

## The relationship of approximate entropy of the heart rate with the structural and functional atrial remodeling, as well as with clinical course of paroxysmal and persistent atrial fibrillation

Zależność między entropią aproksymacji rytmu serca a strukturalną i funkcjonalną przebudową przedsionków oraz przebiegiem klinicznym napadowego i przetrwałego migotania przedsionków

Viktor A. Snezhitskiy<sup>1</sup>, Ekaterina S. Yatskevich<sup>1</sup>, Tamara Sergeevna Dolgoshej<sup>2</sup>,  
Alexandr Rubinskiy<sup>2</sup>, Galina A. Madekina<sup>2</sup>

<sup>1</sup>The first Department of Internal Diseases, Grodno State Medical University, Grodno, Belarus

<sup>2</sup>Department of Arrhythmology, Grodno Regional Clinical Cardiology Centre, Grodno, Belarus



Ekaterina Yatskevich finished a postgraduate doctoral course in 2014 and has defended a PhD thesis in August 2015. Her research work was about the relationship of structural and functional remodeling of atria with the level of homocysteine, proline, glycine and aldosterone synthase C344/T gene polymorphism in patients with atrial fibrillation. Her supervisor was Professor Viktor Alexandrovich Snezhitskiy, MD, PhD, the Head of the Grodno State Medical University. At present, she works as a lecturer at the first Department of Internal Diseases of the Grodno State Medical University and as a doctor at the Department of Arrhythmology in Grodno Regional Clinical Cardiology Centre. Her professional activity combines teaching, clinical practice and the research. She is the author or co-author of 22 publications in national and international journals, including *Family Medicine & Primary Care Review* (Yatskevich K., Snezhitskiy V., Kurbat M., Stepuro T. The relationship between –C344/T aldosterone synthase

(CYP11B2) gene polymorphism, enzyme activity level and increased risk of nonvalvular atrial fibrillation. *Fam. Med. Prim. Care Rev.* 2015; 17 (2): 136–139). She participated in many medical conferences of young scientists, including these held in Bialystok and Gdansk. Her main hobby is social activity. In 2013 she worked in television, hosting her own medical show called 'Doctor is listening to you!', where teaching physicians from the medical university were invited to discuss in the form of dialogue various medical problems, so the audience could ask questions. She would like to continue these activities in the future.

### Abstract

**Introduction.** Atrial remodeling due to atrial fibrillation (AF) is characterized by electrical and structural changes of cardiomyocytes that are in response for arrhythmia self-perpetuation and resistance to sinus rhythm conversion. This project was designed to study nonlinear methods of heart rate variability (HRV) (such as approximate entropy of heart rate [ApEn]) that can best characterize LA structural and functional remodeling and its association with clinical course in patients with paroxysmal and persistent AF.

Address for correspondence: Ekaterina S. Yatskevich MD, PhD, 1<sup>st</sup> Department of Internal Diseases, Grodno State Medical University, Grodno, Belarus, tel. +375 292 26 32 44, fax +375 152 43 53 41, e-mail: ekaterina-yackevich@yandex.ru

**Material and methods.** Traditional time and frequency domain HRV indices were analyzed in 75 patients (mean age 55 [49–62] years, 79% male) with paroxysmal or persistent AF on a background of ischemic heart disease (IHD) and/or hypertension without significant structural myocardial damage and in 19 control patients without AF (mean age 56 [49–61] years, 63% male). Echocardiography was performed to assess size and function of left atrium (LA).

**Results.** In patients with paroxysmal or persistent AF the ApEn value was significantly lower than in the control patients group. Echo-parameters of LA, characterizing its structure and function, were correlated with ApEn value. The AF duration was negatively correlated with the ApEn value. Its values less than 0.93 was associated with a larger LA size (> 39 mm) and more frequent AF.

**Conclusions.** There is a strong correlation of ApEn value and atrial remodeling. ApEn values less than 0.93 are related to AF recurrence and can be considered as prognostic risk factor of structural and functional remodeling of the heart muscle in patients with AF.

**Key words:** atrial fibrillation, left atrium, echocardiography, structural and functional remodeling, heart rate variability, nonlinear analyses, approximate entropy.

Folia Cardiologica 2017; 12, 2: 154–161

## Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting approximately 1% of the general population and up to 8% of subjects over the age of 80 years [1]. AF is a major contributor to cardiovascular mortality and morbidity, associated with decreased quality of life, increased incidence of congestive heart failure, embolic phenomena, including stroke, and a 30% higher risk of death [2–4].

AF is more prominent in the context of alterations in atrial tissue properties – due to disease, arrhythmias, or age – known as remodeling. In fact, AF itself leads to remodeling, causing electrophysiological (“electrical”), contractile, and structural changes [5]. Although AF can typically be reversed in its early stages, it becomes more difficult to eliminate over time due to such remodeling – hence the expression “AF begets AF” [6].

The atrial chambers may have substantial geometric remodeling (chamber remodeling) during evolving AF [7]. Predictably, structural remodeling will be more difficult to reverse as compared to the electrical one [8].

### Autonomic modulation and AF

Many factors related to the autonomic nervous system can influence AF [9]. Heart rate variability (HRV) analysis has been used extensively in the study of atrial fibrillation. These observations suggest that the mechanisms involved in cardiovascular regulation can interact with each other in a nonlinear way, so HR time series analysis by nonlinear metrics has recently gained great interest [10]. Furthermore, chaotic behavior can be interpreted in the diseased heart with atrial fibrillation (AF) at cellular level and atrial electrophysiological remodeling during this arrhythmia is a far-from-linear process [11]. Thereby, several meas-

ures of entropy, such as sample entropy (SampEn) and approximate entropy (ApEn), together with the detrended fluctuation analysis (DFA) have been applied to study the HRV complexity evolution in the minutes preceding spontaneous paroxysmal AF onset. ApEn provides a measure of the degree of irregularity or randomness within a series of data [12]. ApEn is a family of statistics that addresses the question, given a sequence of two (or three or four) interbeat intervals, what is the probability that the next consecutive interval falls within a predetermined range. Thus, ApEn is a measure of short-range correlation. ApEn, in general, represents the information contained in a time series. A low value indicates that the signal is deterministic; a high value indicates randomness [13].

This nonlinear index of HR dynamics has provided information on the vulnerability to AF [14]. As for structural remodeling, it has been shown that atrial fibrosis in the setting of AF is the result of a complex interactive effect among profibrotic signaling pathways, inflammation and oxidative stress, the first two contributors being extensively studied [15].

Nevertheless, based on the available data it is not stipulated whether there is an association between ApEn value and atrial remodeling, and its correlation with AF duration.

The aims of this study was to establish the relationship of nonlinear index of HRV, such as ApEn, with echocardiographic parameters of left atrium (LA) and AF clinical course in patients with paroxysmal and persistent AF.

## Materials and methods

A total of 75 patients with AF admitted to the Arrhythmology Department of the Grodno Regional Clinical Cardiology Centre (Belarus) due to AF have been recruited into the study.

These patients included 48 subjects with paroxysmal AF and 27 subjects with persistent AF, with the background of ischemic heart disease and/or arterial hypertension, without significant structural myocardial damage. Persistent AF was defined as AF which is sustained beyond seven days, or lasting less than seven days but necessitating pharmacological or electrical cardioversion. The study control group included 19 patients with no history of AF. All study participants had background history of coronary artery disease and/or hypertension. Patients with thyroid dysfunction, acute stroke, acute myocardial infarction, acute myocarditis, known chronic heart failure (NYHA  $\geq 2$ ) and higher, diabetes, severe chronic diseases (e.g., severe renal or liver failure) or pregnancy were excluded from the study.

Routine laboratory and physical examinations were used to exclude cardiovascular diseases.

All patients underwent instrumental and laboratory study after signing an informed consent form that was approved by our institution's committee on human investigation.

On the admission AF patients were subjected to pharmacological or direct current cardioversion. In all patients with persistent atrial fibrillation, cardioversion was performed with a transthoracic electrical shock of 200 to 360 J. None of patients have been performed radiofrequency catheter ablation. All patients were successfully cardioverted and remained in sinus rhythm at discharge. So all of our patients were examined on sinus rhythm.

### Heart rate variability

To assess the functional state we used a standardized 5-min analysis of HR after an overnight fast. Patients stop taking drugs in 2 days before the study. The RR intervals were recorded in the supine position with an HR monitor of QRS complexes "Intekard" ("Intekard", Belarus) and software for it "Breeze XP" [13]. A series of 250 beats was selected to analyze nonlinear parameter, such as ApEn. Additionally, standard HRV measures were determined: time domain (SDNN, pNN50, rMSSD) and frequency domain methods (by four components: total-frequency (TF) component (0.01 to 0.5 Hz), low-frequency (LF) component (0.04 to 0.15 Hz), very low-frequency (VLF) component (below 0.04 Hz) and high-frequency (HF) component (0.15 to 0.5 Hz). Two component ratio (LF/HF) expressing the sympathovagal balance was also calculated.

### Echocardiography

Two-dimensional transthoracic echocardiography was performed using Philips IE-33 system and broadband phased array probe (S5-1, 1–5 MHz, Philips, USA) The following parameters were obtained: left atrial systolic diameter (LASD), LV end-systolic diameter (LVESD), LV end-diastolic diameter (LVEDD), LV mass (LVM) and LV mass index (LVMI) [16].

In addition to standard echocardiographic parameters, left atrial (LA) geometry and function was assessment by measurement of LA volume, LA volume index, LV stroke volume, LA ejection fraction using bi-plane area-length method as reported previously [17–19].

### Statistical analysis

Normally distributed data are presented as mean  $\pm$  standard deviation and non-normally distributed data are reported as median and interquartile range. To non-normal distribution of data, multiple comparisons among three groups were conducted by Kruskal-Wallis H test and differences between two groups were assessed by Mann-Whitney U test for post hoc analysis. Proportional data were compared with a chi square test. A one way ANOVA test was used for assessing the statistical significance where appropriate. To identify the relationship between indicators of an abnormal distribution the Spearman rank correlation coefficient ( $r_s$ ) was used, and the Student's test for the normal distribution of the sign. Correlation between ApEn value and AF duration was examined by simple logistic regression. In assessing the significance of differences in the frequency of quality indicators the two-sided Fisher's exact test was used. General Classification Regression Tree Models Analyze was used to determine an affecting of some indicators on other variables, their hierarchy of influence, thereby defining its prognostic significance [14]. The differences were considered statistically significant when  $p < 0.05$  (2-tailed). The analysis was performed using Statistica 6.0 software package (Statsoft, US).

### Results

There was no significant difference in age, gender, renal function, history of coronary artery disease and hypertension between the studied patients groups (Table 1).

Table 2 shows medications used for pharmacological cardioversion and after direct current cardioversion, whereas Table 3 shows echocardiographic parameters.

The analysis has shown that the ApEn level in the control group was 1.03 (0.94–1.10), that was significantly ( $p < 0.05$ ) higher than in groups 1 and 2 – 0.09 (0.007–0.96) and 0.02 (0.003–0.88), respectively, while no statistically significant differences between the two groups of patients – with paroxysmal and persistent AF – have been revealed (Table 4).

Further analysis revealed significant correlation between the ApEn value and echocardiographic parameters of LA in patients of all groups: LA systolic diameter ( $R = -0.24$ ,  $p = 0.043$ ), LA systolic volume ( $R = -0.30$ ,  $p = 0.040$ ), the LA ejection fraction ( $R = 0.36$ ,  $p = 0.013$ ). Logistic regression revealed a significant associations between the AF duration and the ApEn value ( $B = -0.31$ ,  $p = 0.028$ ).

**Table 1.** Characteristics of the studied patients groups

Patients characteristics	Paroxysmal AF (n = 48)	Persistent AF (n = 27)	Controls (n = 19)	p value (by Kruskal-Wallis H test)
Age [years]	56 (50–64)	53 (46–61)	56 (49–61)	0.72
Male gender, n [%]	37 (77)	22 (81)	12 (63)	0.91
Hypertension, n [%]	39 (81)	22 (81)	17 (89)	0.99
Coronary artery disease, n [%]	41 (85)	21 (78)	14 (74)	0.49
eGFR [ml/min/1.73 m <sup>2</sup> ]	68 ± 13	66 ± 13	72 ± 18	0.74

AF – atrial fibrillation; eGFR – estimated glomerular filtration rate

**Table 2.** Medications used for pharmacological cardioversion (Group 1) and after direct current cardioversion (Group 2)

Medications	Paroxysmal AF (n = 48)	Persistent AF (n = 27)	p value (by Kruskal-Wallis H test)
Beta-blocker, n [%]	12 (25)	13 (48.1)	0.07
Amiodarone, n [%]	20 (41.7)	12 (44.4)	1.0
Sotalolol, n [%]	9 (18.8)	1 (3.7)	0.08
Aethacizin, n [%]	7 (14.6)	1 (3.7)	0.25
Warfarin, n [%]	23 (47.9)	27 (100)	< 0.0001

AF – atrial fibrillation

**Table 3.** Echocardiographic parameters

	Paroxysmal AF (n = 48)	Persistent AF (n = 27)	Control (n = 19)	p value (by Kruskal-Wallis H test)
<b>Left atrial parameters</b>				
Systolic diameter, mm	38 ± 3*	41 ± 4*#	36 ± 2	0.0015
Stroke volume, ml	35 ± 10	30 ± 9	35 ± 10	0.15
Diastolic volume [ml]	70 ± 16	78 ± 18*	61 ± 18	0.10
Systolic volume [ml]	34 ± 14	47 ± 18*#	26 ± 9	0.0008
Systolic volume index, [ml/m <sup>2</sup> ]	16 ± 6	24 ± 10*#	13 ± 4	0.0005
Diastolic volume index, ml/m <sup>2</sup>	34 ± 7	39 ± 10	31 ± 8	0.08
Ejection fraction [%]	52 ± 11	37 ± 11*#	58 ± 7	0.0001
<b>Left ventricular parameters</b>				
Mass index [g/m <sup>2</sup> ]	118 ± 25	119 ± 22	105 ± 14	0.23
End-diastolic volume [ml]	128 ± 20	131 ± 29	121 ± 26	0.44
End-systolic volume [ml]	42 ± 10	52 ± 23*	37 ± 9	0.06
Stroke volume [ml]	84 ± 14	79 ± 14	81 ± 17	0.22
Ejection fraction [%]	66 ± 5	61 ± 8*#	68 ± 5	0.0027

\*Significant differences compared with control group; #significant differences compared with group 1 (by Mann-Whitney U test); AF – atrial fibrillation

On the next step we used General Regression Tree Model Classification as a prediction model that can be represented as a decision tree [14]. The ApEn value < 0.93 was associated with a larger LA size (> 39 mm) (Figure 1).

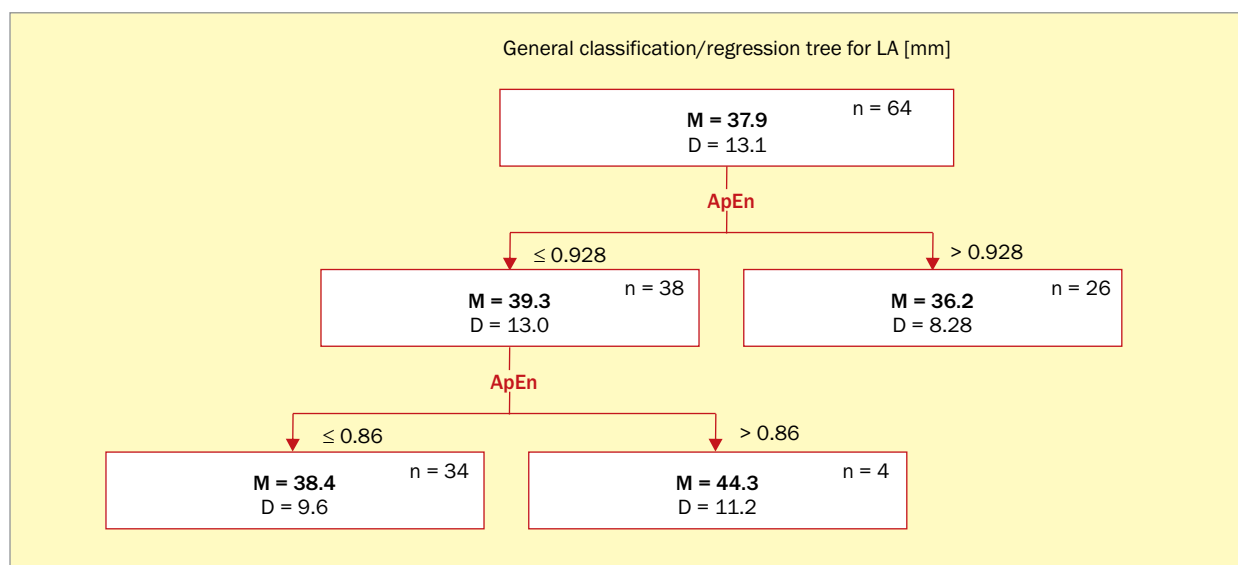
Then all three patients groups (n = 75) were divided into groups according to the level of ApEn (0.93) (Table 5).

In the group with the ApEn value greater than 0.93 the percentage of patients without AF episodes was significantly higher (p = 0.0008), while the ApEn value less than 0.93 was associated with a new-onset AF (p = 0.02). AF recurrences were significantly more frequent if ApEn value was less than 0.93 (p = 0.0045), while its higher values

**Table 4.** Heart rate variability parameters

Parameter	Group 1 Paroxysmal AF (n = 48)	Group 2 Persistent AF (n = 27)	Group 3 Control (n = 19)	p value (by Kruskal-Wallis H test)
SDNN [ms]	36.1 (25.6; 69.4)	41.3 (27.0; 51.3)	32.4 (26.4; 50.9)	0.58
rMSSD [ms]	27.3 (16.6; 55.6)	29.75 (17.3; 53.8)	27.95 (20.7; 44.7)	0.82
NN50	3.0 (0.000; 13.0)	4.0 (0.5; 10.5)	2.5 (1.0; 5.0)	0.74
pNN50 [%]	1.0 (0.000; 4.6)	1.3 (0.15; 4.1)	0.75 (0.3; 1.3)	0.58
HF [%]	51.3 (41.4; 61.5)	50.1 (42.65; 55.85)	41.75 (38.1; 52)	0.58
LF [%]	33.50 (28; 39.5)	34.35 (28.3; 38.95)	36.15 (31.60; 42.10)	0.81
VLF [%]	15.20 (9.00; 19.30)	15.55 (11.35; 19.95)	17.10 (14.40; 22.20)	0.28
LF/HF	0.65 (0.64; 0.68)	0.69 (0.66; 0.70)	0.87 (0.83; 0.81)	0.21
<b>ApEn</b>	<b>0.09 (0.007; 0.96)*</b>	<b>0.02 (0.003; 0.88)*</b>	<b>1.03 (0.94; 1.10)</b>	<b>0.0098</b>
HF [ms <sup>2</sup> ]	328.1 (294.8; 590.9)	811.8 (246.4; 1026.3)	510.4 (321.1; 666.0)	0.22
LF [ms <sup>2</sup> ]	303.6 (250.0; 420.7)	530.1 (245.9; 860.5)	299.7 (259.2; 480.2)	0.38
VLF [ms <sup>2</sup> ]	149.3 (131.2; 176.1)	255.5 (107.3; 313.4)	160.7 (117.6; 268.1)	0.71
TP [ms <sup>2</sup> ]	1210.50 (766.40; 2430.70)	1125.25 (788.0; 2018.55)	1021.15 (659.5; 1444.9)	0.58

\*Significant differences compared with the control group (p < 0.05) (by Mann-Whitney U test); AF – atrial fibrillation; SDNN – standard deviation of normal-to-normal R-R intervals; rMSSD – the root mean square of successive differences; NN50 – count, defined as the mean number of times per hour in which the change in consecutive normal sinus (NN) intervals exceeds 50 ms; pNN50 = (NN50 count) / (total NN count) – the fraction of consecutive NN intervals that differ by more than 50 ms; LF – low-frequency; VLF – very low-frequency; ApEn – approximate entropy; TP – total power



**Figure 1.** Classification for the left atrial according to approximate entropy (ApEn) value; LA – left atrium; M – mean value; D – a dispersion of the sample

were associated with no AF recurrence during a year (Table 6). As we can see from the table, the sensitivity of this detection is about 70% and specificity – 66%.

### Discussion

The studies show that persistent or recurrent AF is constantly associated with the phenomenon of atrial remodeling characterized by electrical and structural changes of myo-

cardium that contributes to the persistence of arrhythmia [20, 21]. Several reports have indicated that duration of AF is associated with the major changes in cardiac electrical properties that may favor arrhythmia recurrence. Structural remodeling has also been considered as a critical pro-arrhythmic factor [22]. Less emphasis has been attributed to the possible role of the autonomic nervous system. In the past, the term vagal or sympathetic AF [9] has been used to characterize the autonomic environment in which AF has

**Table 5.** The association of approximate entropy (ApEn) value and atrial fibrillation (AF) frequency

AF frequency	ApEn < 0.93 (n = 43)		ApEn > 0.93 (n = 32)		p value
	n	%	n	%	
Without AF	4	9	14	44	0.0008*
New-onset AF	12	28	2	6	0.02*
Up to 1 per year	5	12	5	16	NS
1 per 3–6 months	8	19	3	9	NS
More than 1 per month	14	32	8	25	NS

NS – non-significant

**Table 6.** The relationship of approximate entropy (ApEn) value and atrial fibrillation (AF) recurrence

AF recurrence	ApEn < 0.93 (n = 43)		ApEn > 0.93 (n = 32)		p
	n	%	n	%	
No AF recurrences	13	30	21	66	0.0045*
AF recurrences	30	70	11	34	0.0045*

been reported to occur. No attention was instead directed to the possibility that a specific autonomic pattern could facilitate AF recurrence after electrical or pharmacological cardioversion.

The mechanisms leading to the initiation of AF have been extensively investigated for the last decade. It has been proposed that the autonomic nervous system might have a role in the initiation of this arrhythmia. Precisely, increased vagal tone can predispose to the development of AF [23].

Vagal mechanisms have been indicated to be predominant when AF onset occurred after meals or during nighttime in absence of significant increases in heart rate, particularly in male patients without evidence of organic heart disease. In contrast, a pro-arrhythmic role of sympathetic activation was suspected when AF was initiated during exercise, emotion, or isoproterenol infusion. However, in most instances, recognition of a specific autonomic pattern is difficult; also, when HRV analysis was used to characterize the role of the autonomic nervous system before AF onset, contrasting results were noticed [24]. The complexity of the problem might be partially explained by the fact that both sympathetic and vagal activation may exert a pro-arrhythmic action by affecting atrial action potential duration and conduction velocity [25, 26]; non-uniform autonomic innervation of the atria may also play a critical role [27].

ApEn assigns a non-negative number to a sequence or time series, with larger values corresponding to greater process randomness or serial irregularity, and smaller values corresponding to more instances of recognizable

features or patterns in the data [12]. ApEn measures the logarithmic likelihood that runs of patterns that are close (within a tolerance window  $r$ ) for length  $m$  continuous observations remain close (within the same tolerance  $r$ ) on next incremental comparison. The input variables  $m$  and  $r$  must be fixed to calculate ApEn. The method can be applied to relatively short time series, but the amounts of data points influence the value of ApEn [28].

Our data indicate the existence of correlation between the ApEn value and LA parameters characterizing its structural and functional state. Being associated with AF clinical course these indicators let us to suggest that the ApEn value less than 0.93 can be prognostic risk factor of both AF recurrence and structural changes in the LA.

## Conclusions

1. In patients with paroxysmal or persistent AF with arterial hypertension and/or coronary artery disease the ApEn value was significantly lower, than in the control group.
2. The ApEn value was associated with the parameters of left atrium that characterize its structure and function.
3. The AF duration was negatively correlated with ApEn value.
4. The ApEn value less than 0.93 was associated with a larger LA size and AF recurrence, while the percentage of patients without AF episodes was significantly higher when ApEn value was greater than 0.93.

## Conflict of interest(s)

None.



## Streszczenie

**Wstęp.** Remodeling przedsionków spowodowany migotaniem przedsionków (AF) charakteryzuje się elektrycznymi i strukturalnymi zmianami kardiomiocytów w odpowiedzi na utrwaloną arytmie i oporność na leczenie mające na celu przywrócenie rytmu zatokowego. Celem tego projektu było zbadanie nieliniowych metod oceny zmienności rytmu serca (HRV) (np. entropia aproksymacji rytmu serca [ApEn]), które najlepiej charakteryzują strukturalny i funkcjonalny remodeling lewego przedsionka (LA) i jego związek z przebiegiem klinicznym u chorych z napadowym i przetrwałym AF.

**Materiał i metody.** Przeanalizowano tradycyjne wskaźniki czasowe i częstotliwościowe HRV w grupie 75 chorych (średnia wieku 55 [49–62] lat, 79% mężczyzn) z napadowym lub przetrwałym AF na podłożu choroby niedokrwiennej serca i/lub nadciśnienia tętniczego bez istotnych strukturalnych uszkodzeń miokardium oraz w grupie kontrolnej złożonej z 19 osób bez AF (średnia wieku 56 [49–61] lat, 63% mężczyzn). Przeprowadzono również badanie echokardiograficzne w celu oceny wielkości i czynności LA.

**Wyniki.** U chorych z napadowym lub przetrwałym AF wartość ApEn była istotnie niższa niż w grupie kontrolnej. Parametry echokardiograficzne LA, charakteryzujące jego strukturę i czynność, były skorelowane z wartością ApEn. Stwierdzono ujemną korelację między czasem trwania AF a wartością ApEn. Wartości ApEn mniejsze niż 0,93 wiązały się z większym rozmiarem LA (> 39 mm) i częstszym AF.

**Wnioski.** Istnieje silna korelacja między wartością ApEn a remodelingiem przedsionka. Wartości ApEn mniejsze niż 0,93 wiążą się z nawrotami AF i mogą służyć jako prognostyczny czynnik ryzyka strukturalnego i czynnościowego remodeling mięśnia sercowego u chorych z AF.

Słowa kluczowe: migotanie przedsionków, lewy przedsionek, echokardiografia, remodeling strukturalny i czynnościowy, zmienność rytmu serca, analizy nieliniowe, entropia aproksymacji

Folia Cardiologica 2017; 12, 2: 154–161

## References

1. Fuster V, Rydén LE, Cannom DS, et al. Task Force on Practice Guidelines, American College of Cardiology/American Heart Association; Committee for Practice Guidelines, European Society of Cardiology, European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). *Eur Heart J*. 2006; 27(16): 1979–2030, doi: [10.1093/eurheartj/ehl176](https://doi.org/10.1093/eurheartj/ehl176), indexed in Pubmed: [16885201](https://pubmed.ncbi.nlm.nih.gov/16885201/).
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991; 22(8): 983–988, indexed in Pubmed: [1866765](https://pubmed.ncbi.nlm.nih.gov/1866765/).
3. Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998; 98(10): 946–952, indexed in Pubmed: [9737513](https://pubmed.ncbi.nlm.nih.gov/9737513/).
4. Stewart S, Hart CL, Hole DJ, et al. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med*. 2002; 113(5): 359–364, indexed in Pubmed: [12401529](https://pubmed.ncbi.nlm.nih.gov/12401529/).
5. Michael G, Xiao L, Qi XY, et al. Remodelling of cardiac repolarization: how homeostatic responses can lead to arrhythmogenesis. *Cardiovasc Res*. 2009; 81(3): 491–499, doi: [10.1093/cvr/cvn266](https://doi.org/10.1093/cvr/cvn266), indexed in Pubmed: [18826964](https://pubmed.ncbi.nlm.nih.gov/18826964/).
6. Wijffels MC, Kirchhof CJ, Dorland R, et al. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation*. 1995; 92(7): 1954–1968, indexed in Pubmed: [7671380](https://pubmed.ncbi.nlm.nih.gov/7671380/).
7. Moe GW, Armstrong P. Pacing-induced heart failure: a model to study the mechanism of disease progression and novel therapy in heart failure. *Cardiovasc Res*. 1999; 42(3): 591–599, indexed in Pubmed: [10533598](https://pubmed.ncbi.nlm.nih.gov/10533598/).
8. Snezhitskiy VA. [Electrophysiological atrial and sinus nodal remodeling phenomenon: mechanisms of development and pathogenesis]. [Article in Russian]. *Klin Med (Mosk)*. 2004; 82(11): 10–14, indexed in Pubmed: [15656391](https://pubmed.ncbi.nlm.nih.gov/15656391/).
9. Coumel P, Olsson SB, Alessie MA, Campbell RW. Autonomic arrhythmogenic factors in paroxysmal atrial fibrillation. In: Zipes D, Jalife J. ed. *Atrial fibrillation: mechanism and therapeutic strategies*. Futura Publishing, Armonk 1994: 171–184.
10. Porta A, Di Rienzo M, Wessel N, et al. Addressing the complexity of cardiovascular regulation. *Philos Trans A Math Phys Eng Sci*. 2009; 367(1892): 1215–1218, doi: [10.1098/rsta.2008.0292](https://doi.org/10.1098/rsta.2008.0292), indexed in Pubmed: [19324704](https://pubmed.ncbi.nlm.nih.gov/19324704/).
11. Bers DM, Grandi E. Human atrial fibrillation: insights from computational electrophysiological models. *Trends Cardiovasc Med*. 2011; 21(5): 145–150, doi: [10.1016/j.tcm.2012.04.004](https://doi.org/10.1016/j.tcm.2012.04.004), indexed in Pubmed: [22732550](https://pubmed.ncbi.nlm.nih.gov/22732550/).
12. Kantz H, Schreiber T. *Nonlinear time series analysis*. Cambridge University Press, Cambridge 2003.
13. Frolov A. Adaptation mechanisms control of cardiac activity in clinic and sports. Monograph, Minsk 2011: 156–159.
14. Loh WY. Classification and regression tree methods. In: Ruggeri F, Kenett RS, Faltin FW. ed. *Encyclopedia of statistics in quality and reliability*. Wiley, Chichester 2008: 315–323.
15. Pellman J, Lyon RC, Sheikh F. Extracellular matrix remodeling in atrial fibrosis: mechanisms and implications in atrial fibrillation. *J Mol Cell*

- Cardiol. 2010; 48(3): 461–467, doi: [10.1016/j.yjmcc.2009.09.001](https://doi.org/10.1016/j.yjmcc.2009.09.001), indexed in Pubmed: [19751740](https://pubmed.ncbi.nlm.nih.gov/19751740/).
16. Lang RM, Bierig M, Devereux RB, et al. Chamber Quantification Writing Group, American Society of Echocardiography's Guidelines and Standards Committee, European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005; 18(12): 1440–1463, doi: [10.1016/j.echo.2005.10.005](https://doi.org/10.1016/j.echo.2005.10.005), indexed in Pubmed: [16376782](https://pubmed.ncbi.nlm.nih.gov/16376782/).
  17. Lester SJ, Ryan EW, Schiller NB, et al. Best method in clinical practice and in research studies to determine left atrial size. *Am J Cardiol.* 1999; 84(7): 829–832, indexed in Pubmed: [10513783](https://pubmed.ncbi.nlm.nih.gov/10513783/).
  18. Pritchett AM, Jacobsen SJ, Mahoney DW, et al. Left atrial volume as an index of left atrial size: a population-based study. *J Am Coll Cardiol.* 2003; 41(6): 1036–1043, indexed in Pubmed: [12651054](https://pubmed.ncbi.nlm.nih.gov/12651054/).
  19. Sievers B, Kirchberg S, Addo M, et al. Assessment of left atrial volumes in sinus rhythm and atrial fibrillation using the biplane area-length method and cardiovascular magnetic resonance imaging with TrueFISP. *J Cardiovasc Magn Reson.* 2004; 6(4): 855–863, indexed in Pubmed: [15646889](https://pubmed.ncbi.nlm.nih.gov/15646889/).
  20. Moe GW, Angus C, Howard RJ, et al. Pathophysiological role of changing atrial size and pressure in modulation of atrial natriuretic factor during evolving experimental heart failure. *Cardiovasc Res.* 1990; 24(7): 570–577, indexed in Pubmed: [2145070](https://pubmed.ncbi.nlm.nih.gov/2145070/).
  21. Rossi A, Cicoira M, Zanolla L, et al. Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. *J Am Coll Cardiol.* 2002; 40(8): 1425, indexed in Pubmed: [12392832](https://pubmed.ncbi.nlm.nih.gov/12392832/).
  22. Snezhitskiy VA, Yatskevich ES, Doroshenko EM EM, et al. The relationship between homocysteine, proline, glycine with structural and functional myocardial remodeling in patients with paroxysmal and persistent forms of atrial fibrillation. *Cardiology in Belarus.* 2014; 5(36): 18–30.
  23. Tuzcu V, Nas S, Börklü T, et al. Decrease in the heart rate complexity prior to the onset of atrial fibrillation. *Europace.* 2006; 8(6): 398–402, doi: [10.1093/europace/eul031](https://doi.org/10.1093/europace/eul031), indexed in Pubmed: [16687424](https://pubmed.ncbi.nlm.nih.gov/16687424/).
  24. Lombardi F, Torzillo D, Cappiello ES. Sympatho-vagal influences in atrial fibrillation. *New Trends Arrhythmias.* 1993; 9: 279–284.
  25. Shimizu W, Tsuchioka Y, Karakawa S, et al. Differential effect of pharmacological autonomic blockade on some electrophysiological properties of the human ventricle and atrium. *Br Heart J.* 1994; 71(1): 34–37, indexed in Pubmed: [8297691](https://pubmed.ncbi.nlm.nih.gov/8297691/).
  26. Waxman MB, Cameron DA, Wald RW, Zipes DP, Jalife J. Interactions between the autonomic nervous system and supraventricular tachycardia in humans. In: Zipes DP, Jalife J. ed. *Cardiac electrophysiology: from cell to bedside.* WB Saunders, Philadelphia 1995: 699–722.
  27. Levy MN, Martin PJ. Neural control of heart rate and atrioventricular conduction. In: Abboud FM, Fozzard HA, Gilmore JP, Reis DJ. ed. *Disturbances in neurogenic control of the circulation.* American Physiological Society, Bethesda 1981: 205–215.
  28. Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. *Am J Physiol Heart Circ Physiol.* 2000; 278(6): H2039–H2049, indexed in Pubmed: [10843903](https://pubmed.ncbi.nlm.nih.gov/10843903/).