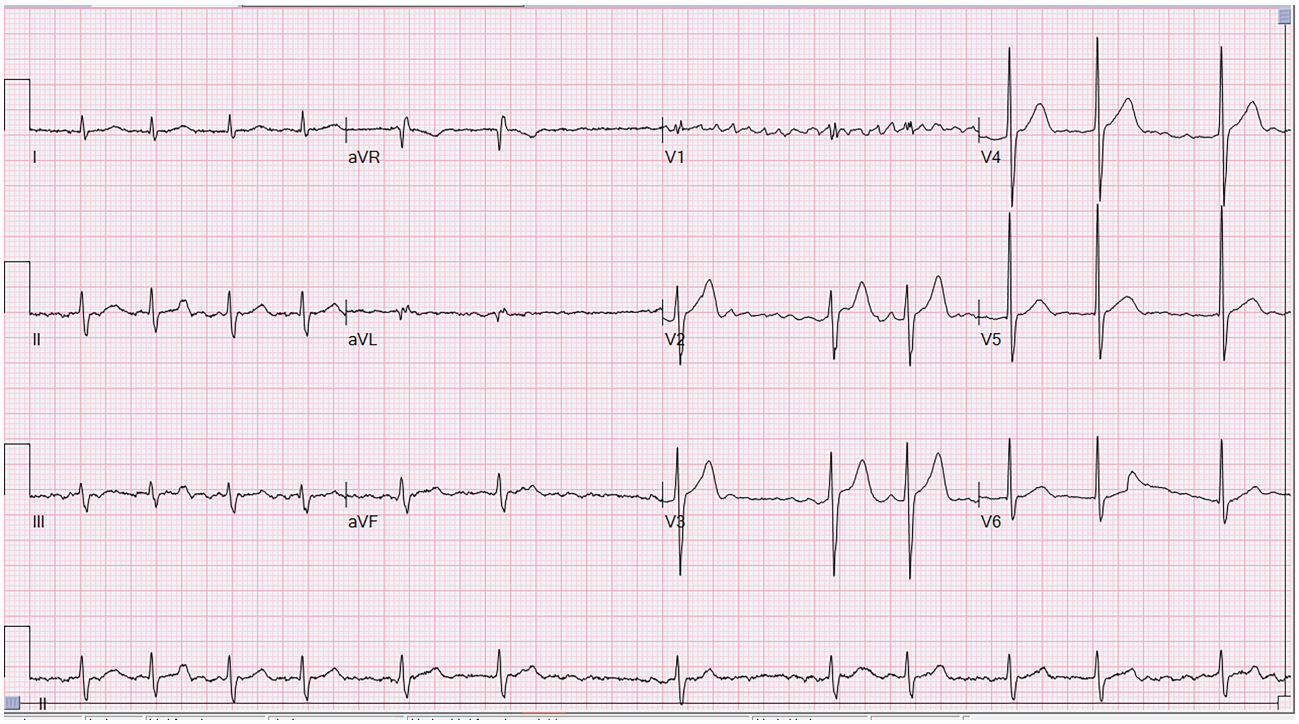

Fig. 2. Representative 24-hour Holter recording of an AF patient.

Table 3. Results of the binary logistic regression analysis.

Variable	B	Standard error	Wald	Degrees of freedom	*p*	OR	OR 95% CI	
							Lower limit	Upper limit
SDNN (ms)	–0.041	0.022	3.636	1	0.057	0.9595	0.920	1.001
SDANN (ms)	0.029	0.020	2.006	1	0.157	1.0289	0.989	1.070
rMSSD (ms)	0.035	0.012	8.156	1	0.004	1.0357	1.011	1.061
pNN50 (%)	0.001	0.025	0.002	1	0.968	1.0010	0.954	1.051
LF/HF	–0.074	0.076	0.947	1	0.330	0.9283	0.799	1.078
LF (Hz)	0.000	0.001	0.329	1	0.566	1.0005	0.999	1.002
PACs	0.000	0.000	28.203	1	0.000	1.0005	1.000	1.001
AT	–0.002	0.001	10.344	1	0.001	0.9976	0.996	0.999
T-wave index (mV)	0.205	0.820	0.063	1	0.802	1.2278	0.246	6.120
ST-segment index (mV)	–6.219	5.988	1.079	1	0.299	0.0020	0.000	249.001
Constant	–0.147	0.461	0.102	1	0.750	0.8631		

B, regression coefficient; OR, odds ratio; CI, confidence interval.

A higher total score represents a greater risk of AF occurrence. As an example, we selected a patient in whom the rMSSD/ms was 39, with a score of 1.26, the PACs was 70, with a score of 0.04, the AT was 2, with a score of 16.63, and the total point score was 17.93. Based on the results showing about 60% risk for AF, the patient belonged to the middle- and high-risk group. Also, the electrocardiogram indicated a clear AF signal (Fig. 2).

Discussion

Current evidence suggests that the high risk for the occurrence and progression of AF is associated with many factors, including hypertension, obesity, and obstructive sleep apnea syndrome. Mechanically, most of these high-risk factors are implicated in the abnormal activity of the cardiac ANS, and ANS activation with the concomitant symptom of AF can further aggravate AF [8]. The role of the central ANS in the onset of AF is based on dynamic electrocardiogram recordings, which help distinguish between vagal AF and adrenergic AF [9,19]. In recent years, it has been documented that there is an increase in sympathetic nerve tone or a decrease in vagal nerve tone before the onset of paroxysmal AF [20]. Reportedly, the sympathetic nerves and the vagus nerve can individually or cooperatively regulate atrial electrical activity and induce AF [21].

HRV is a non-invasive method for assessing ANS activity based on changes in heart rate [22]. HRV reflects the

differences between successive sinus heartbeats, as measured by the RR interval, and the physiological variability in heart rate is determined using time and frequency analysis methods [23]. SDNN and SDANN are the primary markers of sympathetic nervous system function and are closely related to LF [24]. Alternatively, rMSSD and pNN50 can be measured to assess parasympathetic nervous system function, and these have an intimate association with HF [25]. The LF/HF ratio is an important indicator of the balance between the sympathetic and parasympathetic nervous systems [26].

In this study, the AF group had significantly lower SDNN, SDANN, T-wave index, and ST-segment index relative to the Control group, consistent with increased sympathetic nervous system activity in patients with paroxysmal AF. In addition, rMSSD, pNN50, PACs, and AT were higher in the AF group than in the Control group, indicating increased parasympathetic nerve activity. The LF/HF ratio and LF in the AF group also showed a decreasing trend compared to the Control group, suggesting a weakened cardiac autonomic regulatory function, enhanced sympathetic nerve activity, impaired parasympathetic nerve function, and an increased risk of malignant arrhythmias.

In this study, binary logistic regression was performed, with the occurrence of AF as the dependent variable, and SDNN, SDANN, rMSSD, pNN50, LF/HF, LF, PACs, AT, T-wave index, and ST-segment index as independent variables. The results showed that both rMSSD, PACs, and AT were significant predictors of AF. Each unit increase in rMSSD and PACs was associated with the incidence rate elevated by a factor of 1.0357 and 1.0005, respectively. For every unit increase in AT, the odds of AF occurrence were decreased by a factor of 0.9976. These findings confirmed that impaired autonomic regulation and heart rate are critical risk factors for patients with AF.

However, in contrast to the Control group, the AF group presented decreased HF, possibly due to their increased number of atrial premature beats and ventricular premature beats. The compensatory interval after premature beats, and the variation in RR interval between the compensatory interval and normal sinus beats, contribute to increased rMSSD and pNN50. A previous study demonstrated that people with high ventricular premature beat burden ($\geq$1000 beats in 24 hours) are prone to AF [27] and that individuals under 60 years old with $\geq$1000 premature ventricular contractions per day have a higher risk of new-onset AF than those $\geq$60 years old. However, the sample size of the AF group was small, which may have contributed to insignificant results for HRV predictors of PVCs; thus, additional studies with larger samples are needed for verification. Furthermore, the relationship between HRV parameters and the occurrence of AF, and the recurrence after ablation, were not discussed in that study. Owing to inconsistent conclusions in various studies, more evidence is needed to support the correlation between HRV and AF.

In addition, our results also revealed that smoking, hypertension, diabetes, and HDL, which have been confirmed to increase susceptibility to AF through indirect or direct mechanisms [28–31], differed significantly between the Control group and the AF group. However, the failure to link these factors to HRV or arrhythmia is a deficiency of this study, thus necessitating additional studies to verify the relationship among these influencing factors.

Conclusion

We established an individualized nomogram model to predict AF occurrence, which was beneficial to the early identification of high-risk patients with AF. 24-hour dynamic electrocardiogram examination has the advantages of being simple, non-invasive, and inexpensive, and can be used to assess cardiac autonomic function. The ANS plays a pivotal role in the occurrence and development of AF. Evaluating changes in HRV and arrhythmia data can contribute to better management of patients with paroxysmal AF.

Availability of Data and Materials

The analyzed data sets generated during the study are available from the corresponding author upon reasonable request.

Author Contributions

HJ and LD designed the research study; BL and JZ collected and analyzed the data. All authors have been involved in drafting the manuscript and all authors have been involved in revising it critically for important intellectual content. All authors have given final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Patients and their families signed written informed consent and voluntarily participated in this study. This study was approved by the ethics committee of Shaoxing People's Hospital (No. IEC-K-AF-016-1.2), and the experiment complied with the Helsinki Declaration.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

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